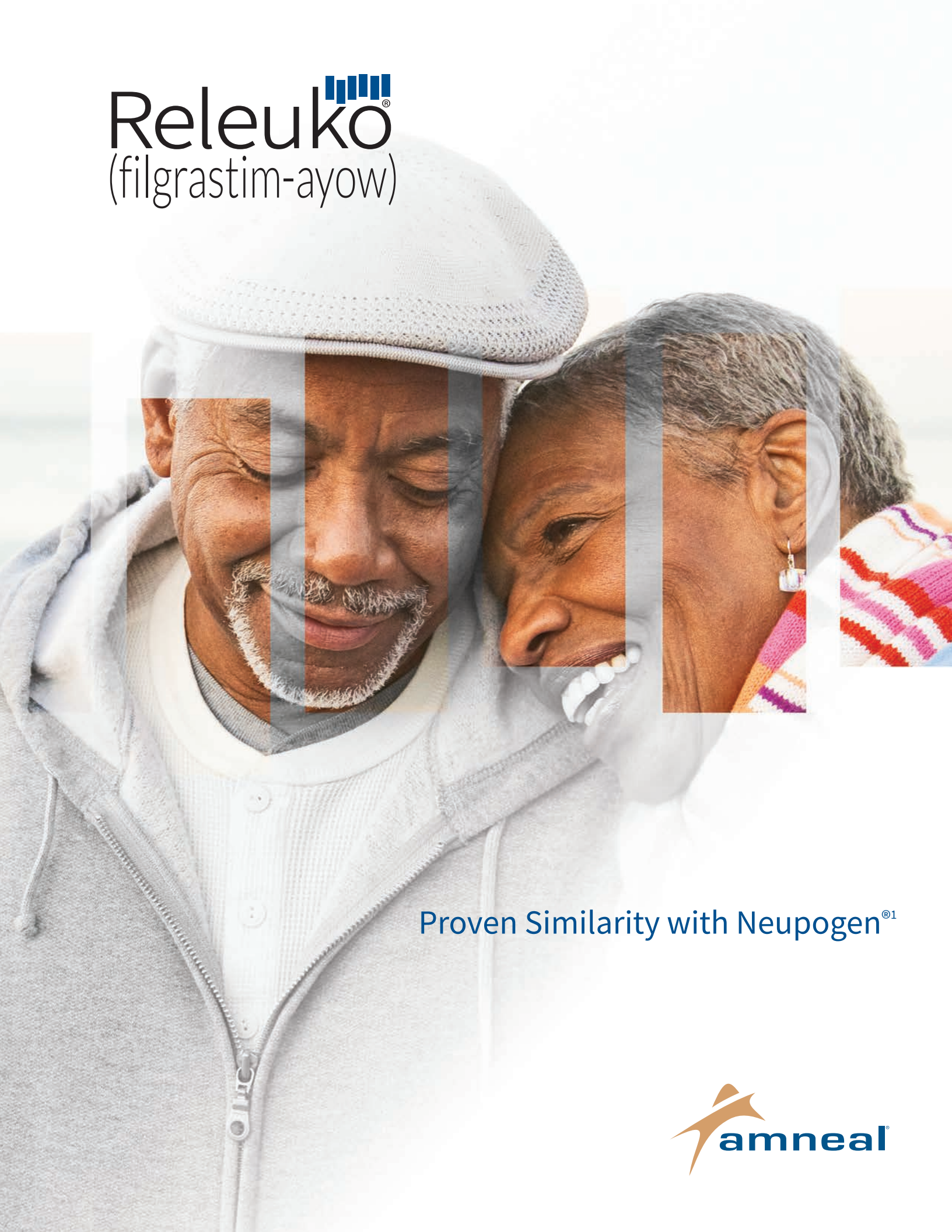
Releuko®
(filgrastim-ayow)



Proven Similarity with Neupogen®[1]

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Releuko® Meets All FDA Requirements for Similarity[1-4]

Releuko® (filgrastim-ayow) **is similar** to Neupogen® based on the totality of evidence, with **no clinically meaningful differences in purity, potency, efficacy, safety, and immunogenicity** compared with Neupogen®.[5,7]

Requirements for Biosimilar Approval[1-3]

Reference Product (RP), Neupogen®[5,7]	Releuko®[4,6]
✓ Full CMC package	✓ Full CMC package + In vitro similarity
✓ Pharmacological assessment	✓ Pharmacological comparability in healthy volunteers
✓ Clinical studies: ✓ Efficacy ✓ Safety ✓ Immunogenicity	✓ Comparative PD studies: ✓ Efficacy (PD surrogate) ✓ Safety ✓ Immunogenicity
✓ Risk management plan	✓ Risk management plan

CMC = Chemistry Manufacturing and Control; PD = Pharmacodynamics; PK = pharmacokinetic; FDA: United States Food and Drug Administration

Releuko® robust evidence proved similarity with Neupogen® [1,6]

Releuko® similarity program was designed based on FDA guidance[2-4]

Contraindications

Releuko® is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products.

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 and lung infiltrates or respiratory distress for ARDS. Discontinue Releuko® in patients with ARDS.

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

Releuko® (filgrastim-ayow)

Releuko® Robust Totality of Evidence[1,5]

Multiple *in vitro* analytical similarity studies[1] using state-of-the-art orthogonal analytical methods demonstrated similarity between Releuko® and Neupogen® in key features such as: primary structure, molecular conformation, charge variants, protein content, purity, and biological activity.[1,5]

Comparative stability studies between Releuko® and Neupogen® under accelerated and forced degradation conditions have demonstrated similar behavior and degradation pathways for the two products.[1,5]

Releuko® clinical comparability includes data from 112 subjects evaluated in 2 PK/PD studies and 134 subjects in 1 immunogenicity/safety study:[1,5]

1. Strong comparability PK package in HV clinical trials: The PK similarity of both products was established.[1,5]

- Statistical analysis of the PK parameters demonstrated similarity between Releuko® and Neupogen®
- Releuko® was generally well tolerated by healthy subjects
- The safety and immunogenicity profile of Releuko® and Neupogen® was determined to be similar following multiple doses

2. Strong Comparability PD package in HV clinical trials: As a surrogate for clinical efficacy, PD similarity of both products was established:[1,5]

- Pharmacodynamic similarity of Releuko® versus Neupogen® was established for ANC (absolute neutrophil count) in two HV studies where bioequivalence was established[1]
- Pharmacodynamic similarity was also established for CD34[1]

Analytical, preclinical and clinical studies have demonstrated Releuko® is similar to Neupogen®[1,5]

Releuko® ~ Neupogen®

Please see accompanying full Prescribing Information.

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The FDA has Approved Releuko® for All Neupogen® Indications Through PK/PD Bioequivalence and Safety[1-4]

The Releuko® clinical development program was **comprised of a pivotal comparative PK/PD study** in healthy volunteers performed with US-licensed Neupogen® as the reference product and a safety and tolerability study conducted on 134 healthy subjects. This data package was **further complemented by safety and PD data** generated in a supporting PK/PD study performed in healthy volunteers.[1]

Releuko® (filgrastim-ayow) met the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act and has been approved by the FDA based on the totality of evidence and scientific justification for all conditions of use for which the RP is licensed.

Releuko® Dosage and Administration*[7]

Indication	Dosage (per kilogram of body weight)	Route
Chemotherapy-induced Febrile Neutropenia Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.	5 mcg/kg/day	Subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion.
Acute Myeloid Leukemia (AML) Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).	5 mcg/kg/day	Subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion.
Cancer Patients Receiving Bone Marrow Transplant (BMT) Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).	10 mcg/kg/day	Intravenous infusion no longer than 24 hours
Severe Chronic Neutropenia Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.	Recommended start: Congenital: 6 mcg/kg twice daily Cyclic or idiopathic: 5 mcg/kg/day	Subcutaneous injection

Warnings and Precautions

Fatal sickle cell crises: Discontinue Releuko® if sickle cell crisis occurs.

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

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Releuko® in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML.

Thrombocytopenia: Monitor platelet counts.

Releuko® (filgrastim-ayow)

*This is an abbreviated summary of the approved indications. For complete dosage and administration instructions, please see Releuko® full Prescribing Information.


Releuko® (filgrastim-ayow) is
manufactured in the United States[1]
Please see accompanying full Prescribing Information.
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Proven Similarity with Neupogen® [1-5]

Releuko® is a biosimilar filgrastim which has been developed in comparison with Neupogen® as the Reference Product (RP).

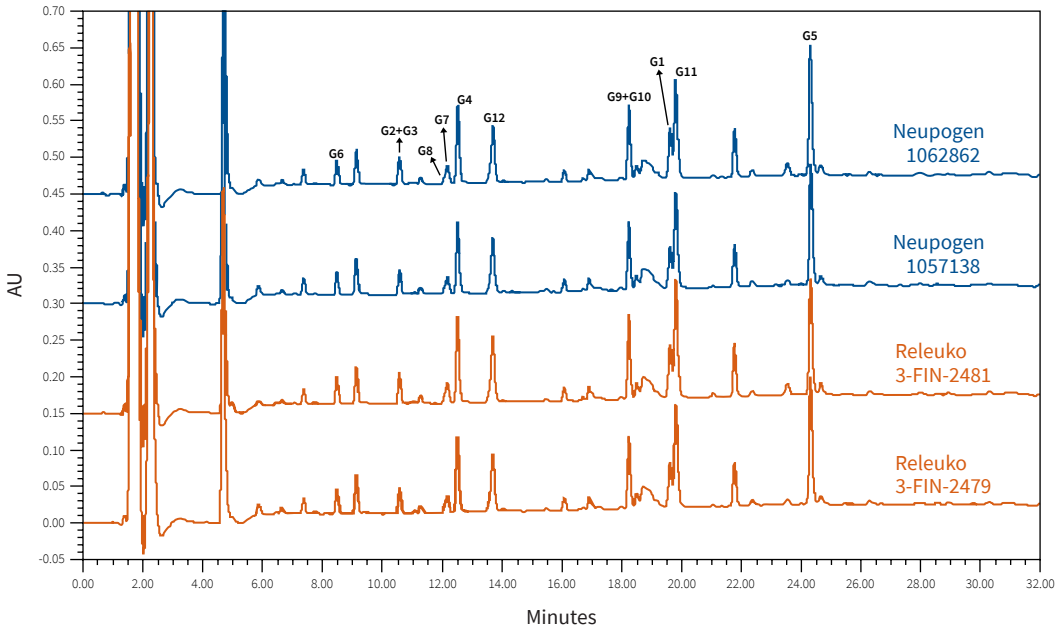
Multiple state-of-the-art analytical methods were applied to evaluate all quality attributes required of the biosimilar and confirmed analytical similarity between Releuko® and Neupogen®:[4]

Primary Structure

The same amino acid sequence is confirmed in Releuko® and Neupogen®.

In the figure below, the same set of twelve (12) primary peptides G1 to G12 are seen from the digestion of Releuko® or Neupogen® by Glu-C for peptide mapping, confirming that the primary structure of Releuko® and Neupogen® is the same.

Representative Peptide Mapping Chromatograms of Releuko® and Neupogen®

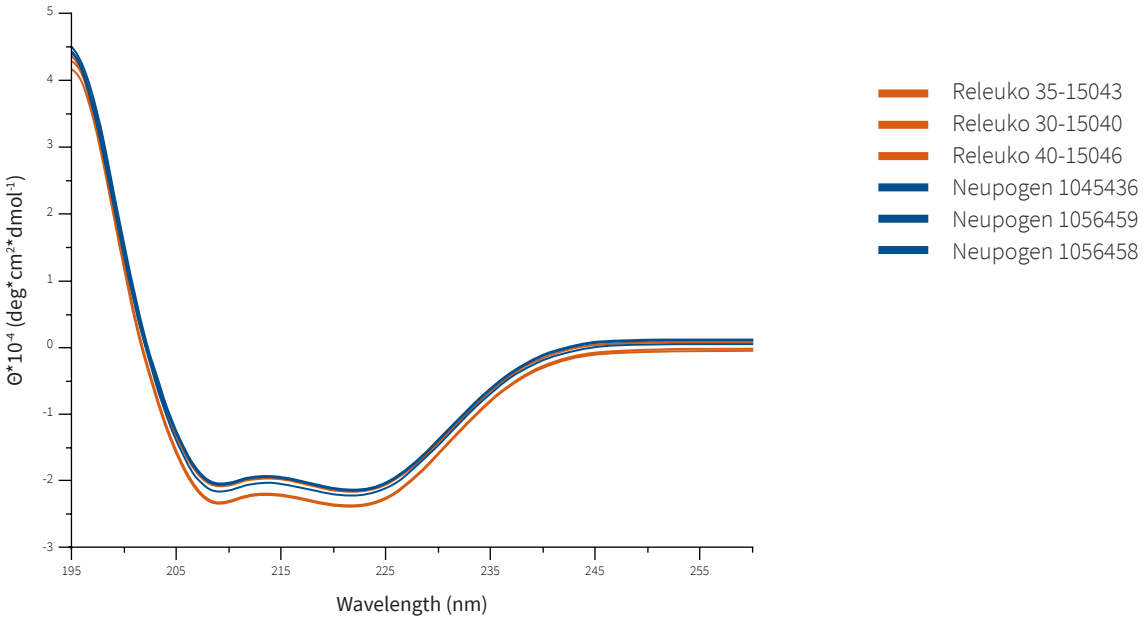


Releuko® (filgrastim-ayow)

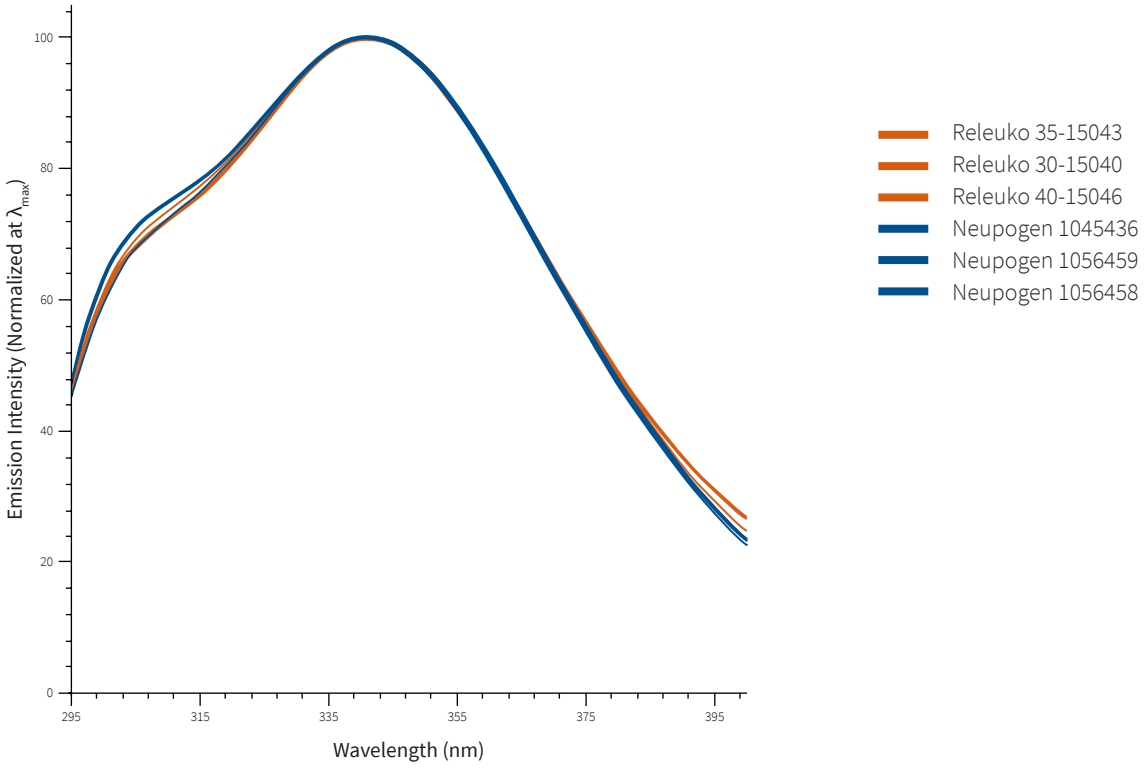
Molecular Conformation

Similarity between Releuko® and Neupogen® in terms of molecular conformation was demonstrated as seen by identical Far-UV CD Spectra, and Intrinsic Fluorescence spectra.

Representative Far-UV CD Spectra of Releuko® and Neupogen®



Overlay of Representative Intrinsic Fluorescence Spectra of Releuko® and Neupogen®



Please see accompanying full Prescribing Information.

Charge Variants

Cation-exchange analysis demonstrated that Releuko® and Neupogen® have similar content of acidic and basic forms.

Protein Content and Purity

Similar protein content and high purity was found in both Releuko® and Neupogen®.

Comparative Stability

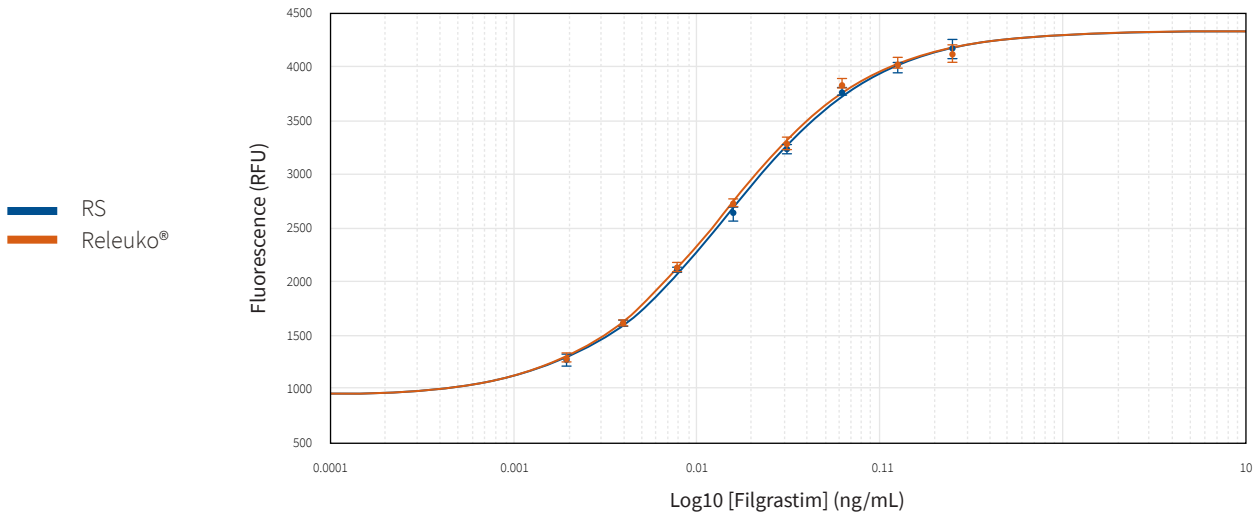
Comparative accelerated and forced degradation studies have shown a similar behavior and degradation profile of Releuko® and Neupogen®.

Biological Activity

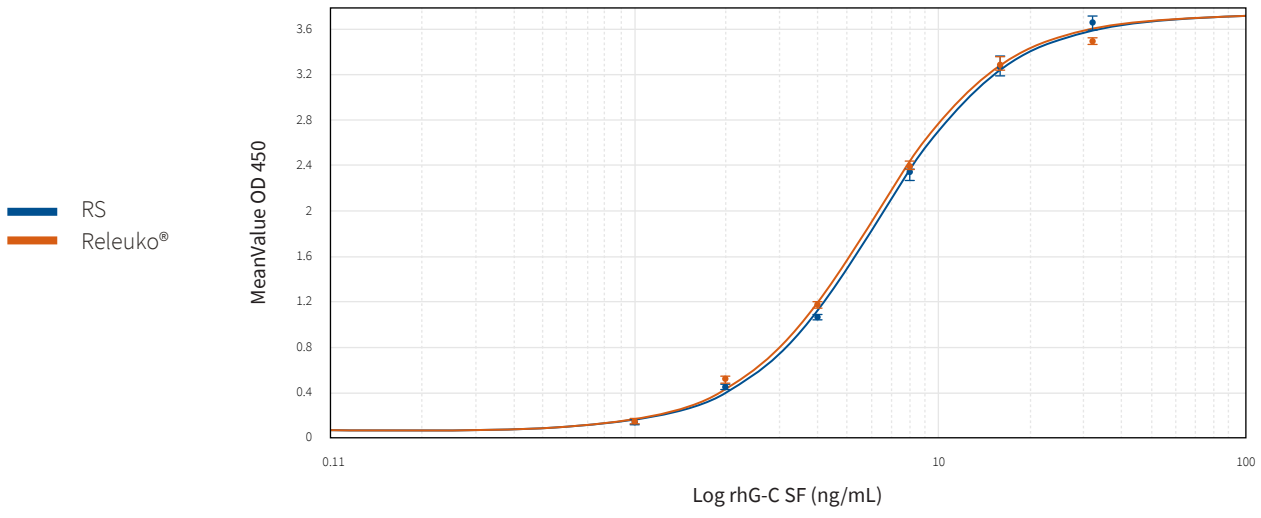
Multiple state-of-the-art orthogonal methods demonstrated the similarity of Releuko® to its RP regarding biological activity.

Highly similar potency of Releuko® and Neupogen® relative to filgrastim reference standard was seen in the M-NFS-60 cell proliferation assay.

Representative Potency Dose Response Curve Showing Similar Potency of Releuko® or Neupogen® versus Filgrastim Reference Standard in Cell Proliferation Assay



Comparative Results of Receptor Binding by ELISA: Representative ELISA Dose Response Curve for RS Versus Releuko®



Releuko® (filgrastim-ayow)

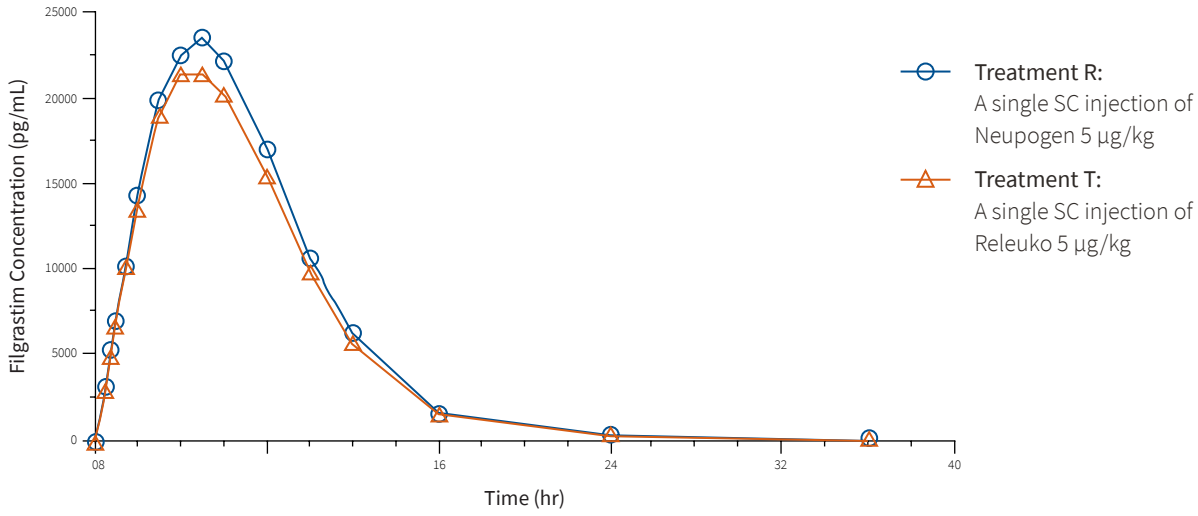
Please see accompanying full Prescribing Information.

Pharmacokinetics Demonstrate Bioequivalence to Neupogen® [1-4]

Two PK/PD studies were carried out in healthy volunteers to investigate and compare the PK profiles of Releuko® and Neupogen® and confirmed bioequivalence between both products.

The PK results for one study are shown below. The peak and overall baseline-corrected blood ANC (as measured by geometric mean Emax and AUEC0-t) were similar following a subcutaneous injection of either Releuko® or Neupogen®, as shown by the less than 10% difference in Emax and AUEC0-t between treatments.

Mean PK Concentration-Time Curve (N=53)*



It is statistically confirmed that comparisons of Releuko® versus Neupogen® were similar for the primary parameters AUC (0-∞) and C_{max}, as the 90% CI were fully contained within the pre-defined bioequivalence limits of 0.80 - 1.25.[1,3]

*Study TPI-CL-106: A Randomized, Comparative Pharmacokinetic/Pharmacodynamics, Double-Blind, Single-Dose, Two-Period Crossover Study Comparing Releuko® to Neupogen® 5 µg/kg in Healthy Subjects.

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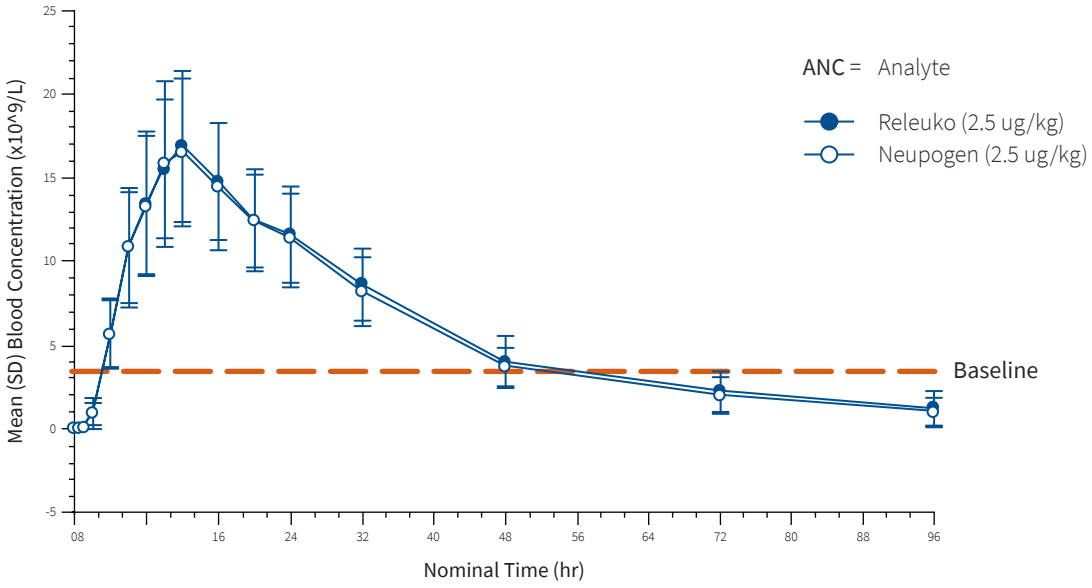
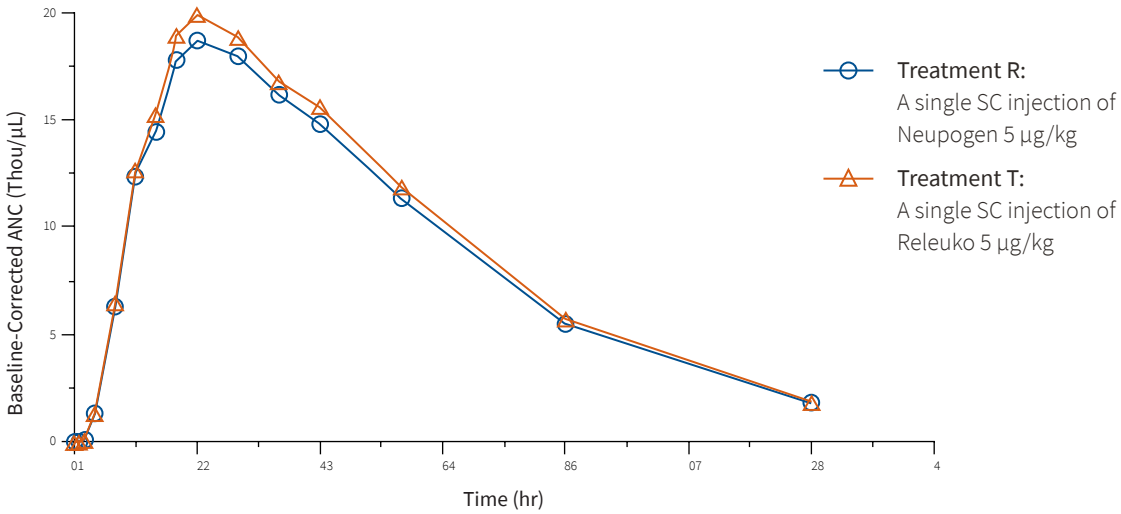
Releuko® was Approved Based on the Totality of Evidence, Including a Comparative PD Study as a Surrogate for Comparative Clinical Efficacy[1-5]

The two PK/PD studies provided the comparative PD characteristics that established PD similarity and hence comparative clinical efficacy for Releuko® versus Neupogen®.

Mean Profile for ANC (N=52)*



Mean Profile for Baseline Corrected ANC (N=53)**



Releuko® (filgrastim-ayow)

Please see accompanying full Prescribing Information →

*Study TPI-CL-101, Cohort A
**Study TPI-CL-106

Similar Efficacy Shown with Neupogen® [1,6]

The two pharmacologic studies support PK and PD similarity between Releuko® and Neupogen®. The data from these studies have established the following:

- Releuko® and Neupogen® display similar pharmacokinetics
- Releuko® and Neupogen® display similar pharmacodynamics
- Releuko® displays similar immunogenicity to Neupogen®
- There are no clinically meaningful differences in their safety profiles

Similar Safety and Immunogenicity to Neupogen® [1,6]

Based on the two PK/PD studies and one immunogenicity study:

- Releuko® demonstrated similar safety and immunogenicity to Neupogen®
- There were no new or unexpected safety signals for Releuko® compared with Neupogen®
- No antibody formation against filgrastim was detected
- No evidence of immunogenicity was noted in the three studies

Multiple subcutaneous administrations of Releuko® and Neupogen® were generally safe and similarly tolerated in the healthy adult subjects.[1]

Over 300 subjects have been exposed to Releuko® along with Neupogen® in the three studies conducted as part of overall biosimilarity assessment. The safety profiles of Releuko® and Neupogen® appear to be safe and equally well tolerated in the healthy adult subjects who were exposed to single SC doses (2.5µg/kg or 5µg kg) or multiple SC doses (5µg/kg) in the three completed clinical pharmacology and safety studies.[1]

Most Common Adverse Reactions

With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea.

With AML (≥ 2% difference in incidence) are pain, epistaxis and rash.

With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash.

With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia.

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Releuko® Product Characteristics[1,6]

Releuko® (filgrastim-ayow) Injection is available in the same pack sizes as Neupogen®[6] with the addition of single-pack vials as well.

Strength	Presentation	Pack of 1 NDC	Pack of 10 NDC
300 mcg/0.5 mL	Prefilled Syringe	70121-1568-01	70121-1568-07
300 mcg/mL	Single-Dose Vials	70121-1569-01	70121-1569-07
480 mcg/0.8 mL	Prefilled Syringe	70121-1570-01	70121-1570-07
480 mcg/1.6 mL	Single-Dose Vials	70121-1571-01	70121-1571-07
HCPCS Code[2]	**Descriptor**		
Q5125	Injection, filgrastim-ayow, biosimilar, (releuko), 1 microgram (effective 10/1/2022)		

Single-dose, prefilled syringe is equipped with 27 gauge, ½ inch needle with an UltraSafe Plus™ Needle Guard.

Store Releuko® refrigerated at 2°C to 8°C (36°F to 46°F) in the original pack to protect from light. Do not leave Releuko® in direct sunlight. DO NOT freeze Releuko®. Avoid shaking. Transport via a pneumatic tube has not been studied.

Releuko® has a shelf life of up to 24 months.

Amneal PATHways® Patient Support Program offers services such as:

- Benefits investigation
- Prior authorization support
- Affordability options
- Claims assistance

Amneal PATHways® Patient Access To Health

References:
1. Releuko® Summary Basis of Approval – Drug Approval Package https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761082Orig1s000TOC.cfm
2. Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.
3. Food and Drug Administration, FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry, 2015.
4. Food and Drug Administration, FDA. Draft Guidance: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, 2019.
5. Neupogen® Summary Basis of Approval – Scientific Discussion https://www.accessdata.fda.gov/drugsatfda_docs/bla/pre96/103353Orig1s000.pdf
6. Releuko® Full Prescribing Information https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=74e1ec6e-1630-4654-895c-2bd355f939e7
7. Neupogen® Full Prescribing Information https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=97cc73cc-b5b7-458a-a933-77b00523e193

See accompanying full prescribing information.

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