INDICATION
UDENYCA® is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Limitations of Use
UDENYCA® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATION: Patients with a history of serious allergic reaction to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products.

Please see Full Prescribing Information in pocket, and Important Safety Information throughout this brochure.
Executive summary

The totality of evidence demonstrates that UDENYCA® is highly similar to Neulasta® (pegfilgrastim), with no clinically meaningful differences between the products. Overall, the totality of evidence supports biosimilarity and the use of UDENYCA® to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. UDENYCA® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

UDENYCA® was approved by the US Food and Drug Administration (FDA) on November 2, 2018. The FDA concluded that UDENYCA® was highly similar to the reference product Neulasta®, with no clinically meaningful differences.

UDENYCA® is highly similar to Neulasta® in terms of molecular structure, biological function, drug purity, and stability.

UDENYCA® is bioequivalent to Neulasta® on the basis of absolute neutrophil count (ANC) pharmacodynamics and drug pharmacokinetics.

There were no clinically meaningful differences in the safety profile of UDENYCA® and Neulasta®. Adverse events were similar between UDENYCA® and Neulasta®. There were no clinically meaningful differences in the immunogenicity profiles of UDENYCA® and Neulasta®. No treatment-emergent neutralizing antibodies were observed in more than 400 UDENYCA®-exposed healthy subjects.

ADVERSE REACTIONS: Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity.

Introduction

Pegfilgrastim (PEGylated recombinant granulocyte colony-stimulating factor [G-CSF]) stimulates the proliferation of white blood cells.1 The primary indication for which Neulasta® is approved is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.2 Neulasta® was approved in 2002 based on demonstration of noninferiority in the duration of severe neutropenia, compared with daily dosed filgrastim.3 PEGylation of filgrastim reduces renal clearance and prolongs its half-life,4 which allows pegfilgrastim to be administered once per cycle of chemotherapy. Therefore, pegfilgrastim reduces the need for patients to return to the clinic for daily filgrastim injections and thus decreases the risk of noncompliance. Pegfilgrastim reduces the risk of infection and hospitalization related to febrile neutropenia.2

Need for Choice

Availability of Neupogen® (filgrastim) and Neulasta® has greatly improved the safety of myelosuppressive chemotherapy regimens used to treat breast cancer and other solid tumors. However, the cost of Neulasta® has increased by more than 100% since 2006.5 Lack of competition has enabled price increases. Although the Centers for Medicare & Medicaid Services and commercial insurers have taken on a great share of the increasing costs, patients too have shared this cost burden through larger copay and coinsurance premiums. Increasing cost reduces access for patients who have a lower ability to pay for supportive care.1 Insurers may be faced with a budgetary trade-off between paying for Neulasta® and providing access to new, innovative cancer therapies and/or more intensive treatment options. Measures to control insurer costs include proposed caps on reimbursement for prescription drugs and restrictions in use. Consequently, some patients for whom consensus guidelines recommend prophylaxis for febrile neutropenia may not always receive it.

Availability of a biosimilar to Neulasta®, such as UDENYCA®, introduces competition to the US marketplace aimed at controlling costs while delivering quality supportive care to patients who need it. Since the introduction of filgrastim biosimilars in the European Union in 2008, there has been increased patient access and adherence to consensus guidelines as reflected by the rapid increase in prescriptions for filgrastim.1 In the United States, the introduction of Zarxio® (filgrastim-sndz), a biosimilar to Neupogen®, resulted in a significant reduction in price per unit of the average short-acting granulocyte colony-stimulating factor (G-CSF).1 UDENYCA® has the potential to expand patient access, decrease cost to payers, and decrease patient copays.
**UDENYCA® Indication, Dose, Strength, and Route of Administration**

The primary indication, dose, strength, formulation, and route of administration for UDENYCA® are the same as those for Neulasta® (pegfilgrastim)—6 mg administered subcutaneously as a unit dose. UDENYCA® is supplied in a prefilled 1-mL syringe to deliver 0.6 mL of drug containing 6.0 mg (based on protein content) of pegfilgrastim in a sterile, clear, colorless, preservative-free solution.

UDENYCA® should be administered once per chemotherapy cycle, no less than 24 hours after cytotoxic chemotherapy. UDENYCA® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

**Structure and Mechanism of Action of UDENYCA®**

UDENYCA® is a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) and monomethoxypolyethylene glycol (PEG; Figure 1). The G-CSF moiety is referred to as filgrastim, which is a water-soluble, nonglycosylated, 175-amino-acid protein with a molecular weight of 19 kilodaltons (kDa). To produce UDENYCA®, a nominal 20 kDa PEG molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The molecular weight of UDENYCA® is approximately 40 kDa.

The mechanism of action of pegfilgrastim involves binding to the G-CSF receptor and activation of signaling pathways leading to the proliferation of myeloid cells, as shown in Figure 1.

**Figure 1. Structure of pegfilgrastim (19 kDa protein + 20 kDa PEG) and mechanisms of action.**

The signalling pathway activated by the G-CSF receptor stimulates proliferation and differentiation of neutrophils from committed progenitor cells, induces cellular maturation, and enhances the survival and function of mature neutrophils, resulting in dose-dependent increases in absolute neutrophil count (ANC). The release of mature neutrophils from the bone marrow can be confirmed with a high degree of sensitivity through the measurement of ANC. As this event directly relates to the biologic effect of the drug, in UDENYCA® studies, ANC was used as a primary measure of the pharmacodynamic effect of UDENYCA® and Neulasta®.

**Biosimilarity development approach**

**Biosimilarity**

Biosimilarity means that the new version of the biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. The UDENYCA® biosimilar development program was designed in accordance with US Food and Drug Administration (FDA) guidance and with the agency’s advice and feedback. The objective of the development program was to demonstrate biosimilarity of UDENYCA® to Neulasta®. Demonstration of biosimilarity requires confirmation of activity but does not require the re-establishment of efficacy (ie, a repeat of the pivotal trials of the reference product). As indicated by the FDA: “The purpose of a biosimilar development program is to support a demonstration of biosimilarity between a proposed product and a reference product, including an assessment of the effects of any observed differences between the products, but not to independently establish the safety and effectiveness of the proposed product.”

**Development Approach**

Demonstration of biosimilarity is based on the totality of the evidence showing that a biosimilar product is highly similar to the reference product and that there are no clinically meaningful differences between the biosimilar and the reference product. A comprehensive comparative evaluation of UDENYCA® and Neulasta® was performed using the recommended stepwise approach as depicted in Figure 2. Each of the steps in the pyramid builds on the one below it to address residual uncertainty.

The sequential steps taken in the UDENYCA® biosimilar development program are outlined below.

- Structural and functional characterization of the reference product (Neulasta®) followed by a comprehensive analytical similarity assessment to demonstrate structural and functional similarity of UDENYCA® and Neulasta®
- Nonclinical studies to demonstrate comparable toxicokinetics, pharmacodynamics (PD), and safety between UDENYCA® and Neulasta®
- Clinical pharmacokinetics (PK) and PD studies in healthy subjects to demonstrate bioequivalence of UDENYCA® and Neulasta®
- Safety and immunogenicity studies in healthy subjects to demonstrate similar safety and immunogenicity profiles of UDENYCA® and Neulasta®
Based on analytics, PK/PD, and in consultation with the FDA, it was determined that there was a high degree of biosimilarity between UDENYCA® and Neulasta® (pegfilgrastim) and that no additional clinical studies were needed. Further studies in cancer patients would not add to the data demonstrating biosimilarity, and as such were not deemed necessary by the FDA.

The stepwise approach for biosimilars is different from the development model used for originator products, in which clinical trial data in the intended patient population provide the basis for approval. In the biosimilar development paradigm, the analytical assessment forms the foundation of the totality of evidence, and the nonclinical data, together with PK/PD, immunogenicity, and safety data, support the demonstration of biosimilarity and eliminate any residual uncertainty.

### Demonstrating Biosimilarity

Recombinant therapeutic proteins are produced in living cells and are purified in complex, multistep processes and, hence, are sensitive to changes in manufacturing conditions. The manufacturing technology for recombinant therapeutic proteins can be divided into multiple process steps (Figure 3). The upstream process refers to the cell culture and harvest and is followed by the downstream process consisting of purification and formulation of the therapeutic recombinant protein. Development of the upstream process includes selection of the cell line, culture media and growth parameters, and overall process optimization to achieve optimal conditions for the therapeutic protein production. The downstream process involves steps required to purify a therapeutic protein from cell culture broth to final purified product. It involves multiple steps to capture the target biomolecule and to remove process- and product-related impurities.

A robust control strategy is needed to ensure lot-to-lot consistency and also to prevent variability in product quality attributes. Variability in raw materials from culture media to formulation can adversely affect the characteristics and quality of drug product. Specifically, lot-to-lot variability of raw materials may influence the quality attributes including those that define the product’s identity, quality, safety, purity, potency, and stability. Because of the complex structures of therapeutic proteins, even minor alterations may adversely affect product consistency and cause drifts in quality attributes. Product drift is defined as an excursion in quality attributes due to unintended or unexplained deviations in manufacturing processes.

Figure 2. Stepwise demonstration of biosimilarity.

Figure 3. Protein production from cloning to validation. Reprinted from Mellstedt H, et al.13
Comparative Analytics

Summary

The analytical assessment is the foundation for the totality of evidence to demonstrate biosimilarity. The UDENYCA® analytical program followed FDA guidance and feedback to assess the quality attributes of UDENYCA® versus Neulasta® ( pegfilgrastim). More than 30 individual quality attributes of UDENYCA® were rigorously assessed using modern analytical assays. Overall, the analytical assessment demonstrated that UDENYCA® is highly similar to Neulasta® based on structural, physiochemical, and functional attributes. Table 1 summarizes the results of the similarity assessments of quality attributes (structure, activity, purity, and stability) comparing UDENYCA® and Neulasta®.

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Similarity Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td></td>
</tr>
<tr>
<td>Primary structure: Amino acid sequence</td>
<td>✓</td>
</tr>
<tr>
<td>Primary structure: Disulfide structure</td>
<td>✓</td>
</tr>
<tr>
<td>Primary structure: Pegylation</td>
<td>No clinically relevant differences observed</td>
</tr>
<tr>
<td>Higher-order structure—Secondary and tertiary</td>
<td>✓</td>
</tr>
<tr>
<td>Activity</td>
<td></td>
</tr>
<tr>
<td>Relative potency</td>
<td>✓</td>
</tr>
<tr>
<td>G-CSF receptor binding affinity</td>
<td>✓</td>
</tr>
<tr>
<td>Protein concentration (strength)</td>
<td>✓</td>
</tr>
<tr>
<td>Purity</td>
<td></td>
</tr>
<tr>
<td>Molar mass</td>
<td>✓</td>
</tr>
<tr>
<td>Hydrophobicity variants (impurities from chemical degradation)</td>
<td>✓</td>
</tr>
<tr>
<td>Size distribution: Aggregates, diPegylated or uniPegylated species</td>
<td>✓</td>
</tr>
<tr>
<td>Electrostatic charge variants—aggregates and Pegylation variants</td>
<td>No clinically relevant differences observed</td>
</tr>
<tr>
<td>Stability</td>
<td></td>
</tr>
<tr>
<td>Comparative stability—Degradation rate at 5°C ± 3°C</td>
<td>✓</td>
</tr>
<tr>
<td>Comparative stability—Degradation rate under stress condition at 25°C ± 3°C</td>
<td>✓</td>
</tr>
<tr>
<td>Analytical analysis result summary</td>
<td>Highly similar</td>
</tr>
</tbody>
</table>

* Slight shift in molecular weight, which was well within the PEG raw material specification, results in a very minor difference in the physical size of the Pegylated protein and does not influence PK, as demonstrated in PK studies. 
* Minor differences observed in the amount of diPEGylated species had no effect on biologic activity as assessed in a cell-based potency assay and were not considered to be clinically significant.

Conclusions

The comprehensive analytical data demonstrate that UDENYCA® is highly similar to the reference product Neulasta®. The primary structure of pegfilgrastim in UDENYCA® and Neulasta® demonstrated identical amino acid sequence, disulfide structure, and site of Pegylation. Also, UDENYCA® was highly similar to Neulasta® in terms of higher-order structure, purity, strength, and in vitro potency, notwithstanding minor differences in clinically inactive components. Levels of diPegylated species are very low (0.1%) in all lots tested, although they qualitatively appear slightly higher in UDENYCA®. The observed differences are deemed too small to have a meaningful clinical impact.

Clinical Development Program

As with analytics, the FDA has provided guidance regarding the assessment of biosimilarity with respect to PD, PK, and immunogenicity. The study population selected should be the most informative for detecting and evaluating differences in PK and PD profiles between the proposed biosimilar product and the reference product. In general, a study in healthy subjects is more sensitive for evaluating the product similarity because it is likely to produce less PK and/or PD variability than a study in patients with potential confounding factors such as underlying and/or concomitant disease and concomitant medications, such as myelosuppressive chemotherapy. As stated in the FDA guidance “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” in certain cases, establishing a similar clinical PK, PD, and immunogenicity profile may provide sufficient clinical data to support a conclusion that there are no clinically meaningful differences between the 2 products. This approach was used in the development of UDENYCA® because there is an established PD biomarker (ANC) that can be assessed in healthy subjects, and the mechanism of action of pegfilgrastim is the same in healthy subjects and patients with cancer.

The UDENYCA® Clinical Development Program was designed to demonstrate the biosimilarity of UDENYCA® to Neulasta® with respect to PK, PD, immunogenicity, and safety in accordance with the FDA guidance on demonstrating biosimilarity including the use of healthy subjects. A clinical trial in cancer patients was deemed not necessary to demonstrate biosimilarity by the FDA. Hence, the Clinical Development Program was conducted in healthy volunteers, the most sensitive subject group in which to identify any potential differences in PK, PD, immunogenicity, and safety.

Rationale for Healthy Subjects

Pegfilgrastim has a well-established mechanism of action, which is the same in healthy subjects as in patients with cancer. Given the high degree of structural and functional similarity between UDENYCA® and Neulasta®, as demonstrated analytically, there is no biologically plausible reason why UDENYCA® and Neulasta® would perform differently in these 2 populations.
Absolute neutrophil count (ANC) is an established PD biomarker in cancer patients, and is a sensitive biomarker for the clinical endpoint of days of severe neutropenia (ANC <500 cells/μL) and, in turn, the risk of infection. In patients at risk for febrile neutropenia, recovery of ANC is the most important prognostic factor. Also, the original approval of pegfilgrastim was based on the clinical endpoint of duration of severe neutropenia as measured by ANC. Thus, ANC was used as a primary measure of the PD effect of UDENYCA® and Neulasta® (pegfilgrastim). Underlying disease, myelosuppressive chemotherapy dose, cycle, and type of agent can all confound ANC pharmacodynamics. Varying chemotherapy agents and doses are associated with varying ANC nadirs, resulting in interpatient and intrapatient variability in ANC pharmacodynamics.

Additionally, the primary mechanism of drug-clearance for pegfilgrastim is neutrophil-mediated. As pegfilgrastim acts to increase the ANC, the resulting neutrophils are responsible for clearance of pegfilgrastim. This has been termed neutrophil-mediated or “self-regulated clearance.” Therefore, any confounder of ANC pharmacodynamics, such as underlying disease or chemotherapy agent, dose, and cycle, will likely confound pegfilgrastim pharmacokinetics.

Figure 4 below illustrates a relationship between ANC (left panel) and pegfilgrastim serum concentration (right panel) in a small sample of cancer patients versus healthy subjects. In healthy subjects, administration of pegfilgrastim results in a rapid peak in ANC followed by gradual normalization of ANC. Although the mechanism of action of pegfilgrastim is the same in patients with cancer as it is in healthy subjects, the response is muted in cancer patients who have been treated with myelosuppressive chemotherapy. Because myelosuppressive chemotherapy reduces neutrophil precursors in the bone marrow, ANC will initially decline to a nadir after administration of chemotherapy, followed by a rapid recovery of ANC as pegfilgrastim exerts its biologic effect.

Myelosuppressive chemotherapy (dose and agent) may be the greatest confounders of ANC-PD. An additional observation from the Neulasta® clinical studies in patients receiving myelosuppressive chemotherapy is that ANC-PD in the first chemotherapy cycle is different from subsequent chemotherapy cycles. This creates intrapatient variability in PD and presumably PK. Healthy subjects have an abundance of neutrophil precursors in their bone marrow and are not subject to confounding factors such as disease state and chemotherapy. Healthy subjects provide the most sensitive population in which to measure increases in ANC after administration of UDENYCA® or Neulasta® and to determine if there is a difference in PD response between the two.

Pegfilgrastim clearance is primarily mediated by neutrophils, resulting in decreasing serum levels. This relationship between ANC and pegfilgrastim clearance can be seen in both cancer patients and healthy subjects. Healthy subjects are an appropriate population in which to assess PK and PD similarity in a way that is sensitive and mechanistically relevant.

Healthy subjects are also considered to be the most sensitive population in which to assess immunogenicity and safety. They are fully immunocompetent and can mount an antidrug antibody (ADA) response. In contrast, cancer patients receiving myelosuppressive chemotherapy have a blunted immune response. Confounding factors, such as an immunosuppressive disease state, chemotherapy, or radiation therapy, could prevent the development of ADA. Lack of these confounding factors also makes healthy subjects a preferred population to evaluate treatment-related adverse events (AEs) that are specific to pegfilgrastim. In patients with cancer, it is often difficult to attribute causality of an AE to a single source such as pegfilgrastim, because there are other possible sources for the event.

In summary, it is reasonable to extrapolate PK, PD, and immunogenicity findings for pegfilgrastim from healthy subjects to patients with cancer. Moreover, in accordance with FDA guidance, additional clinical studies in patients with cancer were deemed not necessary to resolve residual uncertainty and would not have added to the totality of evidence demonstrating the biosimilarity of UDENYCA® and Neulasta®.

Figure 4. Illustrative PD/PK profiles of pegfilgrastim in healthy subjects and patients receiving myelosuppressive chemotherapy.
Clinical Studies Overview

PK, PD, immunogenicity, and safety were assessed in each of the 4 studies in the UDENYCA® Clinical Development Program (Table 2).

- **Study 05**—the confirmatory PK/PD equivalence study—was a 3-sequence, 3-period crossover study in 122 subjects that demonstrated PK and PD bioequivalence between UDENYCA® and Neulasta® (pegfilgrastim).

- **Study 04** was a stand-alone immunogenicity study in 303 subjects that demonstrated similar immunogenicity between UDENYCA® and Neulasta®.

- Two additional studies (03 and 01) are included in the integrated immunogenicity and safety analyses:
  - Study 03 was a supportive PK/PD study in 116 subjects that demonstrated PD bioequivalence but did not meet PK bioequivalence for area under the curve (AUC).
  - Study 01 was an early PK bioequivalence study in 78 subjects that was conducted with early development material (noncommercial product). Study 01 was an active-controlled study initiated under the 351(a) innovator pathway prior to the formation of the 351(k) biosimilar pathway, and thus was not used for the UDENYCA® registration program.

Study 02, a study to be conducted in breast cancer patients, was not initiated as discussions with the FDA determined that it was not necessary to establish biosimilarity.

### Table 2. Overview of UDENYCA® clinical studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Endpoint</th>
<th>Study Description</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmatory studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>PK/PD</td>
<td>3-sequence, 3-period crossover</td>
<td>N = 122</td>
</tr>
<tr>
<td>04</td>
<td>Immunogenicity</td>
<td>2 sequential-dose, parallel-arm study</td>
<td>N = 303</td>
</tr>
<tr>
<td><strong>Supportive studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>PK/PD</td>
<td>Single-dose, 2-period crossover</td>
<td>N = 116</td>
</tr>
<tr>
<td>01</td>
<td>PK</td>
<td>Single-dose, 2-period crossover (noncommercial product)</td>
<td>N = 78</td>
</tr>
</tbody>
</table>

**Note:** Study 05 was conducted at 4 Clinical Pharmacology Units (CPUs): San Antonio, TX; Cincinnati, OH; West Bend, WI; and Cypress, CA; Study 03 was conducted at 1 CPU in San Antonio, TX; and Study 04 was conducted at 4 CPUs: San Antonio, TX; Cincinnati, OH; West Bend, WI; and Overland Park, KS.

- Study 02 was not initiated; discussions with FDA determined that it would not add to the development program.
- Study 01 was not included in the PK/PD bioequivalence analysis because it was conducted with an early noncommercial product.

Across all studies, the PK endpoints were maximum concentration (C_{max}) and AUC from time 0 to infinity (AUC_{0-inf}). The PD endpoints were maximum absolute neutrophil count (ANC_{max}) and ANC AUC_{0-last}.

To demonstrate bioequivalence, the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) between the treatments had to fall between 80% and 125% for all PK and PD endpoints. The PD endpoints were met in all clinical studies and PK bioequivalence was established in Study 05.

**Pharmacokinetics and Pharmacodynamics**

**Study 05**

Study 05 was a randomized, single-blind, partial reference-replicate, 3-sequence, 3-period crossover study (Figure 5). Within each sequence, subjects received 1 dose of UDENYCA® and 2 doses of Neulasta®. The design of Study 05 was informed by the prior Studies 03, 04, and 01. High intrasubject variability (coefficient of variation [CV] >50%) was observed in Study 03, which resulted in it being insufficiently powered to meet PK bioequivalence with respect to AUC criteria. In Study 04, in which subjects received 2 doses of UDENYCA® or 2 doses of Neulasta®, intrasubject variability was also high and similar between UDENYCA® and Neulasta® arms (CV=59.7% and 53.7% for AUC, respectively). This observation informed the design and powering of the pivotal Study 05.

Study 05 was designed as a partial reference-replicate, 3-sequence, 3-period study to assess not only the primary PK bioequivalence between UDENYCA® and Neulasta®, but also the intrasubject variability of PK of Neulasta® to Neulasta®.

**Figure 5.** Study 05 schema.

A

UDENYCA® 6 mg SC

N=37

B

Neulasta® 6 mg SC

C

UDENYCA® 6 mg SC

N=42

Dose 1

Period 1

(28 days)

Dose 2

Period 2

(28 days)

Dose 3

Period 3

(28 days)

**Primary PK endpoint:** AUC from time 0 to infinity (AUC_{0-inf}) and peak plasma pegfilgrastim concentration (C_{max}).

**Secondary PK endpoints:** Time to C_{max} (T_{max}), AUC_{0-inf}, AUC_{0-t}, and terminal elimination half-life (t_{1/2}).

**Primary PD endpoints:** Maximum observed ANC (ANC_{max}), ANC AUC calculated from 0 to the last measured observation (ANC AUC_{0-last}), and ANC AUC calculated from 0 to 480 hours (ANC AUC_{0-480}).

UDENYCA

pegfilgrastim-cbqv
The 3-period design of Study 05 allowed an interim analysis, which was planned after the first cohort of 122 subjects had completed all 3 periods and PK data were available. The interim analysis was intended to allow a protocol-specified sample size adjustment depending on the intrasubject CV% for AUC\textsubscript{0-\textinfty} for the Neulasta®-to-Neulasta® comparison only. The interim analysis was designed to enable an interim analysis of PK variability. If above 50%, enrollment would be increased. An independent statistician performed the interim analysis and evaluated only intrasubject variability between the 2 Neulasta® ( pegfilgrastim) doses for AUC\textsubscript{0-\textinfty} to determine whether the prespecified CV thresholds had been met.

The protocol allowed up to 218 subjects to be enrolled if the CV% for the Neulasta®-to-Neulasta® AUC\textsubscript{0-\textinfty} comparison was >48%. If the intrasubject CV% was >43% and ≤48%, up to 178 subjects could be enrolled. If the prespecified CV% threshold was ≤43%, no additional subjects beyond those in the first cohort of 122 subjects could be added. The interim analysis for the intrasubject CV% for AUC\textsubscript{0-\textinfty} for the 2 doses of Neulasta® in Study 05 was determined to be 34.5%. Therefore, 122 subjects with ≥78 evaluable subjects would be sufficient to maintain the power to meet bioequivalence and, thus, as specified in the protocol, no additional subjects were added to the study.

A total of 122 subjects (43 subjects in Sequence A, 37 subjects in Sequence B, and 42 subjects in Sequence C) were randomized in a 1:1:1 ratio between the treatment sequences. Healthy subjects were drawn from a population available to the clinical pharmacology unit. All 122 subjects received ≥1 dose of either UDENYCA® or Neulasta®; these constituted the safety population. Biosimilarity was demonstrated in the PK- or PD-evaluable population, which included subjects who received ≥1 dose of UDENYCA® or Neulasta® and had sufficient sampling data.

Overall, demographics and baseline characteristics were balanced between the treatment groups. Subjects were primarily male (71.3%) and white (44.3%). The median age for all subjects was 29.5 years, ranging from 18 to 45 years. The overall mean body mass index was 24.03 kg/m\textsuperscript{2}.

Results of Study 05 demonstrated the PK and PD bioequivalence (80% to 125%) of UDENYCA® and Neulasta® (Figures 6 and 7). Mean C\textsubscript{\textmax} and AUC\textsubscript{0-\textinfty} appeared similar between treatment groups. The GMR was 101.73% (90% CI, 92.37%-112.03%) for C\textsubscript{\textmax} and 95.77% (90% CI, 86.82%-105.65%) for AUC\textsubscript{0-\textinfty} (Figure 6). The 90% CIs for the GMRs were entirely within the range of 80% to 125% for AUC\textsubscript{0-\textinfty} and C\textsubscript{\textmax}, thus meeting the criteria for PK bioequivalence. Likewise, mean ANC AUC\textsubscript{0-\textlast} and ANC\textsubscript{\textmax} appeared similar between treatment groups. The GMR was 96.7% for ANC AUC\textsubscript{0-\textlast} and 99.6% for ANC\textsubscript{\textmax} (Figure 7). The 90% CIs for the GMR of ANC\textsubscript{0-\textlast} and ANC AUC\textsubscript{0-\textlast} fell well within the 80% to 125% boundaries, thus meeting the criteria for PD bioequivalence.
Immunogenicity

Study 04

Study 04 was a multidose parallel-arm study with UDENYCA® and Neulasta® (pegfilgrastim) that was designed with immunogenicity as the primary endpoint (Figure 8). A total of 268 of 303 subjects who were evaluable in Study 04 received 2 sequential doses of either UDENYCA® or Neulasta®.

The study was designed to assess the immunogenicity similarity of UDENYCA® and Neulasta® based upon the development of treatment-emergent neutralizing antibodies (NAbs), having the potential to neutralize the effects of pegfilgrastim, and the percent difference in treatment-emergent, confirmed positive, titer ≥2, persistent ADAs.

Validated assays were used to screen, confirm, and characterize the ADA responses to UDENYCA® and Neulasta® and identify NAbs.  

Study 04 demonstrated immunogenicity similarity for UDENYCA® and Neulasta®. There were no treatment-emergent NABs for UDENYCA® and no clinically meaningful differences in the development of treatment-emergent ADAs. The treatment-emergent ADAs for UDENYCA® and Neulasta® were non-neutralizing, typically of low titer, and PEG-reactive. PEG-reactive ADAs are commonly present in healthy subjects. Additionally, there was no significant impact of treatment-emergent ADAs on pharmacokinetics, pharmacodynamics, or safety.
**Safety**

Data from all clinical studies were included in the pooled safety analyses. Pooling of the safety data from all clinical studies was possible based on similarity among the studies. Studies were similar in terms of dose, reference product, study population, and safety endpoints. An integrated safety database was constructed from the individual study databases.

The overall incidence and types of TEAEs reported were similar for subjects receiving UDENYCA® (377 subjects; 84.5%) and Neulasta® (pegfilgrastim) (401 subjects; 87.0%) in the pooled analysis (Table 3), and were consistent with the known safety profile of Neulasta®. The 35 subjects deemed inevaluable in Study 04 were included in the pooled safety analysis.

**Table 3. Most frequently reported TEAEs (≥2% in any treatment group).**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>UDENYCA® (N=446), n (%)</th>
<th>Neulasta® (N=461), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>377 (84.5)</td>
<td>401 (87.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>254 (57.0)</td>
<td>259 (56.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>215 (48.2)</td>
<td>243 (52.7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>65 (14.6)</td>
<td>72 (15.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>59 (13.2)</td>
<td>72 (15.6)</td>
</tr>
<tr>
<td>Pain</td>
<td>44 (9.9)</td>
<td>34 (7.4)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>34 (7.6)</td>
<td>31 (6.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (6.7)</td>
<td>43 (9.3)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>22 (4.9)</td>
<td>25 (5.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19 (4.3)</td>
<td>14 (3.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (3.6)</td>
<td>23 (5.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (3.6)</td>
<td>17 (3.7)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>16 (3.6)</td>
<td>16 (3.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (3.4)</td>
<td>17 (3.7)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (2.9)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>12 (2.7)</td>
<td>15 (3.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11 (2.5)</td>
<td>17 (3.7)</td>
</tr>
<tr>
<td>Noncardiac chest pain</td>
<td>9 (2.0)</td>
<td>11 (2.4)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>8 (1.8)</td>
<td>12 (2.6)</td>
</tr>
<tr>
<td>Pain in jaw</td>
<td>7 (1.6)</td>
<td>13 (2.8)</td>
</tr>
</tbody>
</table>

Most TEAEs were considered related to study drug per the investigator (81.4% for the UDENYCA® group and 82.0% for the Neulasta® group), and most were of mild or moderate severity (Table 4). Thirteen subjects each in the Neulasta® and UDENYCA® groups had severe events, and 2 subjects in the Neulasta® group had life-threatening events (multiorgan trauma secondary to motorcycle accident and stab wound in left shoulder). Three subjects in the UDENYCA® group and 4 subjects in the Neulasta® group experienced serious AEs. Two of these events (hypersensitivity and leukemoid reaction) in the UDENYCA® group were considered related to study drug by the investigator. None of the AEs reported in UDENYCA® clinical studies represented new safety signals; these AEs have been previously described in the pegfilgrastim safety profile.

**Table 4. TEAEs by severity and drug-related AEs.**

<table>
<thead>
<tr>
<th>Subjects with any TEAE</th>
<th>UDENYCA® (N=446), n (%)</th>
<th>Neulasta® (N=461), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum severity of TEAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>177 (40)</td>
<td>175 (38)</td>
</tr>
<tr>
<td>Moderate</td>
<td>187 (42)</td>
<td>211 (44)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (3)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Any study drug–related TEAE per investigator</td>
<td>363 (81)</td>
<td>378 (82)</td>
</tr>
<tr>
<td>Any serious adverse event (SAE)</td>
<td>3 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Any study drug–related SAE per investigator</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

The incidence of the most frequently reported TEAEs was generally similar between UDENYCA® and Neulasta® in the pooled analysis. The most frequently reported TEAEs (Table 3) for both treatment groups were back pain (UDENYCA®: 57.0%; Neulasta®: 56.2%), headache (UDENYCA®: 48.2%; Neulasta®: 52.7%), pain in extremity (UDENYCA®: 14.6%; Neulasta®: 15.6%), and arthralgia (UDENYCA®: 13.2%; Neulasta®: 15.6%). These AEs are consistent with the mechanism of action and known safety profile of pegfilgrastim. The TEAEs reported at a numerically higher rate (±1% difference) for UDENYCA® versus Neulasta® were pain (9.9% vs 7.4%), dizziness (4.3% vs 3.0%), and muscle spasms (2.9% vs 1.7%).

UDENYCA® displayed a similar safety profile to Neulasta® with no unexpected or significant safety findings. The safety profile of UDENYCA® was consistent with the well-characterized mode-of-action of pegfilgrastim. There were no clinically relevant differences in the incidence, frequency, or duration of TEAEs between UDENYCA® and Neulasta®. Overall, the AE profile of UDENYCA® is similar to that reported for commercially available Neulasta®.1
UDENYCA® is manufactured in the United States using state-of-the-art technology.

The US manufacturing facility was purposefully designed to produce PEGylated filgrastim.

The Coherus filgrastim protein is expressed in *Escherichia coli* (E. coli), as is the rHu-met-filgrastim used in the manufacture of Neulasta® (pegfilgrastim), and both proteins are nonglycosylated. The protein is obtained from the bacterial fermentation of a strain of *E. coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. Coherus filgrastim is expressed intracellularly, and the protein is harvested as insoluble inclusion bodies, followed by a series of unit operations to generate correctly folded, active, PEGylated, purified, and formulated product.

To produce UDENYCA®, a nominal 20-kDa PEG molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The molecular weight of UDENYCA® is approximately 40 kDa. Pegfilgrastim has a longer half-life and slower elimination rate compared with filgrastim. Using industry-standard operations, the UDENYCA® drug substance is aseptically filled into syringes. To ensure the safety of healthcare providers and caregivers who administer this product, the syringe cap does not contain natural rubber latex. Additionally, the syringe is presented with a needle guard that automatically deploys over the needle after injection is completed.

UDENYCA® has been developed by Coherus to address rising costs and increase patient access to growth factor therapy. Coherus has conducted a development program following FDA guidance and feedback to demonstrate the biosimilarity of UDENYCA® to Neulasta®.

The analytical assessment, which forms the foundation of the totality of evidence for biosimilarity, demonstrated that UDENYCA® is highly similar to Neulasta® based on primary and higher-order structure, PEGylation, strength, receptor binding, potency, and purity.

The clinical program, conducted in healthy subjects, demonstrated the bioequivalence of UDENYCA® and Neulasta® with respect to PK and PD. Immunogenicity and safety were found to be similar. The demonstration of biosimilarity in healthy subjects follows FDA guidance, which suggests that healthy subjects are a more sensitive population compared with patients with cancer for detecting and evaluating differences between UDENYCA® and Neulasta® in terms of PK, PD, immunogenicity, and safety. This approach is feasible because there is an established PD biomarker (ANC) that can be assessed in healthy subjects, and the mechanism of action of pegfilgrastim is the same in healthy subjects and patients with cancer. Although PK and PD profiles are expected to differ between healthy subjects and patients with cancer, given the demonstration of bioequivalence, there is no biologically plausible reason why UDENYCA® and Neulasta® would perform differently in these 2 populations. Therefore, it is reasonable to extrapolate from healthy subjects to patients with cancer.

Pharmacokinetic bioequivalence between UDENYCA® and Neulasta® was demonstrated, based on AUC_{0-infty} and C_{max} in Study 05. Absolute neutrophil count pharmacodynamic bioequivalence between UDENYCA® and Neulasta® was demonstrated, based on ANC_{max} and ANC AUC_{0-last} across Studies 03 and 05, involving >230 healthy subjects.

There were no clinically meaningful differences between UDENYCA® and Neulasta® with respect to immunogenicity, demonstrated under the protocol analysis in Study 04. Finally, there were no clinically meaningful differences between UDENYCA® and Neulasta® in regard to safety, with no unexpected toxicity, and no new safety signals were identified.

The totality of evidence, therefore, demonstrates that UDENYCA® is highly similar to Neulasta®, with no clinically meaningful differences between the products. Overall, the totality of evidence supports biosimilarity and the use of UDENYCA® to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. UDENYCA® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.
References


Glossary

351(a) pathway: FDA licensure pathway to register for reference product exclusivity for therapeutic biologic products under 351(a) of the Public Health Service Act

351(k) pathway: FDA licensure pathway that permits a biosimilar biologic product to be licensed under 351(k) of the Public Health Service Act

absolute neutrophil count (ANC): Measure of the number of neutrophil granulocytes present in the blood; frequently used to assess neutropenic fever in chemotherapy patients

ANC max: Maximum absolute neutrophil count

antidrug antibody (ADA): An antibody immunogenic to a given treatment that may cause loss of efficacy and other undesirable effects

area under the curve (AUC): Plot of drug concentration in blood plasma versus time

AUC 0-480: AUC from dosing up to 480 minutes

AUC 0-inf: AUC from dosing up to infinity

AUC 0-last: AUC up to the last measured concentration

arthralgia: Joint pain

binding affinity: Strength of the binding interaction between a single biomolecule (eg, protein or DNA) to its ligand/binding partner (eg, drug or inhibitor)

binding competition assay: Assay used to determine the presence of selectivity for a particular ligand for receptor subtypes, which allows the determination of the density and proportion of each subtype

bioequivalence: The property wherein 2 drugs with identical active ingredients or 2 different dosage forms of the same drug possess similar bioavailability and produce the same effect at the site of physiologic activity

biologic: Product made from living organisms or containing components of living organisms

biomarker: A measurable indicator of the severity or presence of some disease state

body mass index: A simple index of weight-to-height that is commonly used to classify underweight, overweight, and obesity in adults; defined as the body mass divided by the square of the body height, and universally expressed in units of kg/m²

C max: The maximum observed concentration

coefficient of variation: The ratio of the standard deviation to the mean (average)

confounding factor: A variable that is related to one or more of the variables measured or manipulated in a study, but not easily identified as such and/or not controlled in the design, so its pure influence (ie, independent of other variables in the study) on the outcome cannot be determined

crossover study: A type of clinical trial in which the study participants receive each treatment in a random order

dimerization: A chemical reaction leading to a combination of 2 identical simpler molecules

drug product: End product that may contain one or more drug substances in combination with excipients; meant for use by humans and animals

drug substance: Pure material that exerts a pharmacologic action

febrile neutropenia: An oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count <0.5×10⁹/L, or expected to fall below 0.5×10⁹/L

geometric mean: A type of mean or average that indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean, which uses their sum)

granulocyte colony-stimulating factor (G-CSF): A glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream

higher-order structure: Includes the secondary, tertiary, and quaternary structures of a protein, which compose the 3-dimensional structures that are necessary for structure and function

hydrophobicity: Physical property of a molecule (known as a hydrophobe) that is seemingly repelled from a mass of water

hypersensitivity: A set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity

immunogenicity: An immune response that a biologic product elicits through formation of antibodies to the administered biologic product

inclusion bodies: Nuclear or cytoplasmic aggregates of stable substances, usually proteins

interim analysis: An analysis of data that is conducted before data collection has been completed

leukemoid reaction: An increased white blood cell count, or leukocytosis, which is a physiologic response to stress or infection (as opposed to a primary blood malignancy, such as leukemia)
lippegfilgrastim: A glycopegylated granulocyte-colony stimulating factor used to reduce the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy

Neulasta®: Pegfilgrastim, a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol

neutropenia: An abnormally low level of neutrophils; counts of less than 1,500 neutrophils per microliter in adults

originator product: The first product for which a marketing authorization was granted to a given marketing authorization holder for a given active substance

parallel-arm study: An experimental study design in which each subject is randomized to 1 of 2 or more distinct treatment/intervention groups

PEGylation: Modification of a protein, peptide, or nonpeptide molecule by the linking of one or more polyethylene glycol (PEG) chains; has been widely used to improve the bioavailability of proteins and low-molecular-weight drugs

primary structure: The characteristic sequence of amino acids forming a protein or polypeptide chain, considered the most basic element of its structure

product drift: Excursions in product attributes due to unintended or unexplained deviations in manufacturing processes

progenitor cells: Early descendants of stem cells that can differentiate to form one or more kinds of cells, but cannot divide and reproduce indefinitely

prognostic factor: A situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease or the chance of the disease recurring

prophylaxis: A measure taken to maintain health and prevent the spread of disease

raw material: General term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or active pharmaceutical ingredients

recombinant: Produced by combining genetic material from different places

renal clearance: The volume of plasma completely cleared of a specific compound per unit time and measured as a test of kidney function

severe neutropenia: An absolute neutrophil count of less than 0.5×10⁹/L (<500/µL)

steric hindrance: Prevention or retardation of inter- or intramolecular interactions as a result of the spatial structure of a molecule

T_max: The time taken to reach the maximum concentration
WARNINGS AND PRECAUTIONS:

• Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

• Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue UDENYCA® in patients with ARDS.

• Serious allergic reactions, including anaphylaxis: Permanently discontinue UDENYCA® in patients with serious allergic reactions.

• Fatal sickle cell crises: Have occurred.

• Glomerulonephritis: Evaluate and consider dose-reduction or interruption of UDENYCA® if causality is likely.

ADVERSE REACTIONS:

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity.

To report SUSPECTED ADVERSE REACTIONS, contact Coherus BioSciences at 1-800-4-UDENYCA (1-800-483-3692) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Neulasta and Neupogen are registered trademarks of Amgen Inc.

Zarxio is a registered trademark of Novartis AG.

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INDICATION
UDENYCA® is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Limitations of Use
UDENYCA® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATION:
Patients with a history of serious allergic reaction to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products.

Please see Full Prescribing Information in pocket, and Important Safety Information throughout this brochure.