Common Drug Review

Subsequent Entry Biologic Review Report

July 2016

Drug	Filgrastim (Grastofil)
Indication	• Cancer patients receiving myelosuppressive chemotherapy • Patients with acute myeloid leukemia • Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation • Cancer patients undergoing peripheral blood progenitor cell collection and therapy • Patients with severe chronic neutropenia • Patients with HIV infection
Listing request	For each indication, list in a similar manner to the public plan listing criteria for Neupogen®.
Dosage form(s)	300 mcg/0.5 mL in single-use pre-filled syringe
NOC date	December 7, 2015
Manufacturer	Apotex Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in oncology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ANC	absolute neutrophil count
ANOVA	analysis of variance
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve from 0 to 24 hours
AUC_{0-32}	area under the curve from 0 to 32 hours
AUC_{0-72}	area under the curve from 0 to 72 hours
AUC_{inf}	area under the curve from 0 extrapolated to infinity
AUC_{ss}	area under the curve at steady-state
AUC_{t}	average concentration over a time interval
BMI	body mass index
$CD34^{+}$	cluster of differentiation 34
CDR	CADTH Common Drug Review
CI	confidence interval
C_{max}	peak concentration
$C_{max,ss}$	peak concentration after the last dose of study medication (last absolute maximum)
DP	drug product
DS	drug substance
DSN	duration of severe neutropenia
ECG	echocardiogram
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	United States Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transpeptidase
IFN	incidence of febrile neutropenia
ITT	intention-to-treat
IV	intravenous
LDH	lactate dehydrogenase
NCCN	National Comprehensive Cancer Network

NDS	New Drug Submission
NOC	Notice of Compliance
PD	pharmacodynamics
PFS	pre-filled syringe
PK	pharmacokinetics
PP	per-protocol
SAE	serious adverse event
SC	subcutaneous
SCN	severe chronic neutropenia
SD	standard deviation
SCNIR	Severe Chronic Neutropenia International Registry
SEB	subsequent entry biologic
$T_{1/2}$	half-life
TAC	docetaxel, doxorubicin, and cyclophosphamide chemotherapy
T_{max}	time at maximum concentration
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

EXECUTIVE SUMMARY

Approach to the Review

The CADTH Common Drug Review (CDR) approach to reviewing Grastofil followed the *Common Drug Review Procedure and Submission Guidelines for Subsequent Entry Biologics* (March 2014). The CDR review team validated the information provided by the manufacturer regarding product information (Section 1), the indication under review (Section 2), the rationale for the reimbursement criteria requested by the manufacturer (Section 3), biosimilarity (Section 4), extrapolation of indications (Section 6), and the comparative cost of the new product (Section 7). CDR reviewers provided a critical appraisal of the clinical evidence (Section 5) and cost comparison (Section 7).

Product Information

Grastofil is a subsequent entry biologic (SEB) based on filgrastim (Neupogen). It has been approved by Health Canada for the following indications:

- Decrease in the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs
- Reduction in the duration of neutropenia, fever, antibiotic use, and hospitalization following induction and consolidation treatment for acute myeloid leukemia
- Reduction in the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients undergoing myeloablative therapy followed by bone marrow transplantation
- Mobilization of autologous peripheral blood progenitor cells to accelerate hematopoietic recovery by infusion of such cells, supported by filgrastim after myelosuppressive or myeloablative chemotherapy
- Chronic administration to increase neutrophil counts and reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic, or idiopathic neutropenia
- In patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal absolute neutrophil count (ANC) (e.g., between 2×10^9/L and 10×10^9/L).

The approved dosage form is Grastofil 300 mcg/0.5 mL pre-filled syringes (PFS). Neupogen has a Notice of Compliance (NOC) for this presentation, although the currently marketed presentations are the 300 mcg per 1 mL vial and the 480 mcg per 1.6 mL vial. Both Grastofil and Neupogen are formulated identically. Grastofil and Neupogen were confirmed to have the same sequence, structure, and biological activity. No impurities were identified in Grastofil that were not also observed in Neupogen; the levels of impurities present in Neupogen were at similar or slightly lower levels in Grastofil.

Clinical Evidence

Five pivotal studies were reviewed: four randomized, double-blind, clinical trials evaluated the pharmacodynamics (PD), pharmacokinetics (PK), and safety of Grastofil compared with Neupogen in healthy volunteers, and one single-group study designed primarily to assess safety was conducted in breast cancer patients receiving chemotherapy. The main PD end point was ANC, and the main PK end points were area under the curve (AUC) and maximum concentration (C_{max}) for filgrastim. The equivalence margin for PD and PK parameters was set at 80% to 125%. The study characteristics of the four comparative studies are presented in Table 1.

TABLE 1: DESIGN OF COMPARATIVE STUDIES OF GRASTOFIL AND NEUPOGEN IN HEALTHY SUBJECTS

	KWI-300-101	KWI-300-102	KWI-300-103	GCSF-SUIN-05SB01-3FA-(5)
Study design	Single-dose, RCT, DB, 2-way crossover, active-controlled, phase 1 Washout period: ≥ 4 weeks	Single-dose, RCT, DB, 2-way crossover, active-controlled, phase 1 Washout period: 4 weeks	Multiple-dose, RCT, DB, parallel-group, active- and placebo-controlled, phase 1	Single-dose, RCT, DB, 3-way crossover, active-controlled, phase 1 Washout period: 4 weeks
Main selection criteria	Included: Healthy male and female subjects, non-smokers, aged 18 to 55 years. Excluded: Treatment with an investigational drug or blood donation < 1 month prior to the study; recent infection; relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, inflammatory, or neurological diseases that may interfere with the aim of the study; pregnancy			
Test product: Grastofil	5 mcg/kg IV (300 mcg filgrastim/0.5 mL in single-use PFS)	75 mcg or 150 mcg SC (300 mcg filgrastim/0.5 mL in single-use PFS)	5 mcg/kg/day × 4 days SC (480 mcg filgrastim/0.5 mL in single-use PFS)	300 mcg SC (300 mcg filgrastim/0.5 mL in single-use PFS)
Reference product: Neupogen	5 mcg/kg IV (480 mcg filgrastim/0.5 mL in single-use PFS) (EU-sourced Neupogen)	75 mcg or 150 mcg SC (300 mcg filgrastim/0.5 mL in single-use PFS) (EU-sourced Neupogen)	5 mcg/kg/day × 4 days SC (480 mcg filgrastim/0.5 mL in single-use PFS) (EU-sourced Neupogen) Placebo: physiological NaCl 0.9%, 0.5 mL SC	300 mcg SC (300 mcg filgrastim/0.5 mL in single-use PFS) (EU-sourced) 300 mcg SC (300 mcg filgrastim/0.5 mL in single-use PFS) (US-sourced)
Outcome measures	PK, PD, AE	PD, PK, AE	PD including absolute $CD34^+$ cell count, PK, AE	PD, PK, AE

AE = adverse event; DB = double-blind; $CD34^+$ = cluster of differentiation 34; EU = European Union; IV = intravenous infusion; NaCl = sodium chloride; PD = pharmacodynamics; PFS = pre-filled syringe; PK = pharmacokinetic; RCT = randomized controlled trial; SC = subcutaneous.

KWI-300-101 was a crossover study in which 36 subjects were administered Grastofil and European Union (EU)–sourced Neupogen at a single dose of 5 mcg/kg, separated by a washout period of four weeks. The primary end point was AUC for filgrastim, and secondary end points included peak ANC and ANC AUC. Study KWI-300-102 was also a crossover study; it enrolled 73 subjects administered a single fixed dose of 150 mcg and 75 mcg of Grastofil or EU-sourced Neupogen, separated by a washout period of four weeks. The primary end point was ANC C_{max} and the co-primary end point was plasma AUC for filgrastim. The third study in healthy subjects, KWI-300-103, was a parallel-group, multi-dose study. Seventy-eight subjects were randomized to receive 5 mcg/kg of Grastofil per day for four days, 5 mcg/kg of EU-sourced Neupogen per day for four days, or placebo. The primary end point was peak ANC after the last dose, and secondary end points included absolute $CD34^+$ cell count on day 5 and AUC for filgrastim. The fourth study in healthy subjects, GCSF-SUIN-05SB01-3FA-(5), was a three-way crossover trial and the only study to compare Grastofil obtained from the manufacturing process intended for the Canadian market with Neupogen (both EU- and US-sourced). Forty-eight subjects were

administered a single 300 mcg dose of Grastofil, EU-sourced Neupogen, and US-sourced Neupogen separated by a washout period of four weeks. The primary PD end points included ANC AUC and ANC C_{max} and the primary PK end points included AUC and the C_{max} of filgrastim.

In all four comparative studies, Grastofil met the predefined equivalence criteria for the PK and PD parameters assessed. For $CD34^+$ counts in Study KWI-300-103, there were no apparent statistical differences between Grastofil and EU- or US-sourced Neupogen in counts at day 5; however, results were only reported descriptively and not tested against the equivalence margin used for ANC and the PK parameters.

Safety was a secondary end point in all four comparative studies in healthy volunteers. The integrated data set for all four studies comprised 186 subjects exposed to both Grastofil and Neupogen. The risk of experiencing at least one adverse event (AE) was similar between Grastofil ([redacted]%) and Neupogen ([redacted]%), and no serious AEs were observed. The most common treatment-emergent adverse events (TEAEs) considered related to treatment were decrease in neutrophil count (Grastofil: [redacted]%; Neupogen: [redacted]%), headache (Grastofil: [redacted]%; Neupogen: [redacted]%), and back pain (Grastofil: [redacted]%; Neupogen: [redacted]%). Another known AE associated with filgrastim is bone pain, which was observed in [redacted]% and [redacted]% of patients in the Grastofil and Neupogen groups, respectively. There were no notable effects on laboratory parameters or vital signs, and no cases of confirmed immunogenicity induced by filgrastim were observed with either Grastofil or Neupogen. Comparative safety is perhaps the area of greatest uncertainty, since there were no comparative studies in indicated populations of patients and the total safety population of healthy subjects exposed to both Grastofil and Neupogen was relatively small. Rarer AEs associated with one or both of Grastofil and Neupogen would not necessarily have been observed in the reviewed trials; therefore, cumulative data from post-marketing surveillance and clinical experience over time will be important to verify the safety profile of Grastofil.

Overall, there were no major limitations to the internal validity of the four comparative studies. The lack of comparative data in patients for whom Grastofil will be indicated represents a limitation; however, the extrapolation of efficacy results from healthy subjects has been accepted by regulators for SEBs of filgrastim, and the clinical expert consulted for this review supported this approach. Other limitations included the lack of data for similarity of Grastofil and Neupogen in children; the descriptive rather than inferential statistics provided for the comparison of $CD34^+$ counts between Grastofil and Neupogen; and the lack of data for similarity at the higher doses of filgrastim used for some indications (i.e., for the mobilization of peripheral blood progenitor cells and for patients undergoing myeloablative therapy). There are indirect data to support the extrapolation of the data from adults to the pediatric population and to higher doses, and there were no apparent statistical differences between Grastofil and Neupogen with respect to $CD34^+$ counts in Study KWI-300-103 (although equivalence was not tested); therefore, and these limitations did not limit the indications granted to Grastofil.

The fifth pivotal study reviewed, KWI-300-104, was a single-group trial that enrolled 120 patients with breast cancer undergoing chemotherapy with docetaxel, doxorubicin, and cyclophosphamide (TAC). Patients received repeat-dose Grastofil 300 mcg or 480 mcg, during six cycles of chemotherapy. The primary end points were the duration of severe neutropenia (DSN) in cycle 1 and incidence of AEs. The mean (standard deviation [SD]) duration of DSN in this study was 1.40 (SD of 1.07) days, which the manufacturer's submission described as being comparable to values reported in the literature for the use of Neupogen in similar populations. DSN is a surrogate for febrile neutropenia, which is the clinical end point that treatment with filgrastim is intended to prevent. A total of 2.5% of patients experienced this end point in Study KWI-300-104, which appeared to be lower than in some studies of Neupogen. In

terms of safety, most AEs were mild in severity and known to be associated with filgrastim. The most common AEs were nausea (53.3%) and bone pain (66.7%). The manufacturer's submission described the AE profile of Grastofil in this study as consistent with AEs listed in the product monograph for Neupogen. Ultimately, in the absence of a control group, Study KWI-300-104 provided no direct information as to whether the efficacy and safety of Grastofil is similar to Neupogen in patients with cancer, although the comparisons with existing literature do not suggest any differences.

Cost Comparison

The manufacturer's submitted price for Grastofil ($144.3135 for 300 mcg/0.5 mL PFS) is 25% lower than the price of Neupogen, when using the Ontario Drug Benefit Formulary list price for Neupogen ($192.4180 for 300 mcg/1 mL vial). This holds for all reviewed indications of usage and available strengths.

Conclusions

The reviewed studies demonstrated biosimilarity in PD and PK parameters between Grastofil and Neupogen in healthy subjects. Extrapolation of these results to relevant patient populations, along with the demonstrated similarity in the physicochemical and quality characteristics of Grastofil and Neupogen, formed the basis for the six indications of Grastofil. With respect to efficacy, the data for biosimilarity were strongest for ANC, while equivalence was not statistically tested for $CD34^+$ counts. The safety profile of Grastofil appeared similar to Neupogen. However, given the small total sample size of the studies, and the lack of head-to-head studies in the types of patients that will receive Grastofil in clinical practice, comparative safety remains somewhat uncertain. Hence, cumulative post-marketing surveillance data over time will be important to verify safety. The only study of Grastofil in a relevant patient population (i.e., breast cancer patients) was uncontrolled and provided no direct information on comparative efficacy and safety, although comparisons with prior studies of Neupogen did not suggest important differences.

1. PRODUCT INFORMATION (MANUFACTURER-SUBMITTED INFORMATION)

TABLE 2: OVERVIEW OF THE SUBSEQUENT ENTRY BIOLOGIC PRODUCT

	Grastofil	Canadian Neupogen		EU-Approved Neupogen	US-Licensed Neupogen
				(RMP used in the Grastofil development program presented in this document)	**(RMP used in the Grastofil 480 mcg/0.8 mL PFS development program presented in this document)**
		300 mcg/0.5 mL PFS 480 mcg/0.8 mL PFS (approved but not yet marketed, as of submission)	**300 mcg/1 mL vial 480 mcg/1.6 mL vial (approved and marketed)**	**300 mcg/0.5 mL PFS 480 mcg/0.5 mL PFS**	**300 mcg/0.5 mL PFS[a,d] 480 mcg/0.8 mL PFS[a,d]**
Non-proprietary name	Filgrastim	Filgrastim			
Manufacturer	Apobiologix	Amgen Canada Inc.		Amgen Europe Besloten Vennootschap	Amgen Inc.
Strength(s)	300 mcg/0.5 mL PFS	300 mcg/0.5 mL PFS[a] 480 mcg/0.8 mL PFS	300 mcg/1 mL vial 480 mcg/1.6 mL vial	300 mcg/0.5 mL PFS 480 mcg/0.5 mL PFS	300 mcg/0.5 mL PFS[a,d] 480 mcg/0.8 mL PFS[a,d]
Dosage form	Sterile solution for injection	Sterile solution for injection			
Route of administration	Intravenous, subcutaneous	Intravenous, subcutaneous			
Drug identification number(s)	02441489	02420104 (0.5 mL PFS) 02420112 (0.8 mL PFS)	01968017 (1 mL vial) 09853464/99001454 (1.6 mL vial)	Not applicable	
Therapeutic classification	Hematopoietic agent: granulocyte-colony-stimulating	Hematopoietic agent: granulocyte-colony-stimulating factor			

	Grastofil	Canadian Neupogen		EU-Approved Neupogen	US-Licensed Neupogen
				(RMP used in the Grastofil development program presented in this document)	**(RMP used in the Grastofil 480 mcg/0.8 mL PFS development program presented in this document)**
		300 mcg/0.5 mL PFS 480 mcg/0.8 mL PFS (approved but not yet marketed, as of submission)	**300 mcg/1 mL vial 480 mcg/1.6 mL vial (approved and marketed)**	**300 mcg/0.5 mL PFS 480 mcg/0.5 mL PFS**	**300 mcg/0.5 mL PFS[a,d] 480 mcg/0.8 mL PFS[a,d]**
	factor				
Excipients	• 10 mM sodium acetate buffer pH 4.0 • 25 mg (i.e., 5% w/v) sorbitol • 0.004% w/v polysorbate 80 • No preservatives are present	**300 mcg/0.5 mL PFS** • 10 mM sodium acetate buffer (pH 4.0) • 5% sorbitol • 0.004% polysorbate 80 • No preservatives are present **480 mcg/0.8 mL PFS** Same as above	**300 mcg/1 mL vial** • 10 mM sodium acetate buffer (pH 4.0) • 5% sorbitol • 0.004% polysorbate 80 • No preservatives are present **480 mcg/ 1.6 mL vial** Same as above	**300 mcg/0.5 mL PFS** • Sodium acetate listed as the excipient in the Neupogen SPC that is formed by titrating glacial acetic acid with sodium hydroxide • 25 mg sorbitol • 0.035 to 0.052 mg (per mL) sodium **480 mcg/0.5 mL PFS** Same as above	**300 mcg/0.5 mL PFS** • 0.295 mg acetate • 0.02 mg polysorbate • 0.0175 mg sodium • 25 mg sorbitol **480 mcg/0.8 mL PFS** • 0.472 mg acetate • 0.032 mg polysorbate • 0.028 mg sodium • 40 mg sorbitol
Impurities[b]	**Product-related** HMW species: Depending on the species, the quantities were either below limit of quantification (0.4%) or below limit of detection (0.2%)	**Product-related** Not available	**Product-related** Not available	**Product-related** HMW species: Depending on the species, the quantities were either below limit of quantification (0.4%) or below limit of detection (0.2%)	**Product-related** HMW species: Depending on the species, the quantities were either below limit of quantification (0.4%) or below limit of detection (0.2%)
Impurities[b]	**Process-related**[c] • Residual host cell protein: [redacted] • Residual host cell DNA: [redacted] of protein	**Process-related** Not available; see explanation at the end of this section	**Process-related** Not available; see explanation at the end of this section	**Process-related** Not available; see explanation at the end of this section	**Process-related** Not available; see explanation at the end of this section

	Grastofil	Canadian Neupogen		EU-Approved Neupogen	US-Licensed Neupogen
				(RMP used in the Grastofil development program presented in this document)	**(RMP used in the Grastofil 480 mcg/0.8 mL PFS development program presented in this document)**
		300 mcg/0.5 mL PFS 480 mcg/0.8 mL PFS (approved but not yet marketed, as of submission)	**300 mcg/1 mL vial 480 mcg/1.6 mL vial (approved and marketed)**	**300 mcg/0.5 mL PFS 480 mcg/0.5 mL PFS**	**300 mcg/0.5 mL PFS[a,d] 480 mcg/0.8 mL PFS[a,d]**
	• Bacterial endotoxin: [redacted] • Others: see following section				

CTD = common technical document; EU = European Union; HMW = high molecular weight; NOC = Notice of Compliance; PFS = pre-filled syringe; RMP = reference medicinal product; SPC = summary of product characteristics; w/v = weight per volume.

[a] Please note that while the presentations between Grastofil and the Canadian reference product Neupogen are identical (300 µg/0.5 mL PFS), the biosimilarity exercises were conducted against both EU-approved and US-licensed Neupogen. Additional details are presented in Section 1.2 Overview of the Reference Product of this document.

[b] Includes both product- and process-related impurities.

[c] Tested at the drug substance level only.

[d] Although the US-licensed Neupogen included both vials and PFSs, for the purpose of this submission, only PFSs information are presented.

Source: Draft Grastofil Product Monograph (1); Neupogen Product Monograph (2); Neupogen Summary of Product Characteristics (3); US Neupogen Prescribing Information (4); CTD 3.2.R; CTD 3.2.S.2.5.

For the current CDR submission, a Notice of Compliance (NOC) was issued by Health Canada for the 300 mcg/0.5 mL pre-filled syringe (PFS) Grastofil New Drug Submission (NDS) for six indications in December 2015.[1] [redacted]

[redacted]

1.1 Pharmaceutical Form

The drug substance for both Grastofil and Neupogen are recombinant methionyl human granulocyte-colony stimulating factor (r-huG-CSF).

1.2 Pharmaceutical Composition

Both Grastofil and Neupogen contain 300 mcg or 480 mcg of filgrastim drug substance for each of the corresponding presentations. For all Grastofil presentations, the drug substance is formulated in 10 mM sodium acetate buffer at pH 4.0, 5% sorbitol, and 0.004% weight/volume of polysorbate 80. Water is added to achieve 0.5 mL (300 mcg) or 0.8 mL (480 mcg) for a final concentration of 600 mcg/mL for injection. For all Neupogen presentations (vials and PFSs), the drug substance is formulated in a 10 mM sodium acetate buffer at pH 4.0, 5% sorbitol, and 0.004% weight/volume of polysorbate 80. Both are formulated identically.

1.3 Dosage Form

Both Grastofil and Neupogen are identical; namely, they are both formulated as sterile solution for injection.

1.4 Strength and Fill

Grastofil is supplied at both 300 mcg/0.5 mL and 480 mcg/0.8 mL (i.e., all are 600 mcg/mL). For the Canadian reference product Neupogen, the currently marketed presentations are the 300 mcg per 1 mL vial and the 480 mcg per 1.6 mL vial. Canadian Neupogen also has a Health Canada NOC for both the 300 mcg/0.5 mL and 480 mcg/0.8 mL PFSs. Both Grastofil and Neupogen are ready-to-use injections. Subcutaneous (SC) injection is the primary route of administration, although the product may be diluted for administration by the intravenous (IV) route (administered by short IV infusion or continuous IV infusion).

1.5 Route of Administration

Both Grastofil and Neupogen can be administered subcutaneously or intravenously depending on indication.

1.6 Purity and Impurities

1.6.1 Product-Related Impurities

Product-related impurities include oxidized variants and high molecular weight species (dimers and aggregates). As per the Grastofil Assessment Report, no additional new product-related impurities have been identified in the Grastofil drug substance in relation to those identified in the Filgrastim Concentrated Solution (2206) monograph in the *European Pharmacopoeia* (5).

1.6.2 Process-Related Impurities

Process-related impurities included [redacted].

Additional details can be found in Common Technical Document 3.2.S.2.5.

1. In terms of residual host cell protein, the level that was detected was at or below [redacted], which is much lower than the acceptance criterion of ≤ 20 ppm.
2. The level of residual host cell DNA was [redacted] of protein, which was also substantially below the expected range of [redacted] of protein.
3. Bacterial endotoxin was also below the expected range of [redacted], confirming the successful removal of endotoxin.
4. Bioburden was successfully controlled as demonstrated by the detection of [redacted] colony-forming units/mL.

Overall, for Grastofil, process-related impurities included host cell contaminants (host cell protein and residual DNA), and these have been shown to be consistently cleared by the manufacturing process. Additives used during manufacture were also shown to be adequately removed (5).

[redacted]

As a general reference, however, the Filgrastim Concentrated Solution (2206) monograph in the *European Pharmacopoeia* contains specified impurities for the reversed-phase and size-exclusion chromatography procedures (oxidized forms, dimers, and aggregates) (5).

1.7 Overview of the Reference Product

[redacted]

Subsequent to the filing of the NDS to Health Canada, Amgen Canada received an NOC from Health Canada for two PFS presentations: 300 mcg/0.5 mL and 480 mcg/0.8 mL (DIN 02420104 and 02420112; NOC date: January 28, 2014), in addition to the pre-existing vial presentation. As such, the European Union (EU) and Canadian Neupogen therefore provide a PFS that is identical in concentration, strength, and dosage-form presentation to that of Grastofil (namely, the 300 mcg/0.5 mL PFS), further establishing the links between the non-Canadian reference product and the Canadian reference product. Thus, the EU-approved Neupogen is a suitable proxy for the Canadian reference product.

1.7.1 Rationale for the Submitted Grastofil Pre-filled Syringe

[redacted]

1.7.2 Source and Indications

The filgrastim drug substance is a recombinant methionyl human granulocyte colony-stimulating factor produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein produced by *Escherichia coli (E. coli)* bacteria. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Granulocyte-colony stimulating factor (G-CSF) regulates the production of neutrophils within the bone marrow by binding to surface G-CSF receptors, thereby stimulating their proliferation, differentiation, commitment, and end cell functional activation. G-CSF has been shown to have minimal direct effects in vivo or in vitro on the production of other hematopoietic cell types.

In Canada, Neupogen (filgrastim) is expected to be indicated for the following (15):

1. **Cancer patients receiving myelosuppressive chemotherapy**
   To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs. Neupogen is indicated in adult and pediatric patients with cancer receiving myelosuppressive chemotherapy.
2. **Patients with acute myeloid leukemia**
   For the reduction in the duration of neutropenia, fever, antibiotic use, and hospitalization following induction and consolidation treatment for acute myeloid leukemia.

3. **Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation**
   To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients undergoing myeloablative therapy followed by bone marrow transplantation.
4. **Cancer patients undergoing peripheral blood progenitor cells (PBPCs) collection and therapy**
   For the mobilization of autologous PBPCs to accelerate hematopoietic recovery by infusion of such cells, supported by Neupogen, after myelosuppressive or myeloablative chemotherapy.
5. **Patients with severe chronic neutropenia**
   For chronic administration to increase neutrophil counts and to reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic, or idiopathic neutropenia.
6. **Patients with HIV infection**
   In patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal absolute neutrophil count (ANC) (e.g., between 2×10^9/L and 10×10^9/L).

2. INDICATIONS (MANUFACTURER-SUBMITTED INFORMATION)

2.1 Health Canada–Approved Indications

Indication(s)[1,2]	Date of NOC
1. Cancer patients receiving myelosuppressive chemotherapy Grastofil (filgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs. Grastofil is indicated in adult and pediatric patients with cancer who are receiving myelosuppressive chemotherapy. A CBC and platelet count should be obtained prior to chemotherapy and twice per week during Grastofil therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, filgrastim therapy was discontinued when the ANC was > 10×10^9/L after expected chemotherapy-induced nadir.	December 7, 2015
2. Patients with acute myeloid leukemia Grastofil is indicated for the reduction in the duration of neutropenia, fever, antibiotic use, and hospitalization following induction and consolidation treatment for acute myeloid leukemia.	December 7, 2015
3. Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation Grastofil is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients undergoing myeloablative therapy followed by bone marrow transplantation. A CBC and platelet count should be obtained at a minimum of 3 times per week following marrow infusion to monitor marrow reconstitution.	December 7, 2015
4. Cancer patients undergoing peripheral blood progenitor cell collection and therapy Grastofil is indicated for the mobilization of autologous peripheral blood progenitor cells to accelerate hematopoietic recovery by infusion of such cells, supported by filgrastim after myelosuppressive or myeloablative chemotherapy.	December 7, 2015
5. Patients with severe chronic neutropenia Grastofil is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic, or idiopathic neutropenia.	December 7, 2015
6. Patients with HIV infection Grastofil is indicated in patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal ANC (e.g., between 2×10^9/L and 10×10^9/L). Grastofil therapy reduces the clinical sequelae associated with neutropenia (e.g., bacterial infections) and increases the ability to deliver myelosuppressive medications used for the treatment of HIV and its associated complications. It is recommended that CBCs and platelet counts be monitored at regular intervals (e.g., initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter or as clinically indicated) during Grastofil therapy.	December 7, 2015

ANC = absolute neutrophil count; CBC = complete blood count; NOC = Notice of Compliance.

2.2 Proposed Indications Under Review by Health Canada

Proposed Indication(s)	Anticipated Date of Notice of Compliance
Not applicable	Not applicable

3. MANUFACTURER'S REQUESTED LISTING CRITERIA

3.1 Requested Listing Criteria

3.1.1 Requested Listing Criteria for Indications to be Reviewed by the CADTH Common Drug Review

a) For Cancer Patients Receiving Myelosuppressive Chemotherapy

- List in a similar manner to the public plan listing criteria for Neupogen.
- Alternatively: to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs. Grastofil is indicated in adult and pediatric patients with cancer receiving myelosuppressive chemotherapy.

b) For Patients With Acute Myeloid Leukemia

- List in a similar manner to the public plan listing criteria for Neupogen.
- Alternatively: for the reduction in the duration of neutropenia, fever, antibiotic use, and hospitalization following induction and consolidation treatment for acute myeloid leukemia.

c) For Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

- List in a similar manner to the public plan listing criteria for Neupogen.
- Alternatively: to reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients undergoing myeloablative therapy followed by bone marrow transplantation.

d) For Cancer Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy

- List in a similar manner to the public plan listing criteria for Neupogen.
- Alternatively: the mobilization of autologous PBPCs to accelerate hematopoietic recovery by infusion of such cells, supported by Grastofil, after myelosuppressive or myeloablative chemotherapy.

e) For Patients With Severe Chronic Neutropenia

- List in a similar manner to the public plan listing criteria for Neupogen.
- Alternatively: chronic administration to increase neutrophil counts and reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic, or idiopathic neutropenia.

f) For Patients With HIV Infection

- List in a similar manner to the public plan listing criteria for Neupogen.
- Alternatively: in patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal ANC (e.g., between 2×10^9 and 10×10^9/L).

3.2 Rationale for Requested Listing Criteria

The overarching rationale for the requested listing criteria for all indications listed earlier is based on the principle of demonstrated biosimilarity between Grastofil and the currently reimbursed reference medicinal product, Neupogen.

First, Grastofil is deemed approvable by Health Canada for all indications approved for Neupogen:

- Grastofil has demonstrated biosimilarity in validated and accepted pharmacodynamics (PD) markers in the most sensitive population of healthy subjects (accepted by the European Medicines Agency [EMA]):
  - The 95% confidence intervals (CIs) for the ratios (Grastofil/Neupogen) of the geometric means were all contained within the regulatory agency–accepted equivalence margin for all key PD outcomes.
- Grastofil has demonstrated efficacy in cancer patients and is comparable to historical data.
- Grastofil does not elicit immunogenicity in healthy volunteers in the studies conducted. Similarly, no sign of immunogenicity was seen in cancer patients in the phase 3 study.
- Grastofil has demonstrated pharmacokinetics (PK) similarity in the most sensitive population of healthy subjects:
  - The 90% CIs of the ratios (Grastofil/Neupogen) of the geometric means were all contained within the regulatory agency–accepted equivalence margin for all key PK outcomes.
- Grastofil is highly comparable physically and functionally (in vitro) to Neupogen, as demonstrated by the results from an extensive series of analytical similarity testing.
- The mechanism of action and the pharmacological properties of recombinant G-CSF are reported to be fundamentally the same in healthy volunteers and in neutropenic patients; that is, activation of neutrophils or PBPCs via G-CSF receptor, regardless of the underlying causes of the requested conditions. (For further details, see Section 6, Extrapolation of Indications.(17)) This supported Health Canada's acceptance of extrapolation of indications to those approved for Neupogen.

Second, Grastofil is developed and formulated to be biosimilar to the reference product, Neupogen:

- An extensive series of orthogonal methods demonstrated the physiochemical properties, as well as the biological activities, of filgrastim between Grastofil and Neupogen to be highly comparable. (See Section 4.1 and Table 61 and Table 62 in Appendix 1 for detailed information.)
- The formulation of Grastofil PFS contains the same excipients (and concentrations) as the Neupogen PFS formulation.

Third, the biosimilarity of Grastofil to Neupogen was demonstrated in a clinical study in healthy Canadian subjects using the Grastofil product manufactured using drug product (DP) [redacted], intended for the Canadian market.

Fourth, Grastofil is commercially available and prescribed:

- Grastofil is approved by the EMA and is marketed in Europe.
- Real-world safety data are available in the form of registries and post-marketing surveillance from Europe.

Fifth, the approved indications for Grastofil are identical to those of the reference medicinal product, Neupogen, for which the drug has more than 25 years of clinical experience.[18]

- Neupogen has been extensively characterized pharmacologically, with extensive clinical experience from both an efficacy and safety standpoint, all of which are well reported in the literature.[3]

Consequently, Grastofil has similar efficacy to Neupogen in all of the approved indications.

From the Canadian reimbursement perspective, filgrastim is currently reimbursed by all CDR-participating drug plans across the country for all indications (with minor exceptions; see Appendix 2). Consequently, we anticipate that Grastofil will receive generally similar listing decisions as Neupogen from these CDR-participating drug plans, assuming that the CADTH Canadian Drug Expert Committee issues a positive recommendation for Grastofil. CDR-participating drug plans that do not currently reimburse Neupogen may find that the economic advantages of Grastofil make it worthy of reimbursement.

Therefore, the requested listing criteria for Grastofil are reasonable and justified based on the totality of evidence, i.e.: i) the demonstrated biosimilarity in terms of physicochemical characteristics and in vitro activities; ii) the highly comparable PK/PD and safety results between Grastofil and Neupogen in the most sensitive population of healthy subjects; iii) the demonstrated safety and efficacy of Grastofil in cancer subjects; and iv) the NOC for all indications by Health Canada as subsequent entry biologic (SEB).

4. BIOSIMILARITY (MANUFACTURER-SUBMITTED INFORMATION)

4.1 Quality Information

Grastofil is produced in accordance with current Good Manufacturing Practices (GMP) guidelines and its manufacturing processes have been validated. An all-encompassing product characterization exercise was conducted using a range of analytical methodologies to ensure that Grastofil and Neupogen are similar in quality, safety, and efficacy. It should be noted that the results of the following analytical-similarity exercises were conducted between Grastofil DP and Neupogen PFSs. For those conducted between Grastofil drug substance (DS) and Neupogen, please refer to Common Technical Document 3.2.S.3.1. Table 3 describes the products compared in different biosimilarity studies (analytical studies). Table 4 in this section presents the summary of results for biosimilarity studies 2, 3, and 4; full details are found in Common Technical Document 2.3.R, 3.2.R.6.3, and 3.2.R.6.4. An additional important note here is that Grastofil DP II was the product used in the KWI-300 series of studies (see Section 4.2), whereas Grastofil DP [redacted] was the product used in the Canadian bridging study GCSF-SUIN-05SB01-3FA-(5).

TABLE 3: FILGRASTIM PRODUCTS USED IN BIOSIMILARITY STUDIES 1, 2, 3, AND 4

Biosimilarity Study	Grastofil		Neupogen			
	DP Process	PFS Presentation		PFS Presentation		PFS Presentation
[redacted]						

DP = drug product; DS = drug substance; PFS = pre-filled syringe.
[a] Grastofil DP manufactured with old process (DP Process II, using DS Process VII).
[b] Grastofil manufactured with DP new process (DP Process III, commercial-scale process intended for the Canadian market, using DS Process IX [improved purification]).

Overall, a variety of orthogonal techniques conclusively demonstrated the primary structures of these products (Grastofil and Neupogen) to be identical and consistent with the expected sequence of filgrastim (Table 4). Additional spectroscopic, chromatographic, and centrifugal studies suggested the products are comparable at higher-order (secondary and tertiary) structures. The comparable structural properties of Grastofil and Neupogen were also confirmed by the comparable biological activity. The purity of these products was assessed using a variety of electrophoretic and chromatographic assays. None of the analytical procedures identified new impurities in Grastofil that were not also observed in Neupogen, although the levels of impurities present in Neupogen were at similar or slightly lower levels in Grastofil.

TABLE 4: SUMMARY OF KEY PHYSICOCHEMICAL AND BIOLOGICAL TEST METHODS FOR COMPARABILITY OF GRASTOFIL DRUG PRODUCT AND NEUPOGEN (REFERENCE MEDICINAL PRODUCT)

Only results for [redacted] are presented. For brevity, references are from Common Technical Document modules with only section numbers listed.

Test Method(s)	Summary of Results	Reference(s)
Primary structure		
N-terminal sequencing ([redacted])	The first five amino acid residues were found to be identical for all lots, consisting of the amino acid sequence: [redacted] Complete sequence was verified by peptide map-MS/MS analysis and was found to be 100% identical to the known amino acid sequence of mature human granulocyte stimulating factor.	3.2.R.6.4.1; 3.2.R.6.6
C-terminal sequencing ([redacted])	C-terminus was identified through MS/MS analysis against the expected sequence.	3.2.R.6.4.2
Peptide map ([redacted])	In all peptide mapping tests [redacted], all product-related peaks of GRF match those of the RMP, with a retention time difference of not more than [redacted] for any peak in parallel analyses. In addition, there was no new peak in GRF that was not in the RMP. In [redacted], peptide sequences were confirmed with MS/MS analysis. The peptide mapping testing confirms that the primary sequence of GRF is identical to that of the RMP.	3.2.R.6.4.3; 3.2.R.6.6
Western blot ([redacted])	Both GRF and the RMP had one predominant immunoreactive band with similar migration distances and intensity. These Western blot data indicate that the primary structures of both the products match each other.	3.2.R.6.4.4; 3.2.R.6.6
ESI MS ([redacted])	All intact mass spectrometry data lie within [redacted] of each other and are also in close agreement with the expected mass of filgrastim of 18,799 Da.	3.2.R.6.4.11; 3.2.R.6.6
Higher-order structure		
CD ([redacted])	The far (secondary structure) UV CD spectra of both GRF and RMP fully overlap with each other, with the same local minima within a range of [redacted]. This indicates the two products have identical structures. The respective minima suggest a predominantly alpha-helical secondary structure, a finding that was confirmed following the calculation of the relative secondary structural elements present in each sample. The thermal stability profiles were also similar ([redacted]), with identical melting temperatures.	3.2.R.6.4.6; 3.2.R.6.6
Fluorescence spectroscopy ([redacted])	Both the products have comparable fluorescence intensity and same emission maximums, indicating that the structural topology with respect to position of tryptophan residues is same in both the products.	3.2.R.6.4.7; 3.2.R.6.6
FTIR ([redacted]	The FTIR spectra of both the products show the peak intensities of amide I bands centred at [redacted], with minor shoulder components at both lower and higher frequencies. The amide I band at [redacted] is normally due to alpha-helical conformation in proteins, indicating that both the products contain alpha-helix as the predominant secondary structure. The observations in FTIR analysis are consistent with the results from the CD analysis.	3.2.R.6.4.8; 3.2.R.6.6

Test Method(s)	Summary of Results	Reference(s)
2D NMR ([redacted])	A one-time assessment was conducted. The GRF and RMP samples provided very similar NMR fingerprints with nearly complete overlap of all resonances.	3.2.R.6.4.9; 3.2.R.6.6
Free cysteine ([redacted])	Since for each molecule of filgrastim there is one free cysteine, 1 mole of cysteine is expected per mole of G-CSF. Both GRF and the RMP showed a value of [redacted] of cys/mole of G-CSF. Therefore, both GRF and RMP contain [redacted] free cysteine residue.	3.2.R.6.4.10; 3.2.R.6.6
Differential scanning calorimetry ([redacted])	All samples show a consistent transition midpoint (T_m), with an average of [redacted] with a variation of less than [redacted]. Therefore, the GRF and RMP batches showed highly similar T_m and calorimetric enthalpy, indicating that both products exhibit highly similar temperature stability behaviour.	3.2.R.6.4.16; 3.2.R.6.6
Charged isoforms or impurities		
c-IEF ([redacted])	The c-IEF profiles for all samples are comparable, and calculated isoelectric points of samples range were [redacted]. The variation in data is less than 0.02 units, which indicates that these values are the same, given the accuracy and precision of the technique. Thus, it can be concluded that the primary sequences of GRF and RMP are identical.	3.2.R.6.4.5; 3.2.R.6.6
RP-HPLC ([redacted])	Impurity levels of all GRF Process III samples are [redacted]. The results of the RP-HPLC similarity assessment show that GRF is regarded as similar to the RMP in terms of RP-HPLC elution characteristics and impurity levels.	3.2.R.6.4.14; 3.2.R.6.6
Isoelectric focusing ([redacted])	The IEF gel results remain consistent throughout all studies. In all cases, the main protein band migrates at the same position, just above the [redacted] marker band and consistent with the reference solution. Also, in all cases, there are no impurity bands observed with intensities greater than the weakest reference band ([redacted]). Therefore, it can be concluded that GRF and RMP are comparable in terms of isoelectric point and charge related impurities.	3.2.R.6.4.17; 3.2.R.6.6
IEX-HPLC ([redacted])	The overall cation-exchange HPLC results from biosimilarity studies 2, 3, and 4 can be compiled and compared with assess biosimilarity of GRF with the RMP. All samples contain the same main active peak. The peak area for impurities of the RMP samples ranged between [redacted]. All GRF Process III DP lots have no quantifiable impurity. Therefore, it can be concluded that GRF is similar to the RMP in terms of overall charge of active ingredient and amount of charge-related impurities.	3.2.R.6.4.18; 3.2.R.6.6
Biological activity		
In vitro biological activity ([redacted])	Average relative potency results ranged between [redacted] for GRF and [redacted] for the RMP, all falling within the 80% to 125% specification limit. Therefore, GRF is comparable to the RMP in terms of biological activity.	3.2.R.6.4.19; 3.2.R.6.6
Receptor binding ([redacted])	Average potency values for all samples were between [redacted] for GRF and [redacted] for the RMP, indicating that the biological activity of GRF and the RMP are comparable.	3.2.R.6.4.20; 3.2.R.6.6

BIOS = biosimilarity study; c-IEF = capillary isoelectric focusing; CD = circular dichroism; cys = cysteine; Da = dalton; DP = drug product; ESI = electrospray ionization; FTIR = Fourier Transform Infrared Spectroscopy; G-CSF = cycle granulocyte-colony stimulating factor; GRF = Grastofil; IEF = isoelectric focusing; IEX-HPLC = ion-exchange high-performance liquid chromatography; MS = mass spectrometry; NMR = nuclear magnetic resonance; RMP = reference medicinal product; RP-HPLC = reversed phase high-performance liquid chromatography; T_m = melting temperature; UV = ultraviolet.

Overall, the analytical procedures employed in the biosimilarity assessment in [redacted] studies demonstrated that the Grastofil manufactured from the proposed commercial process (DP Process [redacted]) intended for the Canadian market is comparable to the non-Canadian reference product (i.e., EU-approved Neupogen PFSs) in terms of structure, purity, and biological activity.

These biosimilarity conclusions are also bridged to the Grastofil from DP Process [redacted], which was used in the KWI-300 series of clinical studies, and to the EU-approved (and US-licensed) Neupogen PFSs via [redacted] studies. [redacted] tests plus additional key characterization tests were employed to demonstrate the comparability of Process [redacted] and Process [redacted] Grastofil DP, as well as the similarity of the US-licensed and EU-approved Neupogen (Common Technical Document Module 3.2.R.6).

Since the Canadian Neupogen has now been approved in the PFS presentation of 300 µg/0.5 mL, which is similar to the proposed presentation of Grastofil, and also to the EU-approved and US-licensed Neupogen (300 µg/0.5 mL) utilized in the Biosimilarity studies discussed above, an [redacted] has been established with the Canadian-licensed Neupogen (300 µg/0.5 mL PFS). This thereby establishes the required link between the Canadian and the non-Canadian reference products (i.e., EU-approved and US-licensed Neupogen) used in the global biosimilar development program for Grastofil.
In summary, the cumulative data lead to the conclusion that the Grastofil described in this submission is analytically and biologically similar to the reference product, Neupogen.

4.2 Pivotal Clinical Studies

4.2.1 Introduction

The filgrastim SEB, Grastofil, currently submitted by Apotex, was originally manufactured and marketed by the Indian company Intas Pharmaceuticals Limited. An Austrian company, Kwizda Pharma, had been working with Intas to develop filgrastim for the European market. Subsequently, in 2008, Kwizda Pharma transferred all of its rights for the Intas filgrastim product to Apotex. Apotex and Intas extended their collaboration for the development of filgrastim for the North American market (US and Canada). Therefore, the trial design under Kwizda Pharma (hence, the study code KWI) in this dossier was based on biosimilar guidance published by the EMA, with extensive consultations and input from the [redacted] in 2006. What was fundamental from both the guidelines and the Scientific Advice was the acceptability of a healthy subject population for the comparative assessment of efficacy for the filgrastim class of products in phase 1 trials in place of a conventional confirmatory-comparative phase 3 efficacy and safety trial. Accordingly, this regulatory framework defined the clinical development pathway for Grastofil. It is noteworthy that, at this time, biosimilar guidelines were not available in Canada or the US, with the first draft SEB guideline released in Canada in 2010 and the first FDA biosimilar guidelines released in 2012, a time at which the clinical development program for Grastofil had been defined and was well underway.

After Apotex obtained the rights from Kwizda, a marketing authorization application was submitted to the EMA on [redacted]. During this application, [redacted]. It should be noted that none of the original KWI-300 series of studies were designed with the aforementioned tighter limit under consideration. Thus, the assessment of data against these limits should provide further assurance of the overall clinical comparability of Grastofil and Neupogen. Indeed, as presented below, for all key efficacy/PD outcomes, all 95% CIs of the ratios of the geometric means were contained within equivalence margins of 80% to 125**%** (please refer to [redacted]).

4.2.2 Overview of Studies

The aim of the Grastofil clinical program was to support a demonstration of biosimilarity of Grastofil with the reference product Neupogen. Five clinical trials were conducted in total. Four of these five studies were conducted in healthy volunteers directly comparing Grastofil with the reference product Neupogen. In these four studies, Grastofil was administered as a single dose intravenously (KWI-300-101) and subcutaneously (KWI-300-102 and GCSF-SUIN-05SB01-3FA-[5]), as well as a repeated dose subcutaneously (KWI-300-103) to healthy volunteers. PK/PD and safety parameters of Grastofil versus Neupogen were compared in these studies.

One phase 3 single-group safety study (KWI-300-104) was conducted to demonstrate the safety (including immunogenicity) of Grastofil in cancer patients. Study KWI-300-104 was carried out in a homogenous patient population (stage IIA, IIB, or IIIA breast cancer patients being treated by adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy given every three weeks for six cycles). This study included assessment of the efficacy parameter for the duration of severe neutropenia (DSN) in chemotherapy cycle 1, incidence of severe neutropenia, and incidence of febrile neutropenia (IFN). Indeed, the primary objective in this study was not to demonstrate the comparative efficacy of Grastofil with Neupogen, which had already been convincingly demonstrated based on the totality of evidence, which included:

- Comparative PD studies in the most sensitive population of healthy subjects using the accepted sensitive and relevant efficacy outcome measure, ANC
- Extensive series of orthogonal methods demonstrating highly comparable physiochemical properties
- Similar biological activities of filgrastim between Grastofil and Neupogen.

Rather, the purpose of this study was to demonstrate the safety of Grastofil in cancer patients receiving myelosuppressive chemotherapy. This study was conducted following the Scientific Advice given by the Committee for Medicinal Products for Human Use (CHMP) (Scientific Advice EMEA/CHMP/SAWP/396628/2006, Procedure No: EMEA/H/SA/777/1/2006/III; Common Technical Document 2.7.3.2.5) and was therefore acknowledged and accepted (7).

As indicated in Common Technical Document Module 2.5, Section 1.3 (Table 1-1), as part of the global development program of Grastofil, Study GCSF-SUIN-05SB01-3FA-(5) was conducted in Canada as a bridging study. This study served partly to bridge the PK/PD/safety data obtained in the KWI-300 series of clinical studies using EU-approved Neupogen (and US-licensed Neupogen), as well as to determine comparative immunogenicity. More importantly, as the Grastofil utilized in the KWI-300 series of studies was manufactured using DP Process [redacted], this study also served to bridge the Grastofil manufactured using the proposed commercial-scale process, DP Process [redacted], which is intended for the Canadian market, to the EU-approved Neupogen (see sections 1.2 and 4.1 of this review as well as common technical documents 3.2.S.2.2 and 3.2.P.2.3). Although this clinical study demonstrated biosimilarity between the proposed commercial Grastofil product and EU-approved (and US-licensed) Neupogen in terms of PK/PD and [redacted] (16). Rather, approval of Grastofil (DP Process III) was based on [redacted]. Nevertheless, data from this study are presented in this document to support the overall similarity between Grastofil (intended for Canadian market) and the reference product, Neupogen, from a clinical perspective.

As presented below, Grastofil (DP Process [redacted]) intended for the Canadian market was demonstrated to be biosimilar to the accepted non-Canadian reference product, EU-approved Neupogen.

4.2.3 Acceptability of Healthy Volunteers

As stated in the EMA's *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues* (EMEA/CHMP/BMWP/42832/2005(21)), for the demonstration of clinical efficacy, comparative PK/PD studies in healthy subjects between the similar biological medicinal product and its reference product may be sufficient to demonstrate clinical comparability, provided that the PK of the reference medicinal product is well characterized; there is sufficient knowledge of the PD properties of the reference medicinal product; and the relationship between dose/exposure and response/efficacy of the reference medicinal product is sufficiently characterized.

The Grastofil clinical program is based on these premises and on the clinical profile of the reference product Neupogen since its development in 1986 (18). Neupogen has been extensively characterized pharmacologically, with extensive clinical experience from both an efficacy and safety standpoint, all of which are well reported in the literature.

The sensitivity and relevance of a healthy subject population for the assessment of PK and PD similarity is further accepted by the FDA as per the most recent guidelines for the assessment of biosimilarity (*Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* [May 2015]*; Draft Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* [May 2014]) (22, 23).

The assessment of the overall efficacy of Grastofil in healthy volunteers was further supported by the fact that the duration of treatment effect, the mechanism of action, and the pharmacological properties of recombinant G-CSF are reported to be fundamentally the same in healthy volunteers and in neutropenic patients (17). In addition, testing a biosimilar recombinant human granulocyte-colony stimulating factor (rHu-G-CSF) preparation in healthy volunteers rather than patients offers the advantage that it is easier to attribute potential AEs to the drug without having the background noise of concomitant disease and side effects in cancer patients receiving combination chemotherapy.

4.2.4 Acceptability of Absolute Neutrophil Count as Efficacy Outcome

As the PK/PD studies KWI-300-101, KWI-300-102, KWI-300-103, and GCSF-SUIN-05SB01-3FA-(5) conducted in healthy volunteers contribute to the clinical efficacy assessment of Grastofil versus Neupogen, the ANC data of these four studies and the cluster of differentiation 34 ($CD34^+$) cell count data of the Study KWI-300-103 are presented here in Section 5, Critical Appraisal of Clinical Studies, and in Common Technical Document 2.7.3, Summary of Clinical Efficacy.

Clinically, filgrastim elicits its effects in the reduction in duration of neutropenia and the incidence of neutropenia in patients undergoing cytotoxic chemotherapy by stimulating proliferation and differentiation of committed progenitor cells of the granulocyte-neutrophil lineage into functionally mature neutrophils, thereby increasing the ANC. It is the ANC that essentially drives diagnosis (e.g., grade of neutropenia), predicts prognosis (duration of severe neutropenia [DSN] correlates with the risk of infection), and is utilized to monitor rHu-G-CSF treatment effects (17). The severity of neutropenia is graded as follows:

- Grade 1: < lower limit of normal to 1.5×10^9 cells/L
- Grade 2: < 1.5 to 1.0×10^9 cells/L
- Grade 3: < 1.0 to 0.5×10^9 cells/L
- Grade 4: < 0.5×10^9 cells/L.

Accordingly, ANC is used in the assessment of relevant efficacy end points for filgrastim medicinal products, as evidenced in the clinical studies that supported the approval of Neupogen (3, 4, 15). This approach is in accordance with the EMA's *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor* (EMEA/CHMP/BMWP/31329/2005)(6). The guidance states that for demonstration of biosimilarity in terms of clinical efficacy: "alternative models, including pharmacodynamic studies in healthy volunteers, may be pursued for the demonstration of comparability if justified." The Annex further states that "The absolute neutrophil count (ANC) is the relevant pharmacodynamic marker for the activity of rHu-G-CSF." The chosen approach was discussed within Scientific Advice EMEA/CHMP/SAWP/396628/2006, Procedure No. EMEA/H/SA/777/1/2006/III (7). Thus, as noted earlier, the clinical development program for Grastofil was designed in accordance with the outcome of this Scientific Advice.

The information presented earlier is also in line with the draft FDA guidelines (*Draft Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,* May 2014 (23)).

Therefore, because the diagnosis of neutropenia is determined by ANC, ANC is scientifically acceptable and is clearly an established primary PD marker that can effectively demonstrate the characteristics of filgrastim's target effects.

4.2.5 Choice of Pharmacodynamics Equivalence Margin

The objective of the studies in healthy volunteers was the demonstration of equivalence in terms of PD (and PK) parameters. Equivalence of the test and reference products was assessed by employing the analysis of variance (ANOVA) on logarithmically transformed parameters. The criteria for equivalence stipulated in the protocols were based on the 90% CI for the "test-reference" differences in the log-transformed PD (and PK) parameters.

For the assessment of the comparability of efficacy (i.e., PD comparability) between Grastofil and Neupogen, as defined a priori in the corresponding study protocols, the 90% CI for the relevant ANC PD end point parameter was to be contained within the standard acceptance range of 80% to 125%. These conventional bioequivalence predefined boundaries were established in part based on the literature. In reviewing the literature, it was noted that for the comparison of proposed filgrastim biosimilars to Neupogen, the 90% CI was to be contained within the acceptance range of 80% to 125% for ANC PD end point parameters (24-27). In addition, it was noted that although other reports in the literature also retrospectively constructed a 95% CI for PD end point parameters (24), the acceptance limits of 80% to 125% were still maintained and accepted by the EMA as evidenced by the marketing authorization of Nivestim (another filgrastim biosimilar). In addition, the marketing authorization of other filgrastim biosimilars, including Tevagrastim, was also based on the acceptance limits of 80% to 125% for ANC PD end point parameters (e.g., area under the curve [AUC] and peak concentration[C_{max}]), thereby suggesting that the acceptance limits of 80% to 125% are appropriate and acceptable for the assessment of PD comparability for filgrastim biologics. Finally, the most recent FDA biosimilar draft guidance (*Guidance for Industry Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* [May 2014]) provided recommendations on the statistical approach for the assessment of PK/PD similarity, which is in line with the approach employed for the clinical program for Grastofil (23). Considering all of the aforementioned factors, these acceptance limits of 80% to 125% were applied to the submitted clinical phase 1 studies for Grastofil submitted in this NDS dossier. As discussed earlier (Section 4.2.1), PD data were reanalyzed using 95% CI. This post-hoc analysis was applied to the data from both intention-to-treat (ITT) and per-protocol (PP) populations.

TABLE 5: SUMMARY OF GRASTOFIL CLINICAL STUDIES

Study Name	Design	Objectives	Population
KWI-300-101	PK/PD, phase 1, randomized, double-blind, single-dose, active-controlled, two-way crossover, single-centre study comparing Grastofil vs. EU-approved Neupogen (both at 5 mcg/kg IV) in healthy volunteers	To assess and compare the two G-CSF medicinal products in healthy volunteers based on PK and PD parameters following IV infusion of a single dose.	The study was conducted in healthy subjects; however, the main therapeutic area was hematological support primarily in an oncology setting (i.e., reduction in the incidence and duration of severe neutropenia). Normal, healthy, non-smoking adult male and female subjects (18 to 55 years of age) were recruited. Key characteristics for the primary efficacy analysis (PP) population: 18 males vs. 17 females; mostly Caucasian; and median age of 29 years (range: 19 to 43 years).
KWI-100-102	PK/PD, phase 1, single-dose, randomized, double-blind, two-way crossover, dose-response, single-centre study comparing Grastofil vs. EU-approved Neupogen (both at 75 mcg and 150 mcg SC, single dose) in healthy volunteers	1. To assess and compare dose response of the two G-CSF medicinal products in healthy subjects based on PD parameters following 75 mcg or 150 mcg single-dose SC administration 2. To assess the pharmaco-kinetics of filgrastim products after SC injection of 150 mcg, single dose.	The study was conducted in healthy subjects; however, the main therapeutic area was hematological support primarily in an oncology setting (i.e., reduction in the incidence and duration of severe neutropenia). Normal, healthy, non-smoking adult male and female subjects (18 to 55 years of age) were recruited. Key characteristics: (PP population) mostly males (44 males vs. 24 females) and median age of 26.5 years (range: 19 to 52).
KWI-300-103	PK/PD, phase 1, repeat-dose, randomized, double-masked, active- and placebo-controlled parallel group, single-centre study comparing Grastofil vs. EU-approved Neupogen (both at 5 mcg/kg SC) in healthy volunteers	1. To assess PD parameters of Grastofil with respect to ANC counts 2. To assess PD parameters of Grastofil with respect to mobilization of $CD34^+$ cells 3. To provide information on the PK of Grastofil after repeat dosing.	The study was conducted in healthy subjects; however, the main therapeutic area was hematological support primarily in an oncology setting (i.e., reduction in the incidence and duration of severe neutropenia) and stem cell mobilization. Normal, healthy, non-smoking adult male and female subjects (18 to 55 years of age with weight not exceeding 96 kg) were recruited. Subjects must have had normal medical history, physical examination, and laboratory values unless the investigator considered an abnormality to be clinically irrelevant. Key characteristics: (PP population) 36 males vs. 39 females and median age of 25 years (range: 18 to 48 years).

Study Name	Design	Objectives	Population
KWI-300-104	Phase 3, non-comparative, single-group, multi-centre, repeat dose safety study in breast cancer patients receiving TAC chemotherapy. Grastofil was given at 5 mcg/kg/day SC rounded to the nearest 300 mcg or 480 mcg PFS.	To evaluate the safety of Grastofil used for the prophylaxis of febrile neutropenia in breast cancer patients undergoing TAC chemotherapy as compared with the safety profile of approved and/or registered products.	The therapeutic area was oncology support (i.e., reduction in the incidence and duration of severe neutropenia) Female patients (≥ 18 of age) with stage IIA, IIB, or IIIA breast cancer and within 60 days of surgical resection of the primary breast tumour; Eastern Cooperative Oncology Group performance status ≤ 2; chemotherapy-naive; suitable for and intended to undergo adjuvant TAC chemotherapy. Subjects must have had ANC ≥ 1.5×10^9/L; platelet count ≥ 100×10^9/L. Key characteristics: all females (120); all Caucasian (120); and average (standard deviation) age of 49.97 (9.52) years.
GCSF-SUIN-05SB01-3FA-(5)	PK/PD bridging study; phase 1, randomized, double-blind, single-dose, active-controlled, comparative three-way crossover, single-centre study comparing Grastofil vs. two reference comparators (EU-approved and US-licensed Neupogen, all at 300 mcg SC) in healthy volunteers	To assess and compare the G-CSF preparations.	The study was conducted in healthy subjects; however, the main therapeutic area was hematological support (i.e., reduction in the incidence and duration of severe neutropenia). Normal, healthy non-smoking male and female volunteers, fasting; 18 to 55 years of age, weight not exceeding 100 kg with absence of significant disease or clinically significant abnormal laboratory values. Key characteristics: (PP population) mostly males (32 males vs. 16 females) and median age of 42 years (range: 18 to 53 years).

ANC = absolute neutrophil count; $CD34^+$ = cluster of differentiation 34; EU = European Union; G-CSF = granulocyte-colony stimulating factor; IV = intravenous; PD = pharmacodynamics; PFS = pre-filled syringe; PK = pharmacokinetics; PP = per-protocol; SC = subcutaneous; TAC = docetaxel/doxorubicin/cyclophosphamide; vs. = versus.

4.2.6 KWI-300-101

a) Study Characteristics

KWI-300-101 was a phase 1, single-dose, randomized, double-blind, active-controlled, two-way crossover, single-centre study designed to assess the comparative PK and PD of Grastofil and Neupogen in healthy subjects. The primary end point was the plasma AUC of filgrastim between Grastofil and Neupogen.

TABLE 6: DETAILS FOR KWI-300 101

Characteristics		Details for KWI-300-101
Study Design	Objective	To assess and compare two recombinant G-CSF medicinal products in healthy volunteers based on PK/PD parameters following IV infusion of a single dose
	Blinding	Double-blind
	Study period	2007–07 to 2007–10
	Study centres	Single-study centre
	Design	Equivalence, 2-way crossover
Study Population	Randomized (N)	36
	Inclusion criteria	• Healthy male or female subjects, aged 18 to 55 years
	Exclusion criteria	• Blood donations during the month prior to this study • Recent infection (within 1 week), as endogenous G-CSF levels increase in acute inflammation • Relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, inflammatory, or neurological diseases, which may interfere with the aim of the study • Ascertained or presumed hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considered might compromise the safety of the volunteers • Clinically relevant abnormal laboratory values indicative of physical illness • Use of medication (except hormonal contraception in female subjects) during the 2 weeks before the start of the study, which the investigator considered might affect the validity of the study; before taking any medication during the 72 hours prior to trial day 1 or 5, the study centre had to be consulted • Pregnancy (positive pregnancy test at screening or during study phase), lactation or unreliable contraception in female subjects with child-bearing potential as specified in Section 7.4 of the study protocol • Symptoms of a clinically relevant illness in the 3 weeks before the first trial day • Signs of dermatitis or skin anomalies affecting the administration area and its surroundings.
Drugs	Intervention	Grastofil (DP manufactured with Process II), 5 mcg/kg body weight (300 mcg filgrastim/0.5 mL in single-use PFSs) administered intravenously as short infusion (20 mL; infusion rate: 2 mL/minute over 10 minutes) after a higher than 1:20 dilution with glucose (5%)
	Comparator(s)	Neupogen (EU-approved and sourced), 5 mcg/kg body weight (480 mcg filgrastim/0.5 mL in single-use PFSs) administered intravenously as short infusion (20 mL; infusion rate: 2 mL/minute over 10 minutes) after a higher than 1:20 dilution with glucose (5%)

Characteristics		Details for KWI-300-101
Duration	Run-in	Not applicable
	Treatment	Subjects were given a 10-minute infusion in each of the 2 treatment periods separated by at least a 4-week washout period. Each period was 4 days in length. The total study duration per subject lasted approximately 45 days, including screening and post-trial examination.
	Follow-up	Subjects returned to the study ward 3 to 14 days after the last trial day for a final post-trial examination.
Outcomes	Primary end point(s)	Evaluation and comparison of plasma AUC between test and reference G-CSF medicinal products.[a]
	Other end points	**Secondary** • **PK parameters:**[a] Evaluation and comparison of C_{max} and $T_{1/2}$ filgrastim in plasma • **PD parameter:** Evaluation and comparison of the ANC as relevant pharmacodynamic marker for the activity of G-CSF (EMEA/CHMP/BMWP/31329/2005) (21). **Tertiary** • PK parameters of filgrastim (T_{max}, C_L, V_d) • General laboratory • Adverse events • Vital signs
Notes	Publications	• (28, 29)

ANC = absolute neutrophil count; AUC = area under the curve; C_L = clearance; C_{max} = peak concentration; DP = drug product; EU = European Union; G-CSF = granulocyte-colony stimulating factor; IV = intravenous; PD = pharmacodynamics; PFS = pre-filled syringe; PK = pharmacokinetics; $T_{1/2}$ = half-life; T_{max} = time at maximum concentration; V_d = volume of distribution.
[a] Results for PK parameters are presented in Section 4.3, Pharmacokinetics.

b) Intervention and Comparators

Subjects received 5 mcg/kg body weight of Grastofil (DP manufactured using Process II; 300 mcg filgrastim/0.5 mL in single-use PFSs) administered intravenously as short infusion (20 mL; infusion rate: 2 mL/minute over 10 minutes) after a higher than 1:20 dilution with glucose (5%). The reference product was Neupogen (non-Canadian, EU-approved, 480 mcg filgrastim/0.5 mL in single-use PFSs) administered in the same manner as Grastofil. Subjects received both products separated by a four-week minimum washout period.

The choice of the IV route of administration allowed for a precise comparison between Grastofil and Neupogen, not influenced by absorption of the formulation after administration subcutaneously.

Concomitant Medications: The use of medication two weeks before the start of the study was not allowed if the investigator suspected this medication might affect the validity of the study. Prior to taking any medication within 72 hours prior to trial day 1 or 5, volunteers were instructed to consult the study centre. Hormonal contraception in female subjects was an exception to this rule.

c) Outcomes

Peak ANC (C_{max}): The key efficacy or PD outcome was peak ANC after a single dose of G-CSF, through which biosimilarity was to be established if the 90% CI for the ratio of geometric means between Grastofil and the EU-approved Neupogen was within the predefined equivalence margin of 80% to

125%. For the assessment of ANC, samples were analyzed using an automated cell counter(s) and ANC values were reported. As part of the post-hoc analysis, 95% CI of the ratio was also calculated.

ANC AUC_{0-72}: The other key efficacy/PD outcome was the AUC of the ANC from 0 hours up to 72 hours (AUC_{0-72}) following filgrastim administration. The AUC of the ANC was calculated by the linear trapezoidal rule.

Safety: The key safety outcomes included general laboratory, local tolerability, adverse events (AEs) and vital signs. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10.0.

d) Statistical Analyses

An ANOVA with treatment, period, and sequence as fixed factors, and the random factor subject within sequence was applied for the log_e-transformed end points area under the curve from 0 to 32 hours [AUC_{0-32}], area under the curve from 0 extrapolated to infinity [AUC_{inf}], and C_{max} of filgrastim (PK) and C_{max} of the ANC (PD). A 90% CI for the ratio of geometric means (Grastofil/Neupogen) was calculated using the back-transformed (exponential) 90% CI for the least squares mean difference "Grastofil minus Neupogen." In accordance with the guidance documents, biosimilarity was postulated if the lower bound of the 90% CI for the ratio of Grastofil to Neupogen was more than 80% and the upper bound was less than 125% (AUC_{0-32}, AUC_{inf}, and C_{max} of filgrastim). The rationale for this definition of equivalence was the same for all applicable studies. (See Section 4.2.5, Choice of Pharmacodynamics Equivalence Margin, for further details).

In addition, in consideration of comments from the EMA, as a post-hoc analysis, the 95% CI of the relative mean ANC C_{max} and ANC AUC were calculated and assessed against the predefined equivalence margins of 80% to 125% for the demonstration of PD similarity. These data are presented in support of the PD similarity of Grastofil and Neupogen.

Analysis Sets: Three analysis populations were defined:

1. **Per-protocol population:** The PP population included all randomized subjects without any major protocol deviations. This was the primary analysis population for efficacy with regard to PK/PD analyses.
2. **Intention-to-treat population:** The ITT population included all randomized subjects with at least one administration of the study treatment. Subjects were analyzed according to the treatment to which they were randomized. This was the secondary analysis population for efficacy.
3. **Safety population:** The safety population included all randomized subjects with at least one administration of the study treatment. Subjects were analyzed according to the actual treatment they received. This was the primary analysis population for safety.

In this study, the ITT population was identical to the safety population.

e) Results

Baseline Characteristics

TABLE 7: STUDY KWI-300-101: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS (ITT POPULATION)

Characteristics	Grastofil/Neupogen (5 mcg/kg) (N = 17)	Neupogen/Grastofil (5 mcg/kg) (N = 19)
Age (years)	36 (19 to 42)	28 (20 to 43)
Gender, no (%)		
Male	10 (58.8)	8 (42.1)

Characteristics	Grastofil/Neupogen (5 mcg/kg) (N = 17)	Neupogen/Grastofil (5 mcg/kg) (N = 19)
Female	7 (41.2)	11 (57.9)
Ethnicity[a]		
Caucasian, n (%)	35 (97.2)	
Other, n (%)	1 (2.8)	
Height (cm)	175.0 (157.0 to 90.0)	168.0 (157.0 to 83.0)
Body weight (kg)	69.0 (56.5 to 9.0)	68.0 (50.0 to 9.0)
BMI (kg/m^2)	22.9 (18.9 to 8.7)	23.0 (17.9 to 2.0)
Oral body temperature (^{o}C)	36.0 (35.0 to 7.1)	36.1 (34.9 to 7.0)

BMI = body mass index; ITT = intention-to-treat.
[a] Ethnicity data unavailable by study arm.
Note: Except where indicated otherwise, values presented represent the median (range).
Source: Clinical Study Report KWI-300-101, Tables 80 to 84, 91.

Overall, the physical characteristics (e.g., height, weight, body mass index [BMI], oral body temperature) were well balanced between the Grastofil/Neupogen and the Neupogen/Grastofil group. The Grastofil/Neupogen group had slightly older subjects. However, considering this was a crossover study, the potential for bias was low.

Concomitant Conditions and Medications: With [redacted], all volunteers had normal baseline results at screening (see Clinical Study Report KWI-300-101, Section 14.1, Table 96, PP population data only). A total of [redacted] subjects presented with abnormal findings at screening (as defined by echocardiogram [ECG]) as specified by sequence group for the ITT population (see Clinical Study Report KWI-300-101, Section 14.1, Table 97). All of these were classified as not clinically relevant by the investigators.

Concomitant medications in the ITT population were taken by [redacted] subjects in the Grastofil/Neupogen group and by [redacted] subjects in the Neupogen/Grastofil group (see Clinical Study Report KWI-300-101, Table 98). Concomitant medications were taken mostly for the following reasons: [redacted], and other indications occurring infrequently (see Clinical Study Report KWI-300-101, Table 100).

Subject Disposition

From a total of 41 screened volunteers, five subjects were not eligible for randomization into this trial (inclusion/exclusion criteria). Among the 36 healthy volunteers (ITT population), one female subject had to be excluded due to pregnancy (major protocol violation) after receiving one cycle of Neupogen in period 1, leaving a group of 35 volunteers receiving both treatment cycles (PP population). With one cycle of administered G-CSF, the analyzed safety population included 36 subjects and was identical to the ITT population (Table 8). Overall, similar number of subjects from both the Grastofil and Neupogen groups initiated and completed the study.

TABLE 8: STUDY KWI-300-101: SUMMARY OF SUBJECT DISPOSITION

Disposition	KWI-300-101	
	Grastofil/Neupogen (5 mcg/kg)	Neupogen/Grastofil (5 mcg/kg)
Screened, N	41	
Randomized, N	17	19
Discontinued, N (%)	[redacted]	[redacted]

Disposition	KWI-300-101	
	Grastofil/Neupogen (5 mcg/kg)	Neupogen/Grastofil (5 mcg/kg)
Major protocol violation, N (%)	[redacted]	[redacted]
WDAEs, N (%)	[redacted]	[redacted]
Withdrawal due to SAEs, N (%)	[redacted]	[redacted]
Lost to follow-up, N (%)	[redacted]	[redacted]
Intention-to-treat, N	[redacted]	[redacted]
Per-protocol, N	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]

SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report KWI-300-101, Section 10.1, Tables 9–1.

Efficacy Results

ANC C_{max} after Single Dose: The key efficacy or PD end point was the peak ANC count (C_{max}) after a single dose of intravenously infused filgrastim. The results of ANOVA showed (for both PP and ITT populations) the 90% CI for the percentage ratio (Grastofil/Neupogen) of geometric means for ANC C_{max} was 93.6% to 105.8%, enclosed within the acceptance interval (Table 9). As part of post-hoc analyses, the 95% CI for the ratio (Grastofil/Neupogen) of geometric means for ANC C_{max} (92.5% to 107.1%) was also contained within the predefined interval. These results indicated that Grastofil is pharmacodynamically similar to Neupogen.

TABLE 9: STUDY KWI-300-101: ANC C_{MAX} AFTER SINGLE INTRAVENOUS INFUSION OF 5 MCG/KG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		Grastofil	Neupogen	% Ratio of Geometric Means	90% CI	95% CI[a]	*P* > [t]
PP Population							
ANC C_{max} (cells × 10^9/L)	N	35	35	99.5	93.6 to 105.8	92.5 to 107.1	0.8972
	Mean	19.02	19.28				
	SD	4.35	5.21				
	Minimum	11.42	11.43				
	Median	18.48	18.74				
	Maximum	29.86	32.55				
ITT Population							
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean						
	SD						
	Minimum						
	Median						
	Maximum						

ANC = absolute neutrophil count; CI = confidence interval; C_{max} = peak concentration; CTD = common technical document; ND = not determined; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
[a] Post-hoc analysis.
Source: CTD 2.7.3, Table 2.7.3–6; Study Report KWI-300-101, Section 11.4 Efficacy Results, Table 34; Clinical Attachment 1, p. 8.

Other ANC Results: For the post-hoc analyses, the 95% CIs for the ratio (Grastofil/Neupogen) of geometric means were also calculated for ANC $AUC_{0\text{-}72}$ (PP: [redacted]; ITT: [redacted]; Table 10), and ANC $AUC_{0\text{-}inf}$ (ITT: [redacted]; Table 11), all of which were also enclosed within the equivalence margin, further supporting biosimilarity between Grastofil and Neupogen.

TABLE 10: STUDY KWI-300-101: ANC $AUC_{0\text{-}72}$ AFTER SINGLE INTRAVENOUS INFUSION OF 5 MCG/KG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

End Point		Grastofil (N = 35)	Neupogen (N = 35)	% Ratio of Geometric Means	95% CI	*P* > [t]
PP Population						
ANC $AUC_{0\text{-}72}$ (cells × 10^9*min/L)	N	35	35	99.1	[redacted]	[redacted]
	Mean	46,137.4	46,601.5			
	SD	8,608.3	9,321.6			
	Minimum	31,838.0	29,727.7			
	Median	46,256.5	44,899.3			
	Maximum	62,765.8	63,213.4			
ITT Population						
ANC $AUC_{0\text{-}72}$ (cells × 10^9*min/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANC = absolute neutrophil count; $AUC_{0\text{-}72}$ = area under the curve from 0 to 72 hours; CI = confidence interval; ITT = intention-to-treat; min = minutes; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Table 2.7.3–6; Study Report KWI-300-101, Section 11.4 Efficacy Results, Table 35; Clinical Attachment 1, p. 1 and 5.

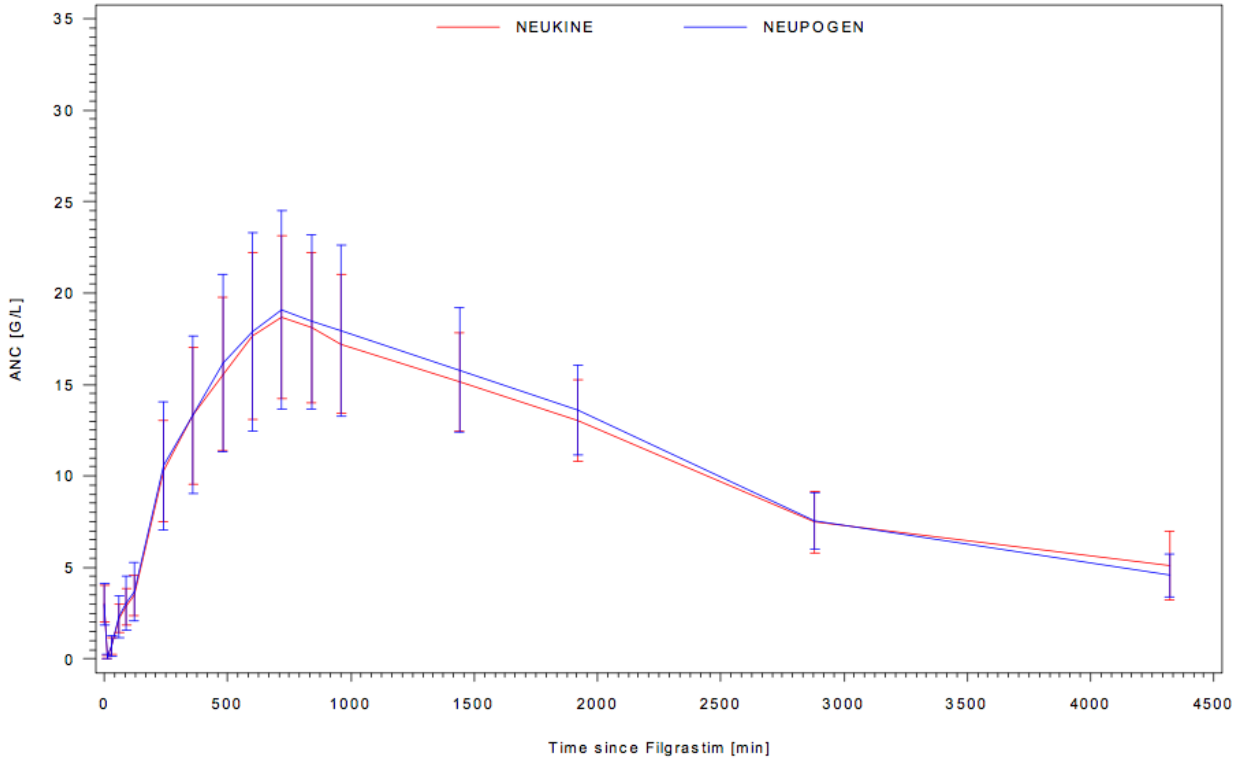
TABLE 11: STUDY KWI-300-101: ANC $AUC_{0\text{-}INF}$ ANALYZED BY ANOVA (PP AND ITT POPULATIONS)

	Grastofil	Neupogen	% Ratio of Geometric Means	95% CI[a]	*P* > [t]
PP Population					
	N = 33	**N = 34**			
ANC $AUC_{0\text{-}inf}$ (cells × 10^9*min/L)	59,483.28 ± 15,488.92	57,619.11 ± 12,222.71	103.40%	97.55 to 109.61	0.2500
ITT Population					
	[redacted]	[redacted]			
ANC $AUC_{0\text{-}inf}$ (cells × 10^9*min/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANC = absolute neutrophil count; ANOVA = analysis of variance; $AUC_{0\text{-}72}$ = area under the curve from 0 to 72 hours; CI = confidence interval; CTD = common technical document; ITT = intention-to-treat; min=minutes; PP = per-protocol; SD = standard deviation.
Source: Clinical Attachment 1, p. 2 and 6.

The mean ANC-time profile in the ITT population following a single 5 mcg/kg intravenous dose of Grastofil and Neupogen shown in Figure 1 below. The profile of the PP population was similar (not shown).

FIGURE 1: STUDY KWI-300-101: MEAN ANC-TIME PROFILE FOLLOWING A SINGLE INTRAVENOUS INFUSION OF 5 MCG/KG OF GRASTOFIL (NEUKINE) OR NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS (ITT POPULATION) (G/L = CELLS × 10^9/L)



ANC = absolute neutrophil count; G/L = grams per litre; ITT = intention to treat; min = minimum.
Source: Study Report KWI-300-101, Figure 12.

Considering that there were no significant differences between Grastofil and Neupogen for the PD parameters of ANC C_{max} and ANC AUC_{0-72} (both PP *and* ITT populations); these PD end points were comparably achieved after administration of Grastofil and Neupogen, independent of the administration sequence; and the point estimates for both the ANC C_{max} and ANC AUC_{0-72} parameters were at or close to 100%, these results suggest that Grastofil and Neupogen behaved essentially identically in the assessment of PD similarity. Lastly, the highly comparable data also suggest that Grastofil and Neupogen's mechanism of action at eliciting the PD response is identical, namely, via identical binding to the G-CSF receptor.

In summary, Study KWI-300-101 revealed that Grastofil exhibits highly comparable PD to the reference product Neupogen, as demonstrated by the 95% CI of the ratios of the geometric means for ANC being contained within the predefined equivalence margin.

Safety Results

In this study, there were a total of 59 treatment-emergent adverse events (TEAEs) involving 22 different subjects (Table 12). Among the total of 59 AEs, 27 occurred in study group Grastofil/Neupogen and 32 occurred in study group Neupogen/Grastofil.

There were a total of 30 drug-related TEAEs involving 13 subjects: this included 13 related TEAEs in 9 subjects in the Grastofil group, and 17 related TEAEs observed in nine subjects in the Neupogen group (see Clinical Study Report KWI-300-101, Tables 43 and 44). Most of these were classified as mild or moderate TEAEs. No deaths occurred during this study. No discontinuations occurred as a result of TEAEs. All types of observed TEAEs have been previously described in the literature. With the exception of one ongoing AE (rhinitis judged as a mild AE), all AEs were fully resolved at the final examination.

TABLE 12: STUDY KWI-300-101: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (SAFETY POPULATION)

	Grastofil[a] (N = 35)	Neupogen[b] (N = 36)	Total (N = 36)
Total number of TEAEs	[redacted]	[redacted]	[redacted]
Related[c]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 TEAE	15 (42.9)	16 (44.4)	22 (61.1)
Related[c]	[redacted]	[redacted]	[redacted]
Total number of SAEs	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 SAE	[redacted]	[redacted]	[redacted]
Total number of AEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 AE leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] As this was a crossover study design, all but one randomized subjects received Grastofil.
[b] As this was a crossover study design, all subjects received Neupogen.
[c] Classified as definitely, probably, or possibly related.
Source: Clinical Study Report KWI-300-101, Tables 40–44.

The most common TEAEs (i.e., occurring in more than one in subject) in the Grastofil group (N = 35) included back pain in five subjects (14.3%), rhinitis in four subjects (11.4%), headache in three subjects (8.6%), and fatigue in two subjects (5.7%). In subjects treated with Neupogen (N = 36), the most common TEAEs included back pain in five subjects (13.9%) and headache in eight subjects (22.2%).

There were no serious adverse events (SAEs) in this study and only one severe AE (diarrhea in one subject that occurred two days after administration of Grastofil in the second period); it was classified by the investigator as not being causally related.

Laboratory Parameters: The course of laboratory parameters were assessed by analyzing three different scenarios: change from baseline values prior to filgrastim administration to one day after drug exposure; change from baseline values prior to filgrastim administration to three days after drug exposure; and change from baseline screening to the final visit covering the whole study period.

In all scenarios, there was generally little difference at various time points compared with baseline in both groups for all parameters. The minor changes observed were small in magnitude and determined to be transient phenomena in clinical practice. One of the notable observations was [redacted] for total bilirubin, although none of the changes were considered to be clinically significant. The other notable observation was that D-dimer values showed [redacted]. This [redacted] was mainly caused by [redacted] subjects

with values outside the normal range. [redacted] of the subjects had a [redacted] in D-dimer manifest at study day 8 with a value of [redacted], which [redacted] at the final visit. The [redacted] only had an [redacted] value for D-dimer ([redacted]) at the final visit. At that time, [redacted]. From a medical point of view, both [redacted] have been classified as not clinically relevant.

Similarly, there was little change in the qualitative urinalysis covering eight parameters over time when considering the interval from screening to the end of the trial. When paying particular attention to the laboratory parameters known to be influenced by G-CSF — i.e., alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and uric acid — there were no clinically relevant changes over time in either study group.

Vitals and Echocardiogram: Abnormal ECG findings at the study end were observed in [redacted] subjects. When compared with the ECG analyses at screening, there were [redacted] more subjects with abnormal ECG findings, whereas [redacted] subjects with abnormal ECG findings at screening were negative at the end of study. The newly diagnosed ECG findings at the final visit included [redacted] ([redacted] subjects) and other singular changes ([redacted] subjects). On the other hand, [redacted] and singular findings of [redacted], [redacted] or abnormal [redacted] were no longer observed at the final visit. All abnormal ECG findings, either present at screening, at the final visit, or during both ECG examinations, were classified as clinically not relevant by the investigators.

In summary, there was little difference in Study KWI-300-101 between AEs in subjects receiving the DP Process II Grastofil or EU-licensed Neupogen. The crossover design of this trial hampers the assignment of side-effect data to study medications, as all subjects of the PP population received both the test item, Grastofil, and the reference item, Neupogen. Nevertheless, the washout period of four weeks was considered sufficient to separate and allow for discrimination of the G-CSF administration cycles.

Overall, the totality of PD and safety data from Study KWI-300-101 demonstrated Grastofil to be biosimilar to the reference filgrastim product, Neupogen.

4.2.7 KWI-300-102

a) Study Characteristics

KWI-300-102 was a phase 1, single-dose, randomized, double-blinded, active-controlled, two-way crossover, dose-response, single-centre study designed to assess the comparative PK/PD of Grastofil and Neupogen in healthy subjects. The primary end point was the evaluation and comparison of ANC between test and reference filgrastim medicinal products in line with the annex to the CHMP guideline *(Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor [EMEA/CHMP/BMWP/31329/2005]* (6)).

TABLE 13: DETAILS FOR KWI-300-102

Characteristics		Details for KWI-300-102
Study Design	Objective	1. To assess and compare dose response of two recombinant G-CSF medicinal products in healthy subjects based on pharmacodynamic parameters following 75 mcg or 150 mcg single-dose SC administration. 2. To assess the pharmacokinetics of filgrastim after SC injection of 150 mcg.
	Blinding	Double-blind
	Study period	2008–07 to 2009–01
	Study centres	Single-study centre
	Design	Equivalence, 2-way crossover
Study Population	Randomized (N)	73
	Inclusion criteria	Healthy male or female subjects, aged 18 to 55 years
	Exclusion criteria	• Blood donations during the 1 month prior to this study • Recent infection (within 1 week), as endogenous G-CSF levels increase in acute inflammation • Relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, inflammatory, or neurological diseases that may interfere with the aim of the study • Ascertained or presumed hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may compromise the safety of the subjects • Clinically relevant abnormal laboratory values indicative of physical illness • Use of medication during 2 weeks before the start of the study that the investigator considers may affect the validity of the study, except hormonal contraception in female subjects; prior to taking any medication during 72 hours before trial days 1 and 5, the study centre should be consulted • Drug, alcohol (> 1 drinks/day, defined according to USDA Dietary Guidelines) • Pregnancy (positive pregnancy test at screening or during study phase), lactation or unreliable contraception in female subjects with child-bearing potential (for details refer to Section 9.5 of the CSR, Pregnancy Test — Contraception) • Symptoms of a clinically relevant illness in the 3 weeks before the first trial day • Signs of dermatitis or skin anomalies affecting the administration area and its surroundings
Drugs	Intervention	Grastofil (DP manufactured with Process [redacted]), 75 mcg and 150 mcg (300 mcg filgrastim/0.5 mL in single-use PFSs) administered SC
	Comparator(s)	Neupogen (EU-approved and sourced), 75 mcg and 150 mcg (300 mcg filgrastim/0.5 mL in single-use PFSs) administered SC
Duration	Run-in	Not applicable
	Treatment	For each of the 75 mcg and 150 mcg dosing cohorts, subjects entered a single treatment period separated by at least a 4-week washout period before a switch to the other filgrastim brand. The total study duration per subject lasted approximately 45 days, including a 4-week washout period.
	Follow-up	Subjects returned to the study ward 3 to 14 days after the last trial day for a final post-trial examination.

Characteristics		Details for KWI-300-102
Outcomes	Primary End Point(s)	**Primary End Point** Evaluation and comparison of ANC between test and reference filgrastim medicinal products **Co-primary End Point for the 150 mcg Dose** Evaluation and comparison of plasma AUC between test and reference filgrastim medicinal products[a]
	Other End Points	**Secondary End Points for the 150 mcg Dose** Evaluation and comparison of PK parameters C_{max} and $T_{1/2}$ filgrastim of filgrastim[a] **Tertiary Outcome Variables** Local tolerability, general laboratory, adverse events, vital signs **Tertiary Outcome Variables for the 150 mcg Dose** PK parameters, filgrastim (F, C_L, V_d, T_{max})[a]
Notes	Publications	(28, 29)

ANC = absolute neutrophil count; AUC = area under the curve; C_L = clearance; C_{max} = peak concentration; CSR = Clinical Study Report; DP = drug product; EU = European Union; F = bioavailability; G-CSF = granulocyte-colony stimulating factor; PFS = pre-filled syringe; PK = pharmacokinetics; SC = subcutaneous; $T_{1/2}$ = half-life; T_{max} = time at maximum concentration; USDA = US Department of Agriculture; V_d = volume of distribution.

[a] Results for PK parameters are presented in Section 4.3, Pharmacokinetics.

Intervention and Comparators

Subjects received 75 mcg or 150 mcg of Grastofil (DP manufactured with Process [redacted]; 300 mcg filgrastim/0.5 mL in single-use PFSs) administered subcutaneously. The reference comparator was 75 mcg or 150 mcg of Neupogen (non-Canadian; EU-approved; 300 mcg filgrastim/0.5 mL in single-use PFSs) administered subcutaneously.

For each of the 75 mcg and 150 mcg dosing cohorts, subjects entered a single treatment period separated by at least a four-week washout period before switching to the other filgrastim medicinal product.

Concomitant Medications: Prior to taking any medication within 72 hours before trial days 1 and 5, subjects were instructed to consult the study centre. Hormonal contraception in female subjects was an exception to this rule.

Outcomes

Peak ANC (C_{max}): The key efficacy/PD outcome was peak ANC after a single dose of G-CSF, through which biosimilarity was to be established if the 90% CI for the ratio of geometric means between Grastofil and the EU-approved Neupogen was within the predefined equivalence margin. For the assessment of ANC, samples were analyzed using an automated cell counter(s) and ANC values were reported. As part of the post-hoc analysis, 95% CI of the ratio was used.

Safety: The key safety outcomes (tertiary end points) included general laboratory, AEs, and vital signs. AEs were coded using the MedDRA Version 10.0.

Statistical Analyses

An ANOVA with treatment, period, and sequence as fixed factors, and the random factor subject within sequence was applied for the log-transformed end points C_{max} of the ANC (PD) and AUC_{0-72}, AUC_{inf}, and C_{max} of filgrastim (PK). 90% CI for the ratio of geometric means (Grastofil/Neupogen) were calculated using the back-transformed (exponential) 90% CI for the least squares mean difference (Grastofil minus Neupogen). For the PD parameter C_{max} of the ANC, 90% CIs were calculated for both cohorts (75 mcg and 150 mcg); for the PK parameters, 90% CI was calculated for only the 150 mcg cohort. Equivalence was postulated if these intervals were completely contained within the predefined equivalence margin. The equivalence margin was set to 80% to 125% for both the PD (C_{max} of ANC) and PK (AUC_{0-72}, AUC_{inf}, and C_{max} of filgrastim) parameters. The rationale for this definition of equivalence was the same for all applicable studies (See Section 4.2.5, Choice of Pharmacodynamics Equivalence Margin for further details).

In addition, in consideration of comments from the EMA, as a post-hoc analysis, the 95% CI of the relative mean ANC C_{max} and ANC AUC were calculated and assessed against the predefined equivalence margins of 80% to 125% for the demonstration of PD similarity. These data were presented in support of the PD similarity of Grastofil and Neupogen.

Analysis Sets: Three analysis populations were defined:

- **Per-protocol population:** The PP population included all randomized subjects without any major protocol deviations. Subjects who experienced an infection between day 1 and day 3 or between day 5 and day 7 (identification of infections based on the AEs documented) were regarded as major protocol deviations based on written confirmation of the principal investigator. The PP population was the primary analysis population for efficacy.
- **Intention-to-treat population:** The ITT population included all randomized subjects with at least one administration of the study treatment. Subjects were to be analyzed according to the treatment to which they were randomized. This was the secondary analysis population for efficacy.
- **Safety population:** The safety population included all randomized subjects with at least one administration of the study treatment. Subjects were to be analyzed according to the actual treatment they received. This was the primary analysis population for safety.

In this study, the ITT population was identical to the safety population.

b) Results

Baseline Characteristics

TABLE 14: STUDY KWI-300-102: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS (ITT POPULATION)

	150 mcg		75 mcg	
	Grastofil/Neupogen (N = 18)	Neupogen/Grastofil (N = 18)	Grastofil/Neupogen (N = 18)	Neupogen/Grastofil (N = 19)
Age (years)	37.0 (21.0 to 49.0)	29.0 (19.0 to 41.0)	24.5 (21.0 to 52.0)	23.0 (19.0 to 35.0)
Gender, no (%)				
Male	13 (72.22)	13 (72.22)	10 (55.56)	12 (63.16)
Female	5 (27.78)	5 (27.78)	8 (44.44)	7 (36.84)
Ethnicity[a]				
Caucasian, n (%)	71 (97.3)			
Other, n (%)	2 (2.7)			
Height (cm)	177.0 (163.0 to 196.0)	179.5 (167.0 to 193.0)	175.5 (153.0 to 186.0)	173.0 (163.0 to 183.0)
Body weight (kg)	77.0 (65.0 to 110.0)	69.0 (54.0 to 98.0)	71.0 (51.0 to 85.0)	70.0 (51.0 to 84.0)

	150 mcg		75 mcg	
	Grastofil/Neupogen (N = 18)	Neupogen/Grastofil (N = 18)	Grastofil/Neupogen (N = 18)	Neupogen/Grastofil (N = 19)
BMI (kg/m^2)	24.3 (20.6 to 29.8)	21.2 (17.8 to 28.4)	23.2 (18.7 to 25.6)	22.6 (18.9 to 26.5)
Oral body temperature (^{o}C)	36.3 (35.3 to 36.7)	36.2 (35.3 to 37.0)	36.3 (34.6 to 36.9)	36.3 (35.0 to 36.8)

BMI = body mass index; ITT = intention-to-treat.
[a] Ethnicity data unavailable by study arm.
Note: Except where indicated otherwise, values are the median (range) is presented.
Source: Clinical Study Report KWI-300-102, Tables 89–93, 100.

Overall, the physical characteristics (e.g., height, weight, BMI, oral body temperature) were well-balanced between the four groups. The 150 mcg group — in particular, the Grastofil/Neupogen group — had slightly older subjects and more male subjects. However, considering this was a crossover study, the potential for bias was low.

Concomitant Conditions and Medications: All subjects had [redacted] baseline results at screening except [redacted] subject with [redacted] (see Clinical Study Report KWI-300-102, Table 23). A total of [redacted] subjects presented with abnormal findings as defined by ECG (see Clinical Study Report KWI-300-102, Table 24). All of these were classified by the investigators as not clinically relevant.

Concomitant medications in the ITT population were taken by [redacted] subjects in study group T150/R150, [redacted] subjects in study group R150/T150, [redacted] subjects in study group T75/R75, and [redacted] subjects in study group R75/T75 (Clinical Study Report KWI-300-102, Table 108). Concomitant medications were taken for the following reasons: [redacted], and other indications occurring infrequently (Clinical Study Report KWI-300-102, Table 26).

Subject Disposition

From a total of 78 screened subjects, five were not eligible for randomization into this trial. Among the remaining 73 healthy subjects (ITT population), 5 had to be excluded from the PP population (infection: two subjects; missing ANC value at study day 8: two subjects; voluntary withdrawal of consent: one subject discontinued), leaving a group of 68 subjects for the PP population. The analyzed safety population included 73 subjects and was identical to the ITT population.

TABLE 15: STUDY KWI-300-102: SUMMARY OF SUBJECT DISPOSITION

Disposition	KWI-300-102			
	150 mcg		75 mcg	
	Grastofil/ Neupogen	Neupogen/ Grastofil	Grastofil/ Neupogen	Neupogen/ Grastofil
Screened, N	78			
Randomized, N	18	18	18	19
Discontinued, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal due to SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up, N (%)	[redacted]	[redacted]	[redacted]	[redacted]

Disposition	KWI-300-102			
	150 mcg		75 mcg	
	Grastofil/ Neupogen	Neupogen/ Grastofil	Grastofil/ Neupogen	Neupogen/ Grastofil
Intention-to-treat, N	[redacted]	[redacted]	[redacted]	[redacted]
Per-protocol, N	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]	[redacted]

SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Excluded 1 subject due to major protocol violation.
[b] Excluded 1 subject due to major protocol violation and 1 discontinued subject (withdrawal of consent).
[c] Excluded 2 subjects due to major protocol violation.
Source: Clinical Study Report KWI-300-102, Tables 10-12, 130, 131.

Efficacy/PD Results

ANC C_{max} After Single Dose: The primary efficacy or PD end point was the peak ANC count (C_{max}) after a single dose of subcutaneously administered filgrastim (150 mcg or 75 mcg). Results of ANOVA showed that for both the PP AND ITT populations, for the 150 mcg dose, the 90% CI for the percentage ratio (Grastofil/Neupogen) of geometric means for ANC C_{max} was 91.9% to 101.0%, enclosed within the equivalence margin (Table 16). For the 75 mcg dose, the 90% CI was 87.9% to 96.2%; although it did not cross 100%, it was within the equivalence margin (Table 17).

As part of post-hoc analyses, the 95% CI for the ratio (Grastofil/Neupogen) of geometric means for ANC C_{max} for the 150 mcg and the 75 mcg were also contained within the predefined equivalence margin (PP: 91.02% to 101.93% and 87.12% to 97.07%, respectively; ITT: [redacted] and [redacted], respectively) (Table 16 and Table 17).

TABLE 16: STUDY KWI-300-102: ANC C_{MAX} AFTER A SINGLE SUBCUTANEOUS INJECTION OF 150 MCG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

End Point		Grastofil 150 mcg	Neupogen 150 mcg	% Ratio of Geometric Means	90% CI	95% CI[a]	*P* > [t]
PP Population							
ANC C_{max} (cells × 10^9/L)	N	35	35	96.3	91.9 to 101.0	91.02 to 101.93	0.1874
	Mean	19.04	19.59				
	SD	3.83	3.29				
	Minimum	11.76	12.25				
	Median	20.00	19.99				
	Maximum	26.53	25.75				
ITT Population							
ANC C_{max} (cells × 10^9/L)	N	36	36	95.3	ND	[redacted]	[redacted]
	Mean	18.88	19.65				
	SD	3.89	3.26				
	Minimum	11.76	12.25				
	Median	19.92	20.12				
	Maximum	26.53	25.75				

ANC = absolute neutrophil count; CI = confidence interval; C_{max} = peak concentration; CTD = common technical document; ITT = intention-to-treat; ND = not determined; PP = per-protocol; SD = standard deviation.
[a] Post-hoc analysis.
Source: CTD 2.7.3, Tables 2.7.3–8, 2.7.3–9; Clinical Attachment 1, p. 14 and 20.

TABLE 17: STUDY KWI-300-102: ANC C_{MAX} AFTER A SINGLE SUBCUTANEOUS INJECTION OF 75 MCG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

End Point		Grastofil 75 mcg	Neupogen 75 mcg	% Ratio of Geometric Means	90% CI	95% CI[a]	*P* > [t]
PP Population							
ANC C_{max} (cells × 10^9/L)	N	33	33	92.0	87.9 to 96.2	87.12 to 97.07	0.0035
	Mean	17.13	18.60				
	SD	3.74	4.11				
	Minimum	10.50	12.72				
	Median	16.61	18.32				
	Maximum	26.01	32.05				
ITT Population							
ANC C_{max} (cells × 10^9/L)	N	37	36	93.2	ND	[redacted]	[redacted]
	Mean	17.25	18.44				
	SD	3.56	3.97				
	Minimum	10.50	12.72				
	Median	17.03	17.78				
	Maximum	26.01	32.05				

ANC = absolute neutrophil count; CI = confidence interval; C_{max} = peak concentration; CTD = common technical document; ITT = intention-to-treat; ND = not determined; PP = per-protocol; SD = standard deviation.
[a] Post-hoc analysis.
Source: CTD 2.7.3, Tables 2.7.3–10, 2.7.3–11; Clinical Attachment 1, p. 11 and 17.

Other ANC Results: For the post-hoc analysis, the 95% CIs for the ratios (Grastofil/Neupogen) of geometric means for both the PP and ITT populations for the 150 mcg dose were also calculated for ANC $AUC_{0\text{-}72}$ (PP: 92.97% to 102.64%; ITT: [redacted], Table 18), both of which were enclosed in the equivalence margin. Similarly, for the 75 mcg dose, the 95% CIs for ANC $AUC_{0\text{-}72}$ for both populations were also contained within the equivalence margin (PP: 91.08% to 98.98%; ITT: [redacted], Table 19). Finally, for the parameter of ANC $AUC_{0\text{-}inf}$, the 95% CIs were contained within the 80% to 125% acceptance interval (150 mcg: [redacted]; 75 mcg: [redacted], Table 20).

TABLE 18: STUDY KWI-300-102: ANC $AUC_{0\text{-}72}$ AFTER SINGLE SUBCUTANEOUS INJECTION OF 150 MCG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

End Point		Grastofil (N = 35)	Neupogen (N = 35)	% Ratio of Geometric Means	95% CI[a]	*P* > [t]
PP Population						
ANC $AUC_{0\text{-}72}$ (cells × 10^9*min/L)	N	35	35	97.7	92.97 to 102.64	0.3420
	Mean	43,209.3	43,979.6			
	SD	7,921.5	6,866.4			
	Minimum	24,674.0	30,334.1			
	Median	41,269.8	43,898.5			
	Maximum	55,836.6	56,331.0			
ITT Population						
ANC $AUC_{0\text{-}72}$ (cells × 10^9*min/L)	N	35	36	[redacted]	[redacted]	[redacted]
	Mean	43,209.3	44,046.9			
	SD	7,921.5	6,779.6			
	Minimum	24,674.0	30,334.1			

End Point		Grastofil (N = 35)	Neupogen (N = 35)	% Ratio of Geometric Means	95% CI[a]	*P* > [t]
	Median	41,269.8	44,078.3			
	Maximum	55,836.6	56,331.0			

ANC = absolute neutrophil count; AUC_{0-72} = area under the curve from 0 to 72 hours; CI = confidence interval; CTD = common technical document; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
[a] Post-hoc analysis.
Source: CTD 2.7.3, Tables 2.7.3–8, 2.7.3–9; Clinical Attachment 1, p. 12 and 18.

TABLE 19: STUDY KWI-300-102: ANC AUC_{0-72} AFTER SINGLE SUBCUTANEOUS INJECTION OF 75 MCG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP POPULATION)

End Point		Grastofil (N = 33)	Neupogen (N = 33)	% Ratio of Geometric Means	95% CI[a]	*P* > [t]
PP Population						
ANC AUC_{0-72} (cells × 10^9*min/L)	N	33	33	95.0	91.08 to 98.98	0.0162
	Mean	35,076.8	37,009.8			
	SD	6,526.3	7,622.5			
	Minimum	21,989.0	25,854.5			
	Median	34,337.2	34,306.3			
	Maximum	49,218.0	58,019.7			
ITT Population						
ANC AUC_{0-72} (cells × 10^9*min/L)	N	36	36	[redacted]	[redacted]	[redacted]
	Mean	35,373.4	36,931.6			
	SD	6,398.8	7,339.4			
	Minimum	21,989.0	25,854.5			
	Median	34,857.1	34,406.6			
	Maximum	49,218.0	58,019.7			

ANC = absolute neutrophil count; AUC_{0-72} = area under the curve from 0 to 72 hours; CI = confidence interval; CTD = common technical document; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
[a] Post-hoc analysis.
Source: CTD 2.7.3, Tables 2.7.3–10, 2.7.3–11; Clinical Attachment 1, p. 9 and 15.

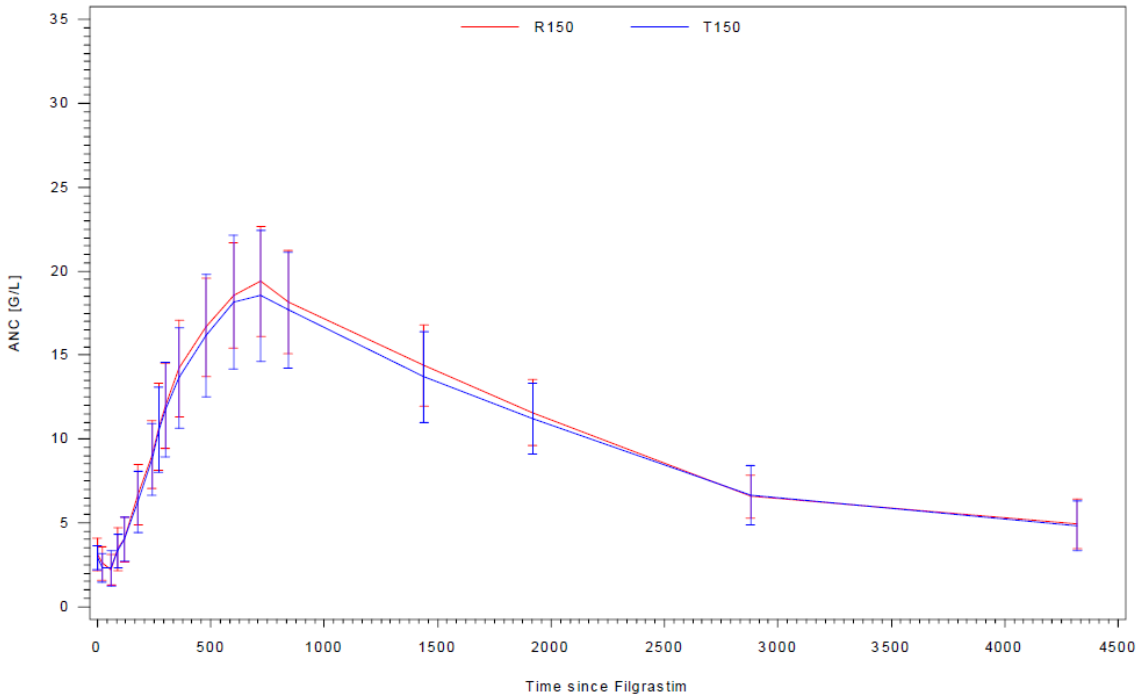
TABLE 20: STUDY KWI-300-102: ANC AUC_{0-INF} ANALYZED BY ANALYSIS OF VARIANCE (ITT POPULATION)

	Dose	Grastofil	Neupogen	% Ratio of Geometric Means	95% CI[a]	*P* > [t]
	N	[redacted]	[redacted]			
ANC AUC_{0-inf} (cells × 10^9*min/L)	150 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	N	[redacted]	[redacted]			
	75 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANC = absolute neutrophil count; ANOVA = analysis of variance; AUC_{0-inf} = area under the curve from 0 extrapolated to infinity; ITT= intention-to-treat.
Source: Clinical Attachment 1, p. 16 and 19.

The mean ANC-time profile following a single 150 mcg subcutaneous dose of Grastofil and Neupogen is shown in Figure 2. The profile for the 75 mcg dose was similar (not shown).

FIGURE 2: STUDY KWI-300-102: MEAN ANC-TIME PROFILE FOLLOWING A SINGLE SUBCUTANEOUS INJECTION OF 150 MCG OF GRASTOFIL OR NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS (ITT POPULATION)



ANC = absolute neutrophil count; G/L = grams per litre; ITT = intention-to-treat; R = Grastofil; T = Neupogen.
Source: Clinical Study Report KWI-300-102, Appendix 12, Figure 18.

Overall, all PD end points investigated for biosimilarity of the test product (Grastofil) and the reference product (Neupogen) met the regulatory requirements on the 90% and 95% CIs, which were within the predefined equivalence margins. Grastofil was therefore demonstrated to be similar to Neupogen with respect to its PD effect on ANC in Study KWI-300-102.

Safety Results

There were a total of 142 AEs experienced in this study. Among them, 10 AEs were experienced prior to the first injection of study medication. The remaining 132 AEs occurred after drug administration (treatment-emergent), mostly classified as mild and moderate AEs (Table 21). No deaths occurred during this study. No discontinuations occurred as a result of TEAEs. All types of observed TEAEs have previously been described in the literature.

TABLE 21: STUDY KWI-300-102: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (SAFETY POPULATION)

	150 mcg		75 mcg		Total (N = 73)
	Grastofil[a] (N = 36)	Neupogen[b] (N = 36)	Grastofil (N = 37)	Neupogen[b] (N = 36)	
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 TEAE	11 (30.6)	11 (30.6)	21 (56.8)	26 (72.2)	48 (61.8)
Related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	150 mcg		75 mcg		Total (N = 73)
	Grastofil[a] (N = 36)	Neupogen[b] (N = 36)	Grastofil (N = 37)	Neupogen[b] (N = 36)	
Total number of SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of AEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 AE leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] As this was a crossover study design, all but one randomized subjects received Grastofil.
[b] As this was a crossover study design, all subjects received Grastofil.
Source: Clinical Study Report KWI-300-102, Tables 43–48, 133.

The most common TEAE that occurred in subjects treated with Grastofil 150 mcg (N = 36) was headache in six subjects (16.67%). In the Neupogen 150 mcg (N = 36) group, the most common TEAEs included headache in four subjects (11.1%), and back pain and dizziness each occurred in three subjects (8.3%). In the Grastofil 75 mcg (N = 37) group, the most common TEAEs included headache in seven subjects (18.9%); nasopharyngitis in four subjects (10.8%); diarrhea, back pain, injection-site hematoma each occurring in three subjects (8.1%); and abdominal pain and fatigue, each occurring in two subjects (5.4%). In subjects treated with Neupogen 75 mcg (N = 36), the most common TEAEs included headache in 11 subjects (30.6%); back pain in four subjects (11.1%); as well as fatigue, feeling hot, injection-site hematoma, nasopharyngitis, and dysmenorrhea, each occurring in two subjects (5.6%) (Clinical Study Report KWI-300-102, Table 50).

There were no SAEs reported in this study. Two severe AEs (one classified as related and one classified as not related) occurred after administration of 150 mcg and 75 mcg of Grastofil. The severe AE that was classified as related by the investigator was erythema at the injection site (150 mcg); it occurred three hours after administration and resolved after approximately one hour without intervention. The other unrelated severe AE was dizziness, which resolved the same day.

Laboratory Parameters: As with Study KWI-300-101, laboratory parameters were assessed by analyzing three different scenarios: change from baseline values prior to filgrastim administration to one day after drug exposure; change from baseline values prior to filgrastim administration to three days after drug exposure; and change from baseline screening to the final visit covering the whole study period.

In all scenarios, there was little difference between the two filgrastim products with regard to the majority of assessed laboratory parameters. The changes in laboratory values were observed in all study groups without any significant difference among the different medications administered or the dose levels of 150 mcg and 75 mcg. From a medical point of view, the observed changes were classified as not clinically relevant (Clinical Study Report KWI-300-102, Tables 62 to 64). For urinalysis, the only clinical relevant abnormality observed was positive nitrite result obtained at the end of the study in one subject ([redacted]) who was treated with Grastofil 75 mcg in period 2; the abnormality was related to painful micturition caused by cystitis (subject was given urinary antispasmodics) (Clinical Study Report KWI-300-102, Tables 26, 128).

Vitals and Echocardiogram: [redacted] subjects experienced abnormal vital signs ([redacted]) before the initiation of the first study medication, and [redacted] abnormal vital signs were observed after administration of the first study drug (Clinical Study Report KWI-300-102, Tables 76 and 87). Abnormal ECGs at the study end were observed in [redacted] subjects of the safety population. When compared with the ECG analyses at screening, there was a [redacted] in the numbers of subjects with abnormal findings at the final visit. [redacted] subjects with abnormal ECG findings at screening were negative at the end of the study, whereas [redacted] subjects with normal ECG findings at screening were abnormal at the end of study. All abnormal ECGs were classified as clinically not relevant by the investigators (Clinical Study Report KWI-300-102, Tables 77 and 78).

Local Tolerability: Local reactions in response to subcutaneous route of filgrastim administration were assessed at up to 60 minutes after drug application (Clinical Study Report KWI-300-102, Tables 51 and 52). Overall, there were no concerns regarding redness and induration at the injection site except one event in the sequence group Grastofil/Neupogen 75 mcg/75 mcg with a redness score of [redacted] and an induration score of [redacted], resulting in a mean score of 0.1 for this study group. The previously mentioned severe AE of injection-site erythema observed in one subject developed three hours after administration of filgrastim; therefore, it was not included in the analysis of local tolerability.

Similar to the assessment of local symptoms, there was reporting of subjective pain in only one treatment group (Neupogen /Grastofil 150 mcg/150 mcg).

In summary, there was little difference between the AEs experienced by subjects receiving the DP Process II Grastofil or EU-licensed Neupogen in Study KWI-300-102.

Overall, the totality of PD and safety data from Study KWI-300-102 further demonstrated that Grastofil is biosimilar to the reference filgrastim product, Neupogen.

4.2.8 KWI-300-103

a) Study Characteristics

KWI-300-103 was a repeat-dose, phase 1, randomized, double-blind, active- and placebo-controlled parallel group, single-centre study designed to assess the comparative PK/PD of Grastofil and Neupogen in healthy subjects. The primary end point was the peak ANC after the last dose of G-CSF.

TABLE 22: DETAILS FOR KWI-300 103

Characteristics		Details for KWI-300-103
Study Design	Objective	1. To assess pharmacodynamic parameters of Grastofil with respect to ANC counts 2. To assess pharmacodynamic parameters of Grastofil with respect to mobilization of $CD34^+$ cells 3. To provide information on the pharmacokinetics of Grastofil after repeat dosing
	Blinding	Double-blind
	Study period	2008–11 to 2009–06
	Study centres	Single-study centre
	Design	Equivalence; parallel study design

Characteristics		Details for KWI-300-103
Study Population	Randomized (N)	78
	Inclusion criteria	• Healthy male or female subjects, aged 18 to 55 years
	Exclusion criteria	• Blood donations during the 1 month prior to this study • Recent infection (within 1 week), as endogenous G-CSF levels increase in acute inflammation • Relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, inflammatory, or neurological diseases that may interfere with the aim of the study • Known spleen enlargement • Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general that the investigator considers may compromise the safety of the subjects • Clinically relevant abnormal laboratory values indicative of physical illness • Use of medications during 2 weeks before the start of the study that the investigator considers may affect the validity of the study, or any medication during 72 hours before study start • Drug, alcohol (> 1 drinks/day, defined according to USDA Dietary Guidelines) • Pregnancy (positive pregnancy test during screening or at baseline), lactation, or unreliable contraception in female subjects with child-bearing potential (for details refer to Section 9.5 of the CSR: Pregnancy Test — Contraception) • Symptoms of a clinically relevant illness in the 3 weeks before the first trial day • Signs of dermatitis or skin anomalies affecting the administration area and the surroundings
Drugs	Intervention	Grastofil (DP manufactured using Process [redacted]), 5 mcg/kg body weight (480 mcg filgrastim/0.5 mL in single-use pre-filled syringes) subcutaneously per day for 4 consecutive days.
	Comparator(s)	Neupogen (EU-approved), 5 mcg/kg body weight (480 mcg filgrastim/0.5 mL in single-use PFSs) subcutaneously per day for 4 consecutive days. Placebo (0.9% NaCl), 0.5 mL subcutaneously per day for 4 consecutive days
Duration	Run-in	Not applicable
	Treatment	The study duration per subject was approximately 20 days, including screening, 4 days of treatment, and post-trial examination
	Follow-up	**Post-trial examination — final visit:** 3 to 14 days after visit 3, the subjects returned to the study ward
Outcomes	Primary end point(s)	Peak ANC after the last dose of G-CSF
	Other end points	**Secondary (Pharmacodynamic)** • Absolute $CD34^+$ cell count on day 5, 24 hours after the last G-CSF dose (ANC AUC_{0-96}) **Secondary (Pharmacokinetic)**[a] • Evaluation and comparison of AUC between test and reference filgrastim medicinal products after the last dose of G-CSF administration (AUC_{ss}) • Assessment of the PK parameters (AUC_{0-24}, AUC_{inf}, C_{max}, T_{max}, $T_{1/2}$, C_L, V_d) profile of both drugs after the first dose administration on day 1 **Tertiary** • Local tolerability • General laboratory • Adverse events

Characteristics		Details for KWI-300-103
		• Vital signs
Notes	Publications	• (28, 29)

ANC = absolute neutrophil count; AUC = area under the curve; AUC_{0-24} = area under the curve from 0 to 24 hours; AUC_{0-96} = area under the curve from 0 to 96 hours; AUC_{inf} = area under the curve from 0 to extrapolated to infinity; AUC_{SS} = area under the curve at steady-state; $CD34^+$ = cluster of differentiation 34; C_L = clearance; C_{max} = peak concentration; CSR = clinical study report; DP = drug product; EU = European Union; G-CSF = granulocyte-colony stimulating factor; IV = intravenous; NaCl = sodium chloride; PFS = pre-filled syringe; PK = pharmacokinetics; $T_{1/2}$ = half-life; T_{max} = time at maximum concentration; USDA = US Department of Agriculture; V_d = volume of distribution.
[a] Results for PK parameters are presented in Section 4.3, Pharmacokinetics.

Intervention and Comparators
Subjects received 5 mcg/kg of Grastofil (DP manufactured with Process [redacted]; 480 mcg filgrastim/0.5 mL in single-use PFSs) subcutaneously per day for four consecutive days. The reference comparator was Neupogen (non-Canadian; EU-approved; 480 mcg filgrastim/0.5 mL in single-use PFSs) injected subcutaneously per day for four consecutive days. A placebo group was also included in this study; these subjects received physiological 0.9% sodium chloride solution subcutaneously per day for four consecutive days in each period.

Concomitant Medications: Prior to taking any medication within 72 hours before trial day 1, subjects were instructed to consult the study centre. Hormonal contraception in female subjects was an exception to this rule.

Outcomes
Peak Absolute Neutrophil Count After Last Dose (Peak Concentration After the Last Dose of Study Medication (Last Absolute Maximum)[$C_{max,ss}$]): The primary efficacy/PD outcome was the peak ANC after the last dose of G-CSF, through which equivalence was to be established if the 90% CI for the ratio of geometric means between Grastofil and the EU-approved Neupogen was within the predefined equivalence margin of 80% to 125%. For the assessment of ANC, samples were analyzed using automated cell counter(s) and ANC values were reported. As part of the post-hoc analysis, 95% CI of the ratio was used.

Absolute $CD34^+$ Cell Count: The key secondary efficacy end points included absolute $CD34^+$ cell count on day 5, 24 hours after the last G-CSF doses. $CD34^+$ (known as cluster of differentiation 34, or hematopoietic progenitor cell antigen CD34) is a cell surface glycoprotein expressed on hematopoietic progenitor stem cells (30). The $CD34^+$ count represents a useful marker for the selection and characterization of cells necessary for both short- and long-term engraftment of stem cells in recipients after myeloablative therapy (17). Thus, the $CD34^+$ count is the most commonly used surrogate for measurement of human progenitor cells (31). Antibodies against CD34 were used to quantify and purify these stems.

Safety: The key safety outcomes (tertiary end points) included local tolerability, general laboratory, AEs, and vital signs. AEs were coded using MedDRA Version 10.0.

Statistical Analyses

The values of the main PD (ANC: $C_{max,ss}$) and PK (area under the curve from 0 to 24 hours [AUC_{0-24}], AUC_{inf}, C_{max}, area under the curve at steady-state [AUC_{ss}]) parameters were compared between treatments using an ANOVA with the fixed factor treatment and a significance level of $\alpha = 0.05$ after logarithmic transformation of the data. A 90% CI for the ratio of geometric means (Grastofil/Neupogen) was calculated using the back-transformed (exponential) 90% CI for the least squares mean difference "Grastofil minus Neupogen". If this interval was completely contained within predefined equivalence margin, biosimilarity was postulated. The equivalence margin was set, as defined in the corresponding guidance documents, to 80% to 125% for all PD and PK parameters. The rationale for this definition of equivalence was the same for all applicable studies (see Section 4.2.5, Choice of Pharmacodynamics Equivalence Margin, for further details).

For the post-hoc analysis of the PD data as per the EMA, as described in Section 4.2.5, 95% CI was also utilized for the PD parameters.

Analysis Sets: Three analysis populations were defined:

1. **Per-protocol population**: The PP population included all randomized subjects without any major protocol deviations. The PP population was the primary analysis population for efficacy.
2. **Intention-to-treat population**: The ITT population included all randomized subjects with at least one administration of the study treatment. Subjects were analyzed according to the treatment to which they were randomized. This was the secondary analysis population for efficacy.
3. **Safety population**: The safety population included all randomized subjects with at least one administration of the study treatment. Subjects were analyzed according to the actual treatment they received. This was the primary analysis population for safety.

In this study, the ITT population was identical to the safety population.

b) Results

Baseline Characteristics

TABLE 23: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDY KWI-300-103 (ITT POPULATION)

Characteristics	Grastofil (5 mcg/kg) (N = 36)	Neupogen (5 mcg/kg) (N = 36)	Placebo (N = 6)
Age (years)	25 (19 to 48)	26 (18 to 44)	25 (20 to 31)
Gender, no (%)			
Male	18 (50)	19 (52.8)	1 (16.8)
Female	18 (50)	17 (47.2)	5 (83.3)
Ethnicity[a]			
Caucasian	75 (96.1)		
Other	3 (3.9)		
Body height (cm)	174.0 (157.0 to 200.0)	173.0 (157.0 to 189.0)	166.0 (158.0 to 182.0)
Body weight (kg)	69.2 (50.0 to 91.0)	67.5 (47.0 to 90.0)	59.0 (50.0 to 95.0)
BMI (kg/m^2)	22.2 (18.6 to 29.7)	22.9 (17.1 to 35.2)	21.0 (17.9 to 28.7)
Oral body temperature (^oC)	36.4 (35.1 to 37.0)	36.2 (34.8 to 37.1)	36.1 (35.2 to 36.6)

BMI = body mass index; ITT = intention-to-treat.

[a] Ethnicity data unavailable by study arm

Note: Except where indicated otherwise, values are the median (range) is presented.

Source: Clinical Study Report KWI-300-103, Tables 101–105 and 113.

Overall, with the exception of gender in the placebo group (N = 6), the study population was well balanced in terms of age, gender (Grastofil and Neupogen), and physical characteristics between treatment groups.

Concomitant Conditions and Medications: Except for [redacted] subjects, all subjects had normal baseline evaluation at screening ([redacted]; all of which were not considered clinically relevant.) (See Clinical Study Report KWI-300-103, Tables 23, 118.) A total of [redacted] subjects presented with abnormal findings as defined by ECG and specified by sequence group for the ITT population in Section 14.1 (Clinical Study Report KWI-300-103, Table 119). All of these were classified as not clinically relevant by the investigators.

Concomitant medications in the ITT population were taken by [redacted] subjects ([redacted]) in the Grastofil group, [redacted] subjects ([redacted]) in the Neupogen group, and [redacted] subjects ([redacted]) in the placebo group. Taken together, [redacted] out of [redacted] subjects in the ITT population were taking concomitant medications (Clinical Study Report KWI-300-103, Table 120). Concomitant medications in the ITT population were taken for the following reasons: [redacted], and other indications occurring infrequently.

Subject Disposition: From a total of 81 screened subjects, three subjects were not eligible for randomization into this trial (inclusion/exclusion criteria). Among the remaining 78 healthy subjects (ITT population), three had to be excluded (infection: two subjects; voluntary withdrawal of consent: one subject was discontinued), leaving a group of 75 subjects classified as PP population. The analyzed safety population included 78 subjects and was identical to the ITT population (Table 24). Overall, a similar number of subjects from both the Grastofil and Neupogen groups initiated and completed the study.

TABLE 24: SUMMARY OF SUBJECT DISPOSITION FOR KWI-300-103 (ITT POPULATION)

Disposition	KWI-300-103		
	Grastofil (5 mcg/kg)	Neupogen (5 mcg/kg)	Placebo
Screened, N	81		
Randomized, N	36	36	6
Discontinued, N (%)	[redacted]	[redacted]	[redacted]
Withdrawal of consent, N (%)	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	[redacted]	[redacted]	[redacted]
Withdrawal due to SAEs, N (N%)	[redacted]	[redacted]	[redacted]
Lost to follow-up, N (N%)	[redacted]	[redacted]	[redacted]
ITT, 78	[redacted]	[redacted]	[redacted]
Per-protocol, 75	[redacted]	[redacted]	[redacted]
Safety, 78	[redacted]	[redacted]	[redacted]

ITT = intention-to-treat; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] One withdrawal of consent.
[b] Excluded two subjects due to infection (both were considered as major protocol violation, and not adverse events).
Source: Clinical Study Report KWI-300-103, Tables 12 and 13.

Efficacy Results

ANC $C_{max,ss}$ After Last Dose: The primary end point was the peak ANC count ($C_{max,ss}$) after four subcutaneously administered doses of filgrastim. As the results of ANOVA showed, the 90% CI for the

percentage ratio (Grastofil/Neupogen) of geometric means for ANC $C_{max,ss}$ (day 4) was 87.3% to 103.9%, enclosed within the predefined equivalence margin (Table 25). In the post-hoc analyses, the 95% CIs for the ratio (Grastofil/Neupogen) of geometric means for ANC $C_{max,ss}$ and $C_{max,0-96}$ for both the PP and ITT populations were also contained within the equivalence margin (85.82% to 105.64% and [redacted], respectively).

TABLE 25: STUDY KWI-300-103: ANC $C_{MAX,SS}$ AND ANC $C_{MAX,0-96}$ AFTER FOUR SINGLE DAILY SUBCUTANEOUS INJECTIONS OF 5 MCG/KG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

End Point		Grastofil	Neupogen	Placebo	% Ratio of Geometric Means[a]	90% CI	95% CI[a]	*P* > [t]
PP Population								
ANC $C_{max,ss}$[b] (cells × 10^9/L)	N	35	34	6	95.2	87.3 to 103.9	85.82 to 105.64	0.3493
	Mean	30.54	32.27	4.14				
	SD	6.15	7.68	0.63				
	Minimum	19.19	20.47	3.01				
	Median	30.57	29.95	4.21				
	Maximum	46.96	51.50	4.81				
ITT Population								
ANC $C_{max,ss}$[c] (cells × 10^9/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]				
	SD	[redacted]	[redacted]	[redacted]				
	Minimum	[redacted]	[redacted]	[redacted]				
	Median	[redacted]	[redacted]	[redacted]				
	Maximum	[redacted]	[redacted]	[redacted]				
ANC $C_{max,0-96h}$ (cells × 10^9/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]				
	SD	[redacted]	[redacted]	[redacted]				
	Minimum	[redacted]	[redacted]	[redacted]				
	Median	[redacted]	[redacted]	[redacted]				
	Maximum	[redacted]	[redacted]	[redacted]				

ANC = absolute neutrophil count; CI = confidence interval; $C_{max,0-96h}$ = maximum concentration between 0 and 96 hours; $C_{max,ss}$ = peak concentration after the last dose of study medication (last absolute maximum); ITT = intention-to-treat; ND = not determined; PP = per-protocol; SD = standard deviation.

[a] Post-hoc analysis.

[b] Results for $C_{max,ss}$ are the same as $C_{max0-96h}$ (which was conducted as part of the post-hoc analysis).

[c] ANC $C_{max,ss}$ differs from ANC $C_{max,0-96h}$ because one subject voluntarily withdrew from the study prior to trial day 4; thus, data for this subject (number 23) is not included in the analyses for ANC $C_{max,ss}$.

Source: Common Technical Document 2.7.3, Tables 2.7.3–14, 2.7.3–15; Clinical Attachment 1, p. 25, 31, and 32.

ANC AUC_{0-96} After Last Dose: Although not part of the secondary end point, ANC AUC_{0-96} was also evaluated. Similar conclusions regarding biosimilarity between Grastofil and Neupogen could also be reached based on the ANC AUC profile after repeated dosing, as demonstrated by the 95% CI for both the PP *and* ITT populations being contained within the predefined equivalence margin.

TABLE 26: STUDY KWI-300-103: ANC AUC_{0-96} AFTER FOUR SINGLE DAILY SUBCUTANEOUS INJECTIONS OF 5 MCG/KG GRASTOFIL OR NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

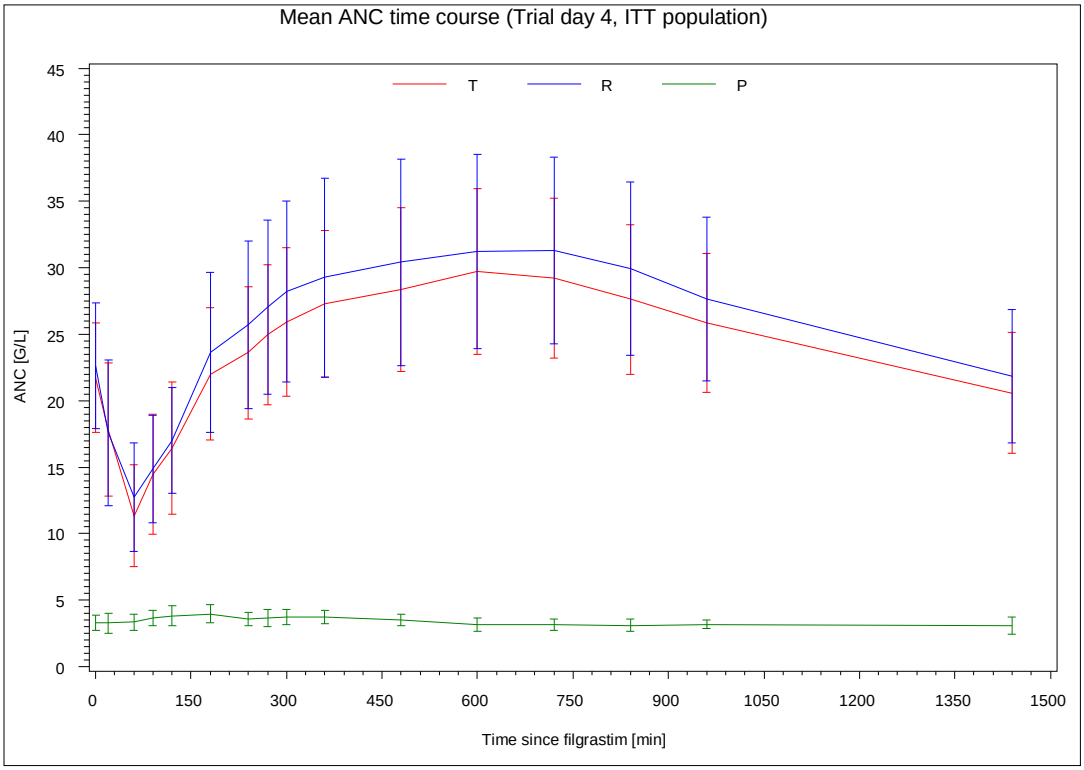
End Point		Grastofil	Neupogen	% Ratio of Geometric Means	95% CI[a]	*P* > [t]
PP Population						
ANC AUC_{0-96} (cells × 10^9*min/L)	N	[redacted]	[redacted]	95.6	88.03–103.82	[redacted]
	Mean	11,4231.65	119,436.41			
	SD	19,345.87	20,700.04			
	Minimum	[redacted]	[redacted]			
	Median	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC AUC_{0-96} (cells × 10^9*min/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Median	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; AUC_{0-96} = area under the curve from 0 to 96 hours; CI = confidence interval; CTD = common technical document; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
[a] Post-hoc analysis.
Source: CTD Module 2.7.3, Tables 2.7.3–14, 2.7.3–15; Clinical Attachment 1, p. 22, 28.

Other ANC Results: The 95% CIs for the ratios (Grastofil/Neupogen) of geometric means were also calculated for ANC $C_{max,24h}$ (PP: [redacted]; ITT: [redacted]) and ANC AUC_{0-24} (PP: [redacted]; ITT: [redacted]) (see Table 56 and Table 57 in Appendix 1). The results from both the PP and ITT populations showed that the PD parameters after a single dose of Grastofil or Neupogen were highly comparable and contained with the equivalence margin.

The mean ANC-time profile following a single 5 mcg/kg subcutaneous dose of Grastofil and Neupogen on day 4 is shown in Figure 3.

FIGURE 3: STUDY KWI-300-103: MEAN ANC-TIME PROFILE FOLLOWING A SUBCUTANEOUS INJECTION ON TRIAL DAY 4 OF 5 MCG/KG OF GRASTOFIL OR NEUPOGEN OR PLACEBO TO HEALTHY MALE AND FEMALE VOLUNTEERS (ITT POPULATION)



ANC = absolute neutrophil count; ITT = intention-to-treat; min = minimum; T = Grastofil; R = Neupogen; P = placebo.
Source: Clinical Study Report KWI-300-103, Figure 20.

Thus, in this study, the more stringent 95% CIs of the geometric mean ratios for all ANC PD parameters (for both PP *and* ITT populations) were all contained within the predefined equivalence margin, therefore demonstrating similarity between Grastofil and Neupogen.

Absolute CD34$^+$ Cell Count 24 Hours After Last Dose: Although absolute CD34$^+$ cell count was considered a secondary end point in this study, descriptive statistics showed there was a very similar baseline level of CD34$^+$ cell count, a similar increase in the mean CD34$^+$ cell count, and similar inter-individual variability when comparing Grastofil and Neupogen after four daily doses of G-CSF (Table 27). Although a slightly higher CD34$^+$ count was observed in the Grastofil group after baseline adjustment, the range of CD34$^+$ count for Grastofil ([redacted]) was comparable to that of Neupogen ([redacted]) (ITT population). The median value was comparable between groups ([redacted], respectively; Table 27).

Overall, these results demonstrated there was a robust [redacted] fold increase in CD34$^+$ cell count for both treatments and, therefore, an excellent signal-over-noise ratio, which rules out that these findings were due to chance. The highly comparable results in CD34 mobilization between Grastofil and Neupogen suggested these products had a similar action.

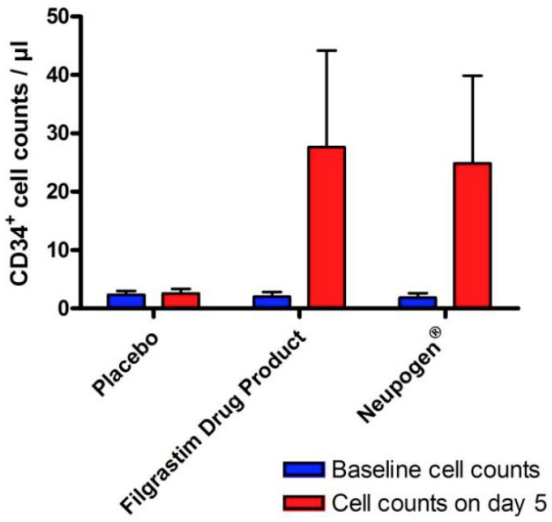
TABLE 27: STUDY KWI-300-103: COMPARISON OF THE MOBILIZATION OF CD34$^+$ CELLS PRIOR TO AND FOLLOWING THE MULTIPLE-DOSE ADMINISTRATION OF 5 MCG/KG DOSE GRASTOFIL AND NEUPOGEN (ITT POPULATION)

		N	Mean	SD	CV	Min	Median	Max
CD34$^+$ at baseline	Grastofil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Neupogen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CD34$^+$ at day 5	Grastofil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Neupogen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline corrected CD34$^+$ at day 5	Grastofil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Neupogen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANC = absolute neutrophil count; CD34+ = cluster of differentiation 34; CV = coefficient of variation ; ITT = intention-to-treat; max; min = minimum; SD = standard deviation.
Source: Common Technical Document 2.7.3, Table 2.7.3-16.

A graphical representation of CD34$^+$ cell counts on day 1 (baseline) and day 5 (24 hours after last filgrastim dose) for Grastofil, Neupogen, and placebo are presented in Figure 4.

FIGURE 4: STUDY KWI-300-103: MEAN CD34$^+$ CELL COUNT ON DAY 1 AND DAY 5 FOLLOWING FOUR SUBCUTANEOUS INJECTIONS OF 5 MCG/KG OF GRASTOFIL (FILGRASTIM DRUG PRODUCT) OR NEUPOGEN OR PLACEBO TO HEALTHY VOLUNTEERS (PP POPULATION)



CD34+ = cluster of differentiation 34; PP = per-protocol.
Source: Common Technical Document 2.7.3, Figure 2.7.3-9; Clinical Study Report KWI-300-103, Figure 3.

As reported in the literature, the mechanism of action and pharmacological properties of recombinant human G-CSF are fundamentally the same in healthy volunteers and neutropenic patients and, furthermore, the bone marrow of healthy volunteer subjects compared with that of myelosuppressed patients is fully responsive to filgrastim treatment (17, 32). This suggests that comparability studies in healthy subjects may be expected to be more sensitive than studies in neutropenic patients at ascertaining differences between the PD effects of test and reference medicinal products for filgrastim. Thus, the lack of differences in CD34$^+$ mobilization between Grastofil and Neupogen in healthy subjects

suggests a comparable effect in $CD34^+$ mobilization can be expected with these two filgrastim medicinal products in a clinical setting.

In summary, the aforementioned data demonstrated the biosimilarity of Grastofil to Neupogen when considering the primary and secondary PD end points as specified in Study KWI-300-103.

Safety Results

There were a total of 201 TEAEs involving 65 different subjects (Table 28). There were a total of 141 drug-related TEAEs involving 58 subjects. This included 71 related TEAEs in 28 subjects in the Grastofil group; 65 related TEAEs observed in 27 subjects in the Neupogen group; and five related TEAEs observed in three subjects in the placebo group (Clinical Study Report KWI-300-103, Table 49). No deaths occurred during this study. No discontinuations occurred as a result of TEAEs. (Two subjects were excluded from the PK/PD analysis due to infection, but these subjects were not discontinued; exclusions of those two subjects and the subject who withdrew consent did not affect the statistical power necessary to document study end points. [See Clinical Study Report KWI-300-103, Section 9.8.2 for details].) All types of observed AEs — except the non-medication–related apicoectomy — have been previously described in the literature.

With regard to the severity of the symptoms, the numbers of drug-related AEs were similar between Grastofil and Neupogen, and most of these were classified as a mild or moderate TEAE.

TABLE 28: STUDY KWI-300-103: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (SAFETY POPULATION)

	Grastofil[a] (N = 36)	Neupogen[b] (N = 36)	Placebo (N = 6)	Total (N = 78)
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Related	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 TEAE	28 (77.8)	31 (86.1)	6 (100)	65 (83.3)
Related	[redacted]	[redacted]	[redacted]	[redacted]
Total number of SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]
Total number of AEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 AE leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 severe AE	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] As this was a crossover study design, all but one randomized subjects received Grastofil.
[b] As this was a crossover study design, all subjects received Grastofil.
Source: Clinical Study Report KWI-300-103, Tables 47–49.

The most common TEAEs that occurred in Study KWI 300-103 in subjects treated with Grastofil (N = 36) included back pain in 24 subjects (66.7%); headache in 14 subjects (38.9%); and pharyngolaryngeal pain in three subjects (8.3%); as well as rhinitis, neck pain, and myalgia, each occurring in two subjects (5.6%). In subjects treated with Neupogen (N = 36), the most common TEAEs included: back pain in 21 subjects (58.3%); headache in 16 subjects (44.4%); fatigue and arthralgia, each occurring in three subjects (8.3%); and nasopharyngitis and pain in the extremities, each occurring in two subjects (5.6%). In subjects

treated with placebo (N = 6), the most common TEAEs included headache in three subjects (50.0%); and back pain and dysmenorrhea, each occurring in two subjects (33.3%).

There were no SAEs in this study. However, [redacted] severe AEs (SAEs) were reported. These included [redacted] AEs in [redacted] subjects in the Grastofil group ([redacted] AE in [redacted] was unrelated); two AEs in two subjects in the Neupogen group (one AE in one subject was unrelated); and one AE in one subject in the placebo group (unrelated) (Clinical Study Report KWI-300-103, Tables 46 and 48). Independent of causality, all SAEs resolved with full recovery of subjects at the final examination.

To address the issue of possible local toxicities associated with SC administration, local skin reactions and induration were assessed by the investigator. Results showed that while the first administration of filgrastim products (both Grastofil and Neupogen) was associated with increased local redness (comparable between treatments), these symptoms subsided rapidly after administration, and similar or lower levels were seen in trial days 2 through 4. These data indicate that repeated administration of Grastofil or Neupogen is not prone to cumulative skin toxicity, but can be safely administered on four consecutive days without escalating skin reaction (Clinical Study Report KWI-300-103, Table 51). With regard to induration, the majority of applications did not result in any induration at all and, for those indurations that did occur, all were mild in severity (Clinical Study Report KWI-300-103, Table 52). These data indicate that repeated administration of both Grastofil and Neupogen is safe without increasing skin reactions. Finally, there was reporting of subjective pain only in single cases. In most subjects, subjective pain was not reported at all (Clinical Study Report KWI-300-103, Table 53).

Laboratory Parameters: The baseline screening results indicated a balanced study population in all three study groups. The vast majority of laboratory parameters analyzed showed no clinically relevant fluctuations larger than those commonly observed in longitudinal studies monitoring laboratory values, i.e., oscillations in the magnitude of a few percentage points. This observation applied to the whole array of laboratory tests, with the exception of the parameters below, which were directly related to the application of filgrastim, independent of the treatment with either filgrastim product.

In terms of alkaline phosphatase, the mean increase (average [redacted]) was essentially identical in both filgrastim groups. The increase was transient as the levels declined at the final visit. ALP level was not affected in the placebo group (Clinical Study Report KWI-300-103, Table 72).

The time course of D-dimer was subject to variation in a range not considered of any clinical significance. Briefly, in each of the three treatment groups the D-dimer values were skewed by a single individual (Grastofil: subject [redacted] [abnormally [redacted] value at baseline due to hemolysis [redacted] rapidly to normal values within two days]; Neupogen: subject [redacted] [due to an [redacted], subject was excluded from PP population due to [redacted]]; placebo: subject [redacted] [transient [redacted]]). All these observations were classified as not clinically relevant or were attributable to clinical events.

One of the safety parameters known to respond to filgrastim exposure in humans is LDH, with changes occurring as a transient phenomenon in clinical investigations. Similar to ALP, mean LDH values increased after four doses of filgrastim but declined at the final visit, indicating toward baseline levels (Clinical Study Report KWI-300-103, Table 72).

Considering the liver enzymes gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), the initial mean decreased in all three parameters from screening

to trial day [redacted] (range of the mean values: [redacted] to [redacted]) and from screening to trial day [redacted] (range of the mean values: [redacted] to [redacted]) and was balanced by a minor [redacted] observed at the final visit with a few exceptions (range of the mean values: [redacted] to [redacted]). Therefore, these liver enzymes did not suggest liver toxicity in the overall picture; among the different filgrastim groups receiving the Grastofil and Neupogen; or when comparing the filgrastim groups with the placebo group over time.

Overall, the comparison of the laboratory baseline screening with the measurements obtained at the final visit indicates the transient nature of the changes observed in these specific parameters. From a medical point of view, the observed changes were classified as not clinically relevant by the investigators.

It should be noted that on an individual basis, there were [redacted] subjects who had laboratory values outside the normal range. However, with the exception of [redacted] laboratory values ([redacted] and [redacted]) out of normal ranges in [redacted] (subject [redacted], [Neupogen group] excluded from the PP population due to [redacted]), none of the observed changes that fell out of normal ranges were classified as clinically relevant by the investigators.

Vitals and Echocardiogram: One subject receiving Neupogen had abnormal vital signs (elevated body temperature) and, as indicated, this subject was excluded from [redacted] analysis.

Abnormal ECGs at study completion were observed in [redacted] subjects of the safety population: Grastofil: [redacted] out of [redacted] subjects; Neupogen: [redacted] out of [redacted] subjects; Placebo: [redacted] out of [redacted] subjects (Clinical Study Report KWI-300-103, Table 89). When compared with the ECG analyses at screening, there was a marginal change in the numbers of subjects with abnormal findings at the final visit ([redacted] versus [redacted] subjects). Among the [redacted] subjects with abnormal ECG findings at screening, [redacted] subjects were negative at the end of the study, whereas [redacted] subjects presented with abnormal ECG findings throughout the study. In contrast, [redacted] subjects with normal ECG findings at screening were abnormal at the end of study. There was no difference in the number of subjects with abnormal ECG findings at screening between the treatment groups receiving filgrastim (Neupogen: [redacted] subjects, Grastofil: [redacted] subjects) or with abnormal ECG findings at final visit (Neupogen: [redacted] subjects, Grastofil: [redacted] subjects). In the placebo group, [redacted] subjects had abnormal ECG findings either at screening or at final visit. All abnormal ECG findings at final visit were classified as not clinically relevant by the investigators.

Thus, the numbers of AEs were similar between the Grastofil and Neupogen groups. There were no new safety concerns or side effects associated with the repeated administration of Grastofil over Neupogen.

In summary, the combined PD and safety results from this subcutaneous, multiple-dose study further substantiate the claim that Grastofil and Neupogen are biosimilar.

4.2.9 GCSF-SUIN-05SB01-3FA-(5)

a) Study Characteristics

GCSF-SUIN-05SB01-3FA-(5) was a double-blind, single-dose, active-controlled, randomized, comparative three-way crossover PK/PD, phase 1 study designed to, in part, bridge the clinical data between Grastofil DP manufactured using new process [redacted] (commercial scale process intended for the Canadian market; using DS Process [redacted] that has improved purification process over the DS Process [redacted]/DP Process [redacted] Grastofil) and EU-approved Neupogen, and to demonstrate similarity between US-licensed Neupogen and EU-approved Neupogen. The primary outcome was to demonstrate equivalence between Grastofil,

EU-approved Neupogen, and US-licensed Neupogen for the ANC parameters of average concentration over a time interval (AUC_t) and C_{max}.

TABLE 29: DETAILS FOR GCSF-SUIN-05SB01-3FA-(5)

Characteristics		Details for GCSF-SUIN-05SB01-3FA-(5)
Study Design	Objective	To assess and compare Grastofil and two reference comparators, US-licensed Neupogen (Amgen Manufacturing, Limited) and EU-approved Neupogen (Amgen Europe B.V.)
	Blinding	Double-blinded
	Study period	2012–02 to 2012–05
	Study centres	Single-study centre
	Design	Equivalence, 3-way crossover
Study Population	Randomized (N)	48
	Inclusion criteria	• Healthy, non-smoker, adult male and female individuals, aged 18 to 55 years • Weight not exceeding 100 kg • BMI between 18.5 to 29.9 kg/m^2 • Absence of significant disease or clinically significant abnormal laboratory values • Provided written informed consent
	Exclusion criteria	• A history or presence of significant asthma; chronic bronchitis; seizure; diabetes; migraine; hypertension; cardiovascular, pulmonary, or neurological conditions; chronic psychiatric conditions; hepatic, renal, hematopoietic, or gastrointestinal or ongoing infectious diseases; or any other significant abnormality as evidenced by a medical history and physical examination • A positive screen for hepatitis B surface antigens, hepatitis C antibodies, HIV, or syphilis • Significant abnormality found on the ECG • Requiring other medication at the time of the study; oral, injectable, or topical contraceptives and contraceptive implants were permitted • History of drug or alcohol abuse within the last 6 months • Any known enzyme-inducing or -inhibiting drug taken within 30 days before the study • History of anaphylaxis, idiopathic urticaria, undiagnosed wheezing • Sickle cell disorder • Use of lithium within 2 weeks of the beginning of the study, or a plan to use lithium during the study or within 2 weeks after the end of the study.
Drugs	Intervention	Grastofil (DP manufactured with Process III from DS Process IX), single fixed dose of 300 mcg (300 mcg filgrastim/0.5 mL in single-use PFSs) administered SC
	Comparator(s)	Neupogen (EU-approved), single fixed dose of 300 mcg (300 mcg filgrastim/0.5 mL in single-use PFSs) administered SC Neupogen (US-licensed), single fixed dose of 300 mcg (300 mcg filgrastim/0.5 mL in single-use PFSs) administered SC
Duration	Run-in	Not applicable
	Treatment	The duration of the study was approximately 67 days, which included the duration covering three periods of the study with a washout period of 4 weeks between doses and the collection of a blood sample for immunogenicity testing at 240 hours (10 days) post-dose in each period.
	Follow-up	Post-study monitoring was performed for 2 weeks post-study and, subsequently, passive safety surveillance was performed for the duration of 4 months.
	Treatment sequence	• US-licensed Neupogen: EU-approved Neupogen: Grastofil • EU-approved Neupogen: US-licensed Neupogen: Grastofil • US-licensed Neupogen: Grastofil: EU-approved Neupogen

Characteristics		Details for GCSF-SUIN-05SB01-3FA-(5)
		• Grastofil: EU-approved Neupogen: US-licensed Neupogen • Grastofil: US-licensed Neupogen: EU-approved Neupogen • EU-approved Neupogen: Grastofil: US-licensed Neupogen
Outcomes	Primary end point(s)	For both the primary pharmacodynamic end points (ANC data) and primary pharmacokinetic end points (filgrastim data)[a]: 1. The 90% CI of the relative mean AUC_t and C_{max} of the test (T) to the US reference (R1) formulation should be within 0.80 to 1.25. 2. The 90% CI of the relative mean AUC_t and C_{max} of the test (T) to the EU reference (R2) formulation should be within 0.80 to 1.25. 3. The 90% CI of the relative mean AUC_t and C_{max} of the US reference (R1) formulation to the EU reference (R2) formulation should be within 0.80 to 1.25.
	Other end points	**Secondary** Pharmacokinetic parameter of $T_{1/2}$, determined using filgrastim data[a] **Tertiary** • Pharmacokinetic end points of AUC_{inf}, T_{max} and K_{el} parameters, determined using filgrastim data[a] • Safety ○ adverse events ○ laboratory tests ○ vital signs ○ immunogenicity
Notes	Publications	(28, 29)

ANC = absolute neutrophil count; AUC_{inf} = area under the curve from 0 extrapolated to infinity; AUC_t = ????; BMI = body mass index; CI = confidence interval; C_{max} = peak concentration; DP = drug product; DS = drug substance; ECG = echocardiogram; EU = European Union; K_{el} = elimination rate constant; PFS = pre-filled syringe; PK = pharmacokinetics; SC = subcutaneously; $T_{1/2}$ = half-life; T_{max} = time of maximum concentration.

[a] Results for PK parameters are presented in Section 4.3, Pharmacokinetics.

Intervention and Comparators

Patients received a single fixed 300 mcg dose of Grastofil (DP manufactured using Process III from DS manufactured using Process IX; 300 mcg filgrastim/0.5 mL in single-use PFSs) administered subcutaneously. The reference products were a single fixed 300 mcg dose of Neupogen (non-Canadian; EU-approved/sourced; 300 mcg filgrastim/0.5 mL in single-use PFSs) and Neupogen (non-Canadian; US-licensed/sourced; 300 mcg filgrastim/0.5 mL in single-use PFSs) administered subcutaneously.

Concomitant Medications: With the exception of [redacted], no [redacted], [redacted] or [redacted] including [redacted] were allowed within the two weeks prior to commencement of the study. In addition, use of [redacted] was not permitted during the study, nor for up to two weeks after the end of the study. During the course of the study, only [redacted] and medications [redacted] were permitted.

Outcomes

Peak ANC (C_{max}): The key efficacy/PD outcome was peak ANC after a single dose of G-CSF, through which equivalence was to be established if the 90% CI for the treatment difference between each of the following was within the predefined equivalence margin of 80% to 125%:

1. Grastofil and the EU-approved Neupogen
2. Grastofil and the US-licensed Neupogen
3. US-licensed Neupogen and the EU-approved Neupogen.

For the assessment of ANC, samples were analyzed using an automated cell counter(s) and ANC values were reported. As part of the post-hoc analysis, 95% CI of the ratio was used.

ANC AUC_t: The co-primary efficacy/PD outcome was the ANC AUC_t after a single dose of G-CSF, through which equivalence was to be established if the 90% CI for the treatment difference between each of the following was within the predefined equivalence margin of 80% to 125%:

1. Grastofil and the EU-approved Neupogen
2. Grastofil and the US-licensed Neupogen
3. US-licensed Neupogen and the EU-approved Neupogen.

As part of the post-hoc analysis, 95% CI of the ratio was used.

Immunogenicity: For immunogenicity testing, blood samples were drawn prior to [redacted] ([redacted] hours) and [redacted] hours ([redacted] days) after [redacted], for each study period.

Other Safety: Other key safety outcomes (tertiary end points) included general laboratory, AEs, and vital signs.

Statistical Analyses

ANOVA was performed on the log-transformed AUC_t and C_{max} parameters for ANC. The ANOVA included sequence, subjects nested within sequence, period and treatment as factors. The significance of the sequence effect was tested using the subjects nested within sequence as the error term. For each of the comparisons, Grastofil to US-licensed Neupogen, Grastofil to EU-approved Neupogen and US-licensed Neupogen to EU-approved Neupogen, PK and PD comparability was demonstrated when the 90% CIs of the relative mean for the log-transformed AUC_t and C_{max} primary end point parameters for filgrastim and ANC were contained within the acceptance range of 80% to 125%. The rationale for this definition of equivalence was the same for all applicable studies (See Section 4.2.5, Choice of Pharmacodynamics Equivalence Margin, for further details.)

In addition, the 95% CI for the ratio between the test and reference means was constructed for ANC.

Analysis Sets:

- **PK/PD subset** was used for efficacy (PK/PD) evaluation, including 45 subjects completing at least two study periods. This population is representative of the PP population.
- **Safety analysis set** was used for safety evaluations, including all 48 randomized subjects with at least one administration of the study treatment.
- **Intention-to-treat:** In accordance with the final study protocol, the original planned and assessed populations did not include an ITT population. However, to also assess the ITT population, a supplementary statistical analysis plan was developed. In accordance with this plan, the ITT population was defined for PD end points only and this population included all randomized subjects

who received at least one of the investigational treatments and had at least one post-dose PD sample measured.

b) Results

Baseline Characteristics

TABLE 30: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDY GCSF-SUIN-05SB01-3FA-(5) BY DOSING SEQUENCE (SAFETY ANALYSIS SET)

Characteristics	G-US-EU	G-EU-US	US-G-EU	US-EU-G	EU-G-US	EU-US-G	Total
N	8	8	8	8	8	8	48
Age (years)	43.5 (28 to 49)	41.0 (29 to 50)	47.5 (43 to 53)	43.0 (23 to 48)	34.0 (18 to 52)	36.0 (19 to 53)	42.0 (18 to 53)
Gender, n (%)							
Male	5 (62.5)	8 (100)	6 (75.0)	6 (75.0)	5 (62.5)	2 (25.0)	32 (66.7)
Female	3 (37.5)	0 (0)	2 (25.0)	2 (25.0)	3 (37.5)	6 (75.0)	16 (33.3)
Ethnicity, n (%)							
Caucasian	5 (62.5)	4 (50.0)	7 (87.5)	3 (37.5)	3 (37.5)	4 (50.0)	26 (54.2)
Hispanic or Latino	2 (25.0)	2 (25.0)	0 (0.0)	4 (50.0)	5 (62.5)	2 (25.0)	15 (31.3)
Other	1 (12.5)	2 (25.0)	1 (12.5)	1 (12.5)	0 (0.0)	2 (25.0)	7 (14.5)
Height (cm)	168.0 (159.5 to 182.5)	172.5 (165.0 to 185.0)	173.5 (154.5 to 195.0)	167.5 (149.0 to 187.0)	172.5 (154.0 to 186.5)	168.0 (156.5 to 187.0)	169 (149.0 to 195.0)
Body weight (kg)	80.0 (63.4 to 92.7)	72.7 (63.7 to 94.9)	81.9 (62.6 to 107.7)	72.7 (63.6 to 99.6)	78.1 (59.0 to 93.2)	67.1 (51.2 to 97.1)	73.5 (51.2 to 108)
BMI (kg/m^2)	27.2 (24.2 to 29.0)	25.0 (22.8 to 29.4)	26.6 (23.2 to 29.7)	26.6 (23.6 to 28.6)	24.7 (24.0 to 29.9)	23.7 (19.6 to 28.7)	26.1 (19.6 to 29.9)

BMI = body mass index; G = Grastofil, US = US-licensed Neupogen; EU = EU-approved Neupogen; ITT = intention-to-treat.
Note: Except where indicated otherwise, values are the median (range) and data from ITT population is presented.
Source: Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Listing 16.2.4.1.

The study population included 48 subjects that were randomized into six dosing sequences. The majority of the subjects were male and Caucasian. In general, considering the small number of subjects, the baseline characteristics were deemed to be balanced.

Concomitant Conditions and Medications: During physical examination at screening, [redacted] subjects ([redacted]) had benign clinical findings that did not prevent study participation.

Concomitant medications were taken by [redacted] subjects in the G-US-EU sequence, [redacted] subjects in the G-EU-US sequence, and by [redacted] in each of the US-EU-G and US-G-EU sequences. The majority of the medications taken were [redacted] or [redacted].

Subject Disposition

Forty-five subjects (29 males and 16 females) completed at least two periods of the study and, of these, 40 subjects (25 males and 15 females) completed all three periods of the study. Consequently, the safety population included all 48 randomized subjects, because all subjects received at least one

administration of the study treatment (32 males and 16 females). The PK/PD dataset included 45 subjects, which is in accordance with the protocol that defined the PK/PD population as subjects who completed at least two periods of the study.

TABLE 31: SUMMARY OF SUBJECT DISPOSITION FOR GCSF-SUIN-05SB01-3FA-(5) BY DOSING SEQUENCE

Disposition	GCSF-SUIN-05SB01-3FA-(5)						
	G-US-EU	G-EU-US	US-G-EU	US-EU-G	EU-G-US	EU-US-G	Total
Screened, N	Not available						66[a]
Randomized, N	8	8	8	8	8	8	48
Discontinued, N (%)	[redacted]						
WDAEs, N (%)	[redacted]						
Withdrawal due to SAEs, N (%)	[redacted]						
Withdrawal of consent, N (%)	[redacted]						
Protocol violation, N (%)	[redacted]						
PK/PD (per protocol), N	[redacted]						
Safety, N	[redacted]						

G = Grastofil, US = US-licensed Neupogen, EU = EU-approved Neupogen, PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event, WDAE= withdrawal due to adverse event.
[a] Checked in for screening.
[b] Although four subjects were discontinued (Clinical Study Report Table 14.1.5), one of the subjects (GC21) was included in the PK/PD population since at least two study periods were completed (per Section 10.1).
Source: Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Section 10.1, Table 14.1.5, Listing 16.2.4.1.

Efficacy/Pharmacodynamic Results

ANC C_{max} After Single Dose: The key efficacy/PD end point was the peak ANC count (C_{max}) after a single dose of subcutaneously administered filgrastim. Table 32 and Table 33, which follow, demonstrate that Grastofil intended for commercial sales exhibits an ANC C_{max} comparable to both the EU-approved and US-licensed Neupogen after a single subcutaneous dose in both the PP and ITT populations. The data also revealed that the variations between the Grastofil product (Process III) and the EU-approved/US-licensed Neupogen were similar to the variation between the EU-approved and US-licensed Neupogen.

TABLE 32: STUDY GCSF-SUIN-05SB01-3FA-(5): ANC C_{MAX} AFTER A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG GRASTOFIL OR US-LICENSED NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		Grastofil	US-Licensed Neupogen	Percentage Ratio of Geometric Means	90% CI	95% CI
PP Population						
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	100	96 to 105	95 to 106
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			

		Grastofil	US-Licensed Neupogen	Percentage Ratio of Geometric Means	90% CI	95% CI
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; CI = confidence interval; C_{max} = peak concentration; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3–18, 2.7.3–21.

TABLE 33: STUDY GCSF-SUIN-05SB01-3FA-(5): ANC C_{MAX} AFTER A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG GRASTOFIL OR EU-APPROVED NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		Grastofil	EU-Approved Neupogen	% Ratio of Geometric Means	90% CI	95% CI
PP Population						
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	103	99 to 108	98 to 109
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; CI = confidence interval; C_{max} = peak concentration; EU = European Union; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3–19, 2.7.3–22.

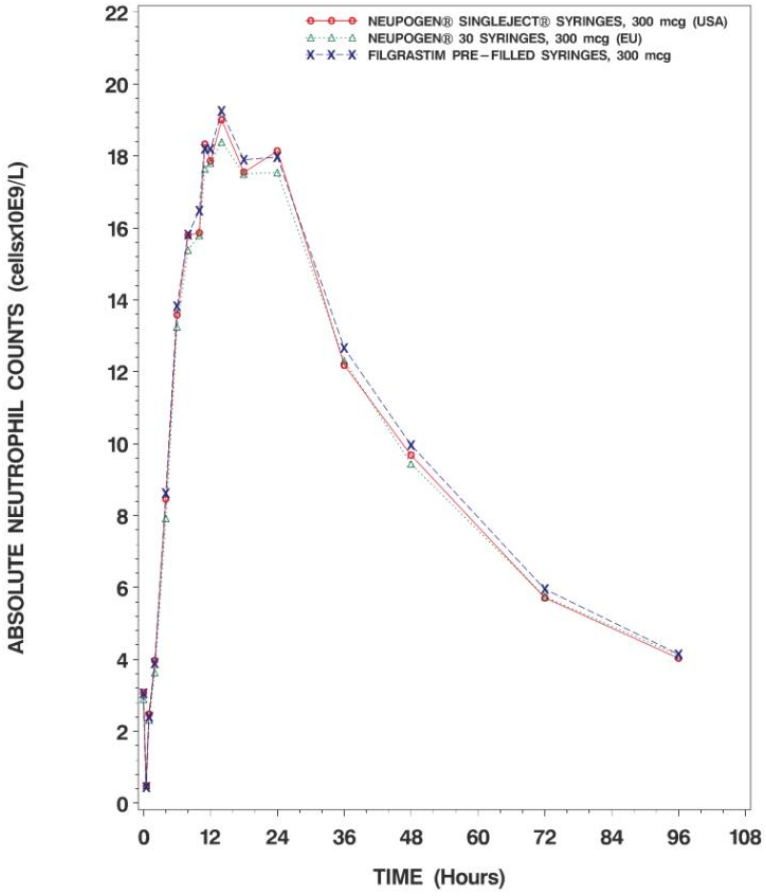
TABLE 34: STUDY GCSF-SUIN-05SB01-3FA-(5): ANC C_{MAX} AFTER A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG US-LICENSED OR EU-APPROVED NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		US-Licensed Neupogen	EU-Approved Neupogen	% Ratio of Geometric Means	90% CI	95% CI
PP Population						
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	104	99 to 109	98 to 110
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC C_{max} (cells × 10^9/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; CI = confidence interval; C_{max} = peak concentration; EU = European Union; ITT = intention-to-treat; max = maximum; min = minimum; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3–20, 2.7.3–23.

Figure 5, which follows, presents the ANC-time profile. As can be seen from the results, the ANC profiles following SC administration of each treatment were virtually superimposable with the ANC levels, peaking at approximately 12 hours post-dose and then returning to baseline levels by 96 hours post-dose.

FIGURE 5: STUDY GCSF-SUIN-05SB01-3FA-(5): MEAN ANC OVER TIME FOLLOWING A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG OF GRASTOFIL, EU-APPROVED NEUPOGEN, OR US-LICENSED NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS (PP POPULATION)



ANC = absolute neutrophil count; EU = European Union; PP = per-protocol.
Source: Common Technical Document 2.7.3, Tables 2.7.3–20, 2.7.3–23.
Source: Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Figure 13.2.4.

ANC AUC_t After Single Dose: The co-primary key efficacy/PD end point was the ANC AUC_t after a single dose of subcutaneously administered filgrastim. As Table 35 and Table 36 demonstrate, the commercial-scale Grastofil exhibits ANC AUC_t comparable with both the EU-approved and US-licensed Neupogen after a single subcutaneous dose in both the PP and ITT populations.

TABLE 35: STUDY GCSF-SUIN-05SB01-3FA-(5): SUMMARY STATISTICS OF ANC AUC_T AFTER A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG GRASTOFIL OR US-LICENSED NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		Grastofil	US-Licensed Neupogen	% Ratio of Geometric Means	90% CI	95% CI
PP Population						
ANC AUC_t (cells × 10^9*h/L)	N	[redacted]	[redacted]	100	97 to 104	96 to 104
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC AUC_t (cells × 10^9*h/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; AUC_t = area under the curve over time interval t; CI = confidence interval; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3–18, 2.7.3–21.

TABLE 36: STUDY GCSF-SUIN-05SB01-3FA-(5): SUMMARY STATISTICS OF ANC AUC_T AFTER A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG GRASTOFIL OR EU-APPROVED NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		Grastofil	EU-Approved Neupogen	% Ratio of Geometric Means	90% CI	95% CI
PP Population						
ANC AUC_t (cells × 10^9*h/L)	N	[redacted]	[redacted]	103	100 to 106	99 to 107
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC AUC_t (cells × 10^9*h/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; AUC_t = area under the curve over time interval t; CI = confidence interval; EU = European Union; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3–19, 2.7.3–22.

TABLE 37: STUDY GCSF-SUIN-05SB01-3FA-(5): SUMMARY STATISTICS OF ANC AUC_T AFTER A SINGLE SUBCUTANEOUS INJECTION OF 300 MCG US-LICENSED OR EU-APPROVED NEUPOGEN TO HEALTHY VOLUNTEERS (PP AND ITT POPULATIONS)

		US-Licensed Neupogen	EU-Approved Neupogen	% Ratio of Geometric Means	90% CI	95% CI
PP Population						
ANC AUC_t (cells × 10^9*h/L)	N	[redacted]	[redacted]	102	99 to 106	99 to 106
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			
ITT Population						
ANC AUC_t (cells × 10^9*h/L)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]			
	SD	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]			

ANC = absolute neutrophil count; AUC_t = area under the curve over time interval t; CI = confidence interval; EU = European Union; ITT = intention-to-treat; PP = per-protocol; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3–20, 2.7.3–23.

The aforementioned results clearly demonstrated that for both primary PD parameters of ANC C_{max} and ANC AUC_t, the 90% and 95% CIs for all product comparison pairs were contained within the predefined equivalence margin.

Overall, this study demonstrated the biosimilarity of Grastofil produced using processes intended for the Canadian market to both US-licensed and EU-approved Neupogen with regard to PD variables after single SC injection of fixed doses of 300 mcg, while also demonstrating the biosimilarity of US-licensed and EU-approved Neupogen. These results supported the lack of clinically meaningful differences between Grastofil and Neupogen while also establishing a scientific bridge to the phase 1 studies (KWI-300-101, KWI-300-102, and KWI-300-103) that were conducted against the EU-approved Neupogen.

Safety Results

TABLE 38: STUDY GCSF-SUIN-05SB01-3FA-(5): SUMMARY OF TEAES (SAFETY ANALYSIS SET)

	Grastofil[a] (N = 43)	US-Licensed Neupogen[b] (N = 45)	EU-Approved Neupogen[c] (N = 45)	Overall (N = 48)
Total number of TEAEs[d]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAEs[d]	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 TEAE[e]	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with related TEAEs				
Definitely	[redacted]	[redacted]	[redacted]	[redacted]
Possible	[redacted]	[redacted]	[redacted]	[redacted]
Probable	[redacted]	[redacted]	[redacted]	[redacted]
Total number of SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]

	Grastofil[a] (N = 43)	US-Licensed Neupogen[b] (N = 45)	EU-Approved Neupogen[c] (N = 45)	Overall (N = 48)
Total number of AEs leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Number (%) of subjects with at least 1 AE leading to permanent study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; EU = European Union; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] As this was a crossover study design, all but 5 subjects received Grastofil.
[b] As this was a crossover study design, all but 3 subjects received US-licensed Neupogen.
[c] As this was a crossover study design, all but 3 subjects received EU-approved Neupogen.
[d] Number of AEs is based on the start date and time of the adverse event related to the dosing dates and times. In case there was no treatment due to check-in day or washout interval, the volunteer and the AE were counted only for **overall** statistics.
[e] One subject from each of the EU- and US-Neupogen arms was not included in the treatment for period 1 because the AE occurred more than 4 weeks after the last dosing in period 1. The AEs for these 2 subjects were included in the **overall** statistics.
Source: Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Tables 14.3.1.1 to 14.3.1.4.

In this study, [redacted] of the 347 total TEAEs could not be categorized by treatment as they occurred during the check-in stage or the washout interval, neither of which could be definitively classified by sequence.

The most common TEAEs in subjects treated with Grastofil included headache (experienced by [redacted] subjects [[redacted]%]), as well as diarrhea, nausea, and catheter-site pain (experienced by [redacted] subjects [[redacted]%] each). For those treated with EU-approved Neupogen, the most common TEAEs included headache (experienced by [redacted] subjects [[redacted]%]); vessel puncture–site hematoma and vessel puncture–site pain (each experienced by [redacted] subjects [[redacted]%]); as well as nausea, catheter-site pain, and back pain (each experienced by [redacted] subjects [[redacted]%]). For those treated with US-licensed Neupogen, the most common TEAEs included nausea, musculoskeletal pain, musculoskeletal stiffness, and cough (each experienced by [redacted] subjects [[redacted]%]).

In this study, laboratory AEs were considered to be in the system organ class of "investigations." Among laboratory AEs considered related, the most common **probably** related AE was decreased neutrophil count ([redacted] events experienced by [redacted] of 48 [[redacted]] of subjects), which was related to the PD of filgrastim. There was no difference noted between treatment groups for the events of decreased neutrophil count (Grastofil: [redacted] subjects experienced [redacted] AEs [[redacted]]; US-licensed Neupogen: [redacted] subjects experienced [redacted] AEs [[redacted]]; EU-approved Neupogen: [redacted] subjects experienced [redacted] AEs [[redacted]]). The most common **possibly** related AEs were increased eosinophil count, decreased blood pressure, headache, and increased neutrophil count. There was no difference noted between treatment groups for the events of increased eosinophil count, decreased blood pressure and headache (Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Table 7). Apart from a slight increase in monocyte count, no relevant changes were observed for other laboratory parameters.

There were no reports of death, SAEs, severe AEs, or any other significant AEs in the study.

Vitals Signs and Echocardiogram: All final vital signs measurements (pulse, blood pressure, oral temperature) were within normal limits or were judged to be not clinically significant by a clinician. The only exception was an increased blood pressure ([redacted] mm Hg) AE for one subject who was lost to follow-up. That AE was judged by the clinician as mild in severity and not related to EU-approved Neupogen.

All final unscheduled ECGs and diagnostic tests were judged normal or not clinically significant, except one subject who had an adverse event of increased urate ([redacted]) judged by a clinician as mild in severity and possibly related to US-licensed Neupogen.

Therefore, based on the PK/PD/safety results of this bridging study and the findings from the KWI-300 series of phase 1 studies (as summarized in section 2.7.2, section 2.7.3, and section 2.7.4), along with the demonstrated analytical comparability of Grastofil (from both DP Process II and DP Process III as summarized in sections 3.2.R and 3.2.S) with the EU-approved Neupogen, it can be concluded the similarity of Grastofil and Neupogen with respect to PK, PD, efficacy, and safety has been adequately demonstrated.

4.2.10 KWI-300-104

a) Study Characteristics

As detailed earlier, the clinical development pathway for Grastofil focused on the demonstration of similarity of efficacy between Grastofil and Neupogen in a healthy subject population which is expected to be the most sensitive population to ascertain differences, if any, between filgrastim medicinal products. Accordingly, the clinical phase 3 Study KWI-300-104, was designed as a single-group safety study with the primary objective of assessing the safety of Grastofil used for the prophylaxis of febrile neutropenia in breast cancer patients undergoing TAC chemotherapy as compared with the safety profile of Neupogen. Additionally, this study was designed to assess the efficacy of Grastofil in a clinical setting in a relevant homogenous patient population. It is noteworthy that this study was designed in accordance with the Scientific Advice provided by the EMA on October 18, 2016 (Procedure Number EMEA/H/SA/777/1/2006/III (7)).

KWI-300-104 was a non-comparative, single-group, multi-centre, repeat-dose safety study of Grastofil in breast cancer patients receiving TAC chemotherapy known to induce neutropenia. The primary end point was the incidence of AEs (all severe and serious) classified by body system, preferred term, frequency, and relationship to investigational product. The efficacy end point was DSN (severe neutropenia is defined as occurrence of ANC below 0.5×10^9/L) in cycle 1.

TABLE 39: DETAILS FOR KWI-100-104

Characteristics		Details for KWI-100-104
Study Design	Objective	To evaluate the safety of Grastofil used for the prophylaxis of febrile neutropenia in breast cancer patients undergoing TAC chemotherapy as compared with the safety profile of Neupogen.
	Blinding	Open-label
	Study period	2008–09 to 2010–05
	Study centres	17 centres in 10 countries
	Design	Single-group
Study Population	Randomized (N)	120
	Inclusion criteria	1. Female, ≥ 18 years of age, suitable for and intended to undergo adjuvant TAC chemotherapy 2. Body weight of subject must be within 40 kg and 120 kg 3. Subject is within 60 days after the complete surgical resection of the primary breast tumour: either lumpectomy or mastectomy with sentinel lymph node biopsy or axillary dissection, with clear margins for both invasive and DCIS 4. Subject has stage IIA, IIB or IIIA breast cancer

Characteristics		Details for KWI-100-104
		5. Subject must have an ECOG performance status ≤ 2 6. Subject is chemotherapy-naive 7. Subject must have an ANC ≥ 1.5 × 10^9/L; platelet count ≥ 100 × 10^9/L 8. Subject must have adequate renal (serum creatinine < 1.5 × upper limit) and hepatic functions (bilirubin < upper limit of normal, transaminases < 1.5 × ULN, and ALP within 1.5 × ULN) 9. Subject has normal cardiac function, as evidenced by left ventricular ejection fraction > 55% 10. Subject has no evidence of metastatic disease outside of breast by physical examination and chest X-ray. Other scans, if done as needed by the patient (e.g., bone scan; abdominal, chest CT; PET or PET/CT; ultrasound; or magnetic resonance imaging), should indicate no evidence of metastatic disease 11. Subject has had baseline bilateral mammography 12. Females must not intend to conceive during or shortly after the study. They must be either post-menopausal, surgically incapable of bearing children, or practising an acceptable method of birth control (e.g., hormonal contraceptives, intrauterine device, or spermicide and barrier) and be willing to continue the same method of birth control during and for 30 days after the last dose of study medication 13. Females of child-bearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose of study drug 14. Willing and able to give written informed consent 15. Willing and able to undergo procedures required by this protocol.
	Exclusion criteria	1. Has any evidence of metastatic disease following surgical resection of the primary tumour, including positive surgical margins, staging work-up, or physical examination suspicious for malignant disease (M1 disease on the tumour node metastasis according to the Classification of Malignant Tumours staging system) 2. Has bilateral breast cancer (concomitant or prior) except in situ lesion, either ductal or lobular, of the contralateral breast 3. Has a history of severe hypersensitivity reaction to drugs intended for use in this protocol 4. Has had neoadjuvant chemotherapy for this breast cancer 5. Has ever had a myocardial infarction or has a history of heart failure, uncontrolled angina, severe uncontrolled arrhythmias, pericardial disease, or electrocardiographic evidence of acute ischemic changes 6. Is receiving concurrent immunotherapy, hormonal therapy (e.g., tamoxifen, gonadal hormone replacement therapy, Herceptin (trastuzumab), or radiation therapy 7. Is receiving concurrent investigational therapy or has received such therapy within the past 30 calendar days 8. Has peripheral neuropathy > Grade 1 9. Has had a major organ allograft or condition requiring chronic immunosuppression (i.e., kidney, liver, lung, heart, bone marrow transplant, or autoimmune diseases). Patients who have received corneal transplants or cadaver skin or bone transplants are eligible 10. Has a serious uncontrolled intercurrent medical or psychiatric illness, including serious viral (including clinically defined AIDS), bacterial, or fungal infection; or history of uncontrolled seizures, or diabetes, or central nervous system disorders deemed by the investigator to be clinically significant, precluding informed consent 11. Has active hepatitis B or hepatitis C with abnormal liver function tests or is known to be HIV positive 12. Has a history of other malignancy within the last 5 years (except cured basal cell

Characteristics		Details for KWI-100-104
		carcinoma of skin, carcinoma in situ of uterine cervix, or DCIS, which could affect the diagnosis or assessment of any of the study drugs) 13. Is pregnant or breastfeeding 14. Is receiving antibiotic treatment 3 days within chemotherapy administration.
Drugs	Intervention	Grastofil (DP manufactured with Process [redacted]), 5 mcg/kg/day, administered subcutaneously from either the 300 mcg/0.5 mL PFS (if body weight 40 kg to 75 kg), or the 480 mcg/0.5 mL PFS (if body weight 76 kg to 120 kg). Injections began on day 2 of every chemotherapy cycle up to 14 days or until post-nadir ANC recovery to normal or near-normal values by laboratory standards, whichever occurs first, for a total of 6 cycles. Patients concomitantly received TAC chemotherapy consisting of docetaxel 75 mg/m^2 IV day 1, doxorubicin 50 mg/m^2 IV day 1, and cyclophosphamide 500 mg/m^2 IV day 1, every 3 weeks for six cycles
	Comparator(s)	None
Duratio	Run-in	Not applicable
	Treatment	18 weeks (6 cycles of TAC)
	Follow-up	30 weeks
Outcomes	Primary end point(s)	• The main efficacy end point was the DSN in cycle 1 (severe neutropenia is defined as occurrence of ANC below 0.5 × 10^9/L) • The primary safety end point was the subject incidence of AEs (all severe and serious) classified by body system, preferred term, frequency, and relationship to investigational product. Vital signs, immunogenicity and clinical laboratory results were also monitored
	Other end points	**Other efficacy end points** • The duration of severe neutropenia in consecutive cycles (2 through 6) • The frequency of grade 3 and 4 severe neutropenia (ANC below 1.0 × 10^9/L and 0.5 × 10^9/L) • The depth of ANC nadir in cycle 1 • The time to the post nadir ANC recovery (ANC >1.5 × 10^9/L) in cycle 1 • The rates of febrile neutropenia by cycle and across the cycles (ANC < 0.5 × 10^9/L and concurrent oral-equivalent temperature ≥ 38.2 °C) • The ANC-time profile in cycle 1 (time from the beginning of chemotherapy to the occurrence of ANC nadir) • The frequency of (culture-confirmed) infections • The incidence of IV antibiotic therapy and hospitalization • The mobilization of CD34$^+$ cells (in selected sites only)
Notes	Publications	(28, 29)

AE = adverse events; ALP = alkaline phosphatase; ANC = absolute neutrophil count; CD34$^+$ = cluster of differentiation 34; CT = computed tomography; DCIS = ductal carcinoma in situ; DSN = duration of severe neutropenia; DP = drug product; ECOG = Eastern Cooperative Oncology Group; EU = European Union; G-CSF = granulocyte-colony stimulating factor; IV = intravenous; PD = pharmacodynamics; PET = positron emission tomography; PFS = pre-filled syringe; PK = pharmacokinetics; PP = per-protocol; SC = subcutaneous; TAC = docetaxel/doxorubicin/cyclophosphamide; ULN = upper limit of normal.

Intervention and Comparators

Patients received repeated doses of Grastofil (manufactured with DP Process [redacted]) of 5 mcg/kg/day rounded to the nearest pre-filled 300 mcg/0.5 mL or 480 mcg/0.5 mL syringe, administered subcutaneously beginning on day 2 of every chemotherapy cycle for up to 14 days or until post-nadir ANC recovery to normal or near-normal values by laboratory standards, whichever occurred first, for a total of six cycles. This dosing regimen is in line with the most recently published National Comprehensive Cancer Network (NCCN) guideline (34) for filgrastim for prophylaxis and treatment of febrile neutropenia, which lists a "daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards." Thus, while the posology in the product monograph for Neupogen specifies that dosing is weight-based, it is evident that in clinical practice, dosing to the nearest PFS size may not be uncommon. Additionally, according to an article authored by the American Society for Clinical Oncology on clinical practice guidelines for hematopoietic colony-stimulating factors, the available data suggest that rounding the dose to the nearest vial size (or in this case PFS size) may enhance patient convenience and reduce costs without clinical detriment (35). Thus, the dose administration of Grastofil at an approximate dosage of 5 mcg/kg is consistent with typical dose administration of filgrastim in clinical practice in which the patient's clinical response guides the duration of therapy. Slight variability in the nominal amount (mcg) administered would not be expected to alter the overall clinical efficacy and safety of Grastofil.

Concomitant Medications: In addition to TAC chemotherapy, premedication with [redacted] and [redacted]) drugs was, according to the protocol, required to improve tolerability of chemotherapy. Secondary [redacted] was allowed upon development of an episode of febrile neutropenia and implemented in accordance with the recommendations of the *NCCN Clinical Practice Guidelines in Oncology,* V.I. 2008 (36). Any treatment considered necessary for the patient's welfare could be given at the discretion of the investigator.

Outcomes

Duration of Severe Neutropenia: The main efficacy end point was the DSN in cycle 1. Severe neutropenia is defined as occurrence of ANC below 0.5×10^9/L. According to published data, most febrile neutropenia events occur during the first cycle of chemotherapy (37-39) and correlate to the DSN after myelosuppressive chemotherapy (40), which justified the focus of the efficacy analysis on the first cycle of chemotherapy. DSN is a reliable end point, as it is strongly predictive of the IFN in chemotherapy-induced neutropenia settings. The relevance of this end point is further supported by the EMA guideline, EMEA/CHMP/BMWP/31329/2005 (6). This guideline recommends that for the assessment of efficacy for G-CSF, the primary efficacy variable should be defined as the DSN (ANC below $0.5x\ 10^9$/L) after cytotoxic chemotherapy in a homogenous patient group. Consequently, cycle 1 was considered to be the most relevant treatment cycle for the assessment of efficacy.

In this first cycle of chemotherapy, blood samples for ANC determination were taken at regular intervals; i.e., on day [redacted], day [redacted], day [redacted], day [redacted] and day [redacted], day [redacted], day [redacted], day [redacted], and day [redacted] to day [redacted]. If visits on these days were not feasible on-site, the ANC assessment could be done through a local laboratory.

DSN in consecutive cycles (2 through 6) was considered as a key secondary efficacy end point. Mandatory ANC determination was scheduled on day [redacted] and day [redacted] per cycle, whereas on day [redacted] to day [redacted] of each cycle, ANC samples were only taken if clinically indicated. The time points for ANC samples in cycles [redacted] to [redacted] (day [redacted] and day [redacted]) were chosen to ensure patients' safety. Systematic daily blood sampling

over all subsequent cycles would have constituted a large burden for the severely ill study patients and was therefore avoided, taking into consideration the nature of the Grastofil single-arm safety trial and the published data on Neupogen and other biosimilar filgrastim DPs (37, 39).

Frequency of Grade 3 and 4 Severe Neutropenia (Cycle 1): This was considered a key secondary efficacy end point. Grade 3 and 4 severe neutropenia are defined as ANC below 1.0×10^9/L and 0.5×10^9/L, respectively.

Incidence of Febrile Neutropenia (Cycle 1): The definition of febrile neutropenia used for the purpose of this study was an observed or imputed ANC of less than 0.5×10^9/L and concurrent oral-equivalent temperature of 38.2°C or higher.

This definition differs slightly from the definition given in the EMA guidelines on clinical trials with hematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy. Specifically, the definition used in the study has a lower threshold than the one given in the EMA guideline, which is, "rise in axillary temperature to above 38.5°C for a duration of more than one hour while having an ANC < 0.5×10^9/L" (41). The threshold used was chosen on the basis of published reference studies (37, 38) to ensure comparability of febrile neutropenia incidence rates observed in this study versus the febrile neutropenia incidence rates available from published data. Also, for the purpose of the protocol, the usage of oral equivalent temperature in the definition of febrile neutropenia ensured there was no deviation among the various European countries following different measurement methods to assess febrile neutropenia.

$CD34^+$ Cell Mobilization: This was another key secondary end point. In this study, $CD34^+$ mobilization was determined by measuring $CD34^+$ cell counts with samples take on day [redacted], day [redacted], and day [redacted] of chemotherapy cycle [redacted].

Safety: The primary safety end point was the incidence of AEs (all severe and serious) classified by body system, preferred term, frequency, and relationship to investigational product.

Immunogenicity: One key safety end point was the determination of immunogenicity to Grastofil in cancer patients. Samples for immunogenicity analysis were taken over the duration (51 weeks) of the study.

Statistical Analyses

Descriptive statistics were used to present the results of the study.

Analysis Sets: Three analysis subsets were considered for analysis:

- **Safety analysis subset** included all enrolled patients who received at least one dose of active treatment
- **Full analysis subset** comprised all enrolled patients who received at least one dose of active treatment and who provided any follow-up data for the primary target variables
- **PP subset** included patients without major protocol deviations or premature termination of the treatment due to reasons that were definitely not related to study medication.

In line with the definition given in the study protocol, the full analysis set was identical to the safety analysis set.

b) Results

Baseline Characteristics

TABLE 40: STUDY KWI-300-104: MAJOR DEMOGRAPHIC AND BASELINE CHARACTERISTICS (FULL ANALYSIS SET)

Characteristics	Grastofil (5 mcg/kg) (N = 120)
Age (years), mean (SD)	49.97 (9.52)
Prior chemotherapy, n (%)	0 (0)
Prior radiotherapy, n (%)	22 (18.33)
Gender, no (%)	
Female	120 (100.00)
Ethnicity	
Caucasian	120 (100.00)
Body height (cm)	164.00 (147.00 to 178.00)
Body weight (kg)	71.00 (46.00 to 119.80)
BMI (kg/m^2)	27.01 (17.43 to 40.90)
Disease stage at entry	
Stage IIA	39 (32.50%)
Stage IIB	44 (36.67%)
Stage IIIA	37 (30.83%)

BMI = body mass index; ITT = intention-to-treat; SD = standard deviation.
Note: Except where indicated otherwise, values are the median (range) and data from ITT population is presented.
Source: Clinical Study Report KWI-300-104, Tables 8 and 9.

The patient population consisted of 120 Caucasian female patients with an average age of 50.0 years, with stage IIA, IIB, or IIIA breast cancer without neoadjuvant chemotherapy for this breast cancer. There were 39 (32.5%) patients at tumour stage IIA, 44 (36.7%) at stage IIB, and 37 (30.8%) at stage IIIA.

Concomitant Conditions and Medications: [redacted] subjects reported concomitant conditions and [redacted] subjects reported concomitant and past conditions (Clinical Study Report KWI-300-104, Table 14.1.2). The most common prior/concomitant medications were [redacted] taken by [redacted] subjects, followed by [redacted] ([redacted] subjects), [redacted] ([redacted] subjects), [redacted] ([redacted] subjects), and [redacted] ([redacted] subjects) (Clinical Study Report KWI-300-104, Table 14.3.6.9).

Patient Disposition

From a total of 152 patients screened at 26 initiated sites in 11 countries, 120 Caucasian female patients were enrolled from 17 investigational sites in 10 countries. Overall, 120 subjects were dosed, 113 patients (94.2%) completed the treatment period, and 109 (90.8%) completed the safety follow-up period. Eleven patients (9.2%) prematurely discontinued the study. The reasons for study discontinuation included withdrawal of consent (five patients [4.2%]), serious protocol deviation (three patients [2.5%]), and AEs (three patients [2.5%]). The first two discontinuations due to AEs were reported as SAEs and led to fatal outcomes reported as metastases and disease progression; the third was due to a non-serious AE (duodenal ulcer). None of these events were considered related to the study drug.

TABLE 41: SUMMARY OF PATIENT DISPOSITION FOR KWI-300-104

Disposition	KWI-100-104
	Grastofil (5 mcg/kg)
Screened, N	152
Initiated, N	120
Discontinued, N (%)	11 (9.17%)
Serious protocol deviation, N (%)	[redacted]
Withdrawal of consent, N (%)	[redacted]
WDAEs, N (%)	[redacted]
Withdrawal due to SAEs, N (%)	2 (1.67%)
Lost to follow-up, N (N%)	[redacted]
Full analysis, N	120
Per-protocol, N	110[a]
Safety, N (%)	120

PP = per-protocol; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] PP population is defined as the full analysis set minus patients with major protocol deviations. In this case, as per the Clinical Study Report, there were 10 patients who were identified as having major protocol deviations, thus leaving 110 subjects in the PP population. Subjects withdrawing or discontinuing would not result in removal from the PP population unless they are missing cycle 1 data; thus, one subject withdrew after cycle 1.
Source: Clinical Study Report KWI-300-104, Table 6; Common Technical Document 2.7.4, Table 2.7.4-6.

Efficacy Results

Duration of Severe Neutropenia in Cycle 1: The primary efficacy end point was DSN in cycle 1. The mean (SD) DSN in cycle 1 was 1.40 (1.07) days in the full analysis set (FAS) and 1.27 (0.95) days in the PP analysis set (Table 42). These results are consistent with results for other filgrastim products reported in the available literature, with mean (SD) DSN in cycle 1 ranging between 1.6 (1.1) (38) and 1.8 (1.4) (37) (versus placebo of 3.8 days). These results demonstrate that Grastofil is effective in the prophylactic treatment of febrile neutropenia in breast cancer patients receiving myelosuppressive TAC chemotherapy, with results consistent with those seen in the literature for Neupogen.

Sensitivity analysis of the data using different imputation methods ([redacted]) for missing data revealed that mean (SD) DSN in cycle 1 ranged between [redacted] for the FAS, and [redacted] in the PP analysis set (Table 42). Imputation method [redacted] was considered to be acceptable by Health Canada as a sensitivity analysis (16) and was performed according to the following rules:

- If ANC measurement was missing on a certain day and if any of the measurements on the preceding or following days were below the threshold, then the flag for the missing measurement was set to [redacted].
- If ANC measurement was missing on a certain day and the measurements on both the preceding and the following days were above the threshold, then the flag for the missing measurement was set to [redacted].

This imputation method was also applied if [redacted].

TABLE 42: STUDY KWI-300-104: ASSESSMENT OF THE DSN IN CYCLE 1 AS MEASURED IN DAYS IN THE FAS AND PP POPULATION SET FOLLOWING TREATMENT WITH GRASTOFIL

Population	DSN in Cycle 1 (Days)					
	Mean ± SD (SE)	Min	Q1	Median	Q3	Max
Standard method						
FAS (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputation method [redacted]						
FAS (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP (N = [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DSN = duration of severe neutropenia; FAS = full analysis set; max = maximum; min = minimum; PP = per-protocol; Q = quartile; SE = standard error; SD = standard deviation.

Source: [redacted].

The values from the imputation method [redacted] remained in the range reported in other filgrastim studies.

In terms of a possible dose-dependent effect of Grastofil on DSN, the dosing regimen employed for Grastofil in this trial did not lead to unexpected results. The mean dosage of Grastofil administered was 5.14 mcg/kg/day, with a range of 3.97 mcg/kg/day to 6.67 mcg/kg/day and, thus, did not deviate significantly from the recommended clinical dosage of 5 mcg/kg/day. Furthermore, an exploratory subgroup analysis indicated there was no apparent dose-dependence in DSN. Specifically, the results for dose per body weight (mcg/kg) in relation to mean DSN were: < 4.5 mcg/kg — [redacted] days; 4.5 mcg/kg to 5.2 mcg/kg: [redacted] days; 5.2 mcg/kg to 5.7 mcg/kg: [redacted] days; and 5.7 mcg/kg and higher: [redacted] days. A recent study by Gascon et al. (17) using the EU-approved filgrastim Hexal at a fixed dose of 300 mcg or 480 mcg administered according to body weight (mean dose by body weight of 6.1 ± 0.9 mcg/kg/day [range 3.7 to 8.4 mcg/kg/day]) showed there was no relationship between the overall and the "by cycle" incidences of grade 3 or 4 neutropenia irrespective of the doses per body weight. The aforementioned evidence suggests that variations around the administered dosage of 5 mcg/kg/day should not alter the safety or efficacy of filgrastim. It is likely that the differences in DSN observed at each of the administered dosage levels for Grastofil were due to the variability of this parameter. The wide inter-individual variability in DSN is supported by reports in the literature. For example, in a study reported by del Giglio et al. (39), following the administration of Neupogen at a weight-based dosage of 5 mcg/kg/day, the mean DSN in cycle 1 was 1.1, and the range around this mean was wide, ranging from 0 to 5 days. Similarly, at this same weight-based dosage, in Green et al. (38), the mean DSN in cycle 1 was 1.6 days; however, the corresponding SD was 1.1 days (CV = 68.8%), clearly demonstrating the wide inter-individual variability in this parameter, despite there being no differences in the nominal amount of filgrastim received (5 mcg/kg). If one compares the efficacy results for Grastofil as measured by the DSN and the incidence of severe neutropenia in cycle 1 in conjunction with the data reported in the literature, the overall efficacy of Grastofil is well supported. As summarized in Table 43, the data for Grastofil are within the range of the reported data for Neupogen and other filgrastim medicinal products. These data clearly demonstrate the clinical efficacy of Grastofil, despite potential dose variability introduced in Study KWI-300-104 as a consequence of dosing 5 mcg/kg/day rounded to the nearest PFS size.

TABLE 43: INCIDENCE AND DURATION OF SEVERE NEUTROPENIA IN CYCLE 1 IN PATIENTS WITH BREAST CANCER FOLLOWING ADMINISTRATION OF FILGRASTIM PRODUCT(S)

G-CSF Product (Study)	Chemotherapy Schedule Number of Cycles	Percentage of Chemotherapy-Naive Patients	Incidence		Duration
			N	n (%)	(Mean ± SD)
Grastofil Dose: 5 mcg/kg (KWI-300-104) (FAS population)	Docetaxel: 75 mg/m^2, doxorubicin: 50 mg/ m^2, and cyclophosphamide: 500 mg/m^2 Q3W, up to 6 cycles	100	120	[redacted]	1.4 ± 1.1
Tevagrastim Dose: 5 mcg/kg (XM02-02-INT)	Docetaxel: 75 mg/m^2, and doxorubicin: 60 mg/ m^2 Q3W, up to 4 cycles	100	140	NA	1.1 ± 1.2
Nivestim Dose: 5 mcg/kg (GCF071)	Docetaxel: 75 mg/m^2, and Doxorubicin: 60 mg/ m^2 Q3W, up to 6 cycles	NA	165	128 (78)	1.6 ± 1.2
Placebo Dose: 5 mcg/kg (XM02-02-INT)	Docetaxel: 75 mg/m^2, and doxorubicin: 60 mg/ m^2 Q3W, up to 4 cycles	100	72	NA	3.8 ± 2.1
Neupogen Dose: 5 mcg/kg (XM02-02-INT)	Docetaxel: 75 mg/m^2, and doxorubicin: 60 mg/ m^2 Q3W, up to 4 cycles	100	136	NA	1.1 ± 1.3
Neupogen Dose: 5 mcg/kg (GCF071)	Docetaxel: 75 mg/m^2, and doxorubicin: 60 mg/ m^2 Q3W, up to 6 cycles	NA	85	58 (68)	1.3 ± 1.1
Neupogen Dose: 5 mcg/kg (38)	Docetaxel: 75 mg/m^2, and doxorubicin: 60 mg/ m^2 Q3W, up to 4 cycles	72	75	(83)	1.6 ± 1.1 [a]
Neupogen Dose: 5 mcg/kg (38)	Docetaxel: 75 mg/m^2, and doxorubicin: 60 mg/ m^2 Q3W, up to 4 cycles	88	147	116 (79)	1.8 ± 1.4 [a]

FAS = full analysis set; G-CSF = granulocyte-colony stimulating factor; NA = not available; Q3W = every three weeks; SD = standard deviation.
[a] Number of consecutive days with ANC < 0.5 10^9/L during cycle 1.
Source: Common Technical Document, 2.7.3, Table 2.7.3-25.

Duration of Severe Neutropenia in Consecutive Cycles (2 Through 6): The DSN in cycles 2 through 6 are shown in Table 44. Cycle 1 results are also presented to demonstrate the reduction of DSN after the first cycle. As the results showed, the majority of subjects with severe neutropenia had a duration of one day, with very few subjects experiencing DSN of two days (in cycles 4 and 5).

TABLE 44: DURATION OF SEVERE NEUTROPENIA IN CYCLES 1 TO 6

Duration of Severe Neutropenia in Cycles 1 to 6 (Days)	Cycle 1 (N = 120)	Cycle 2 (N = 114)	Cycle 3 (N = 114)	Cycle 4 (N = 114)	Cycle 5 (N = 113)	Cycle 6 (N = 113)
0	27 (22.50)	110 (96.49)	106 (92.98)	109 (95.61)	104 (92.04)	101 (89.38)
1	39 (32.50)	4 (3.51)	8 (7.02)	3 (2.63)	8 (7.08)	10 (8.85)
2	38 (31.67)	0 (0.00)	0 (0.00)	2 (1.75)	0 (0.00)	2 (1.77)
3	12 (10.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.88)	0 (0.00)
4	3 (2.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	5 (0.83)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Source: Clinical Study Report KWI-300-104, Tables 12 and 17.

Incidence of Severe (Grade 3 and 4) Neutropenia in Cycle 1: The incidence of severe neutropenia (grade 4, defined as ANC below 0.5 × 10^9/L) in chemotherapy cycle 1 was 77.5% (93 out of 120 patients) (Table 43). The incidence of grade 3 neutropenia (defined as ANC below 1.0 × 10^9/L) in cycle 1 was 88.3% (106 out of 120 patients). As reported in the literature, the majority of severe neutropenia cases occur during cycle 1 of chemotherapy (37-39). For example, in the study published by Holmes, the incidence of grade 4 neutropenia under Neupogen was higher in chemotherapy cycle 1 (79%) as compared with cycles 2, 3, and 4 (56%, 60%, and 55%).

Incidence of Severe Neutropenia in Consecutive Cycles (2 through 6): Blood sampling in cycles 2 to 6 was performed on day [redacted] and day 9 of each cycle. As severe neutropenia most often occurred on cycle day 7, the neutropenia had most probably recovered in the majority of patients by the time of blood sampling on D9. However, the reason for collecting fewer blood samples was to ensure the safety of patients as discussed in the previous Outcomes section (Key Efficacy/Pharmacodynamic and Safety Outcomes). Severe neutropenia was detected in four out of 114 patients (3.5%) in cycle 1; 8 out of 114 patients (7.0%) in cycle 2; 5 out of 114 patients (4.4%) in cycle 3; 9 out of 113 patients (8.0%) in cycle 4; and 12 out of 113 patients (10.6%) in cycle 5.

Despite the lack of regular sampling for the assessment of ANC levels (and thus by extension, DSN) in cycles 2 through 6, available data from day [redacted] and day 9 still provided meaningful information on the efficacy of Grastofil in maintaining ANC levels in patients for each cycle. Close examination of the available data between day [redacted] and day 9 for each of the cycles (including cycle 1) shows that ANC levels were [redacted] across all cycles (Figure 6). In fact, when assessing the difference in ANC level between day 9 and day [redacted] for all six cycles, a [redacted] analysis of the differences demonstrated there was [redacted] in the change in ANC level between day 9 and day [redacted] over the six cycles (*P* = [redacted]). This indicates that Grastofil is also efficacious in controlling ANC levels after cycle 1.

FIGURE 6: STUDY KWI-300-104: ANC-TIME PROFILE FOR CYCLE 1 (DAY 0 TO DAY 9) AND CYCLE 2 TO CYCLE 6 (DAY 0 AND DAY 9)

Figure redacted upon manufacturer's request.

Furthermore, as presented in Table 58 in Appendix 1, the time to the post-nadir ANC recovery (ANC > 1.5 × 10^9/L) in cycle 1 occurred after a median of nine days and a mean ± SD of 9.11 days, ± 1.32 days. Given the overall [redacted] of ANC levels across all cycles at day 9 (Figure 6), this noted time of

post-nadir ANC recovery further demonstrates the expected similarities across all cycles for the assessment of DSN and, by extension, days of ANC nadir, and the day of ANC recovery.

Incidence of Febrile Neutropenia: The IFN in chemotherapy cycle 1 was 2.5% (3 out of 120 patients) in the FAS and [redacted]% ([redacted] out [redacted] patients) in the PP population. Sensitivity analysis based on a more conservative definition of febrile neutropenia showed the IFN increased only marginally (FAS: [redacted] out of 120 [[redacted]%]; PP: [redacted] out of [redacted] [[redacted]%] (13)). [redacted] patients experienced febrile neutropenia in subsequent cycles. As mentioned earlier, the definition of febrile neutropenia used for the purpose of this study was the oral equivalent body temperature of [redacted]°C, which is [redacted] than the EMA's axillary temperature of 38.5°C; this could have resulted in [redacted] febrile neutropenia reports than would have been the case if applying the EMA-recommended definition.

Although the IFN in cycle 1 of the Grastofil study was [redacted] than those seen in other studies in filgrastim-treated patients ([redacted]% to [redacted]%) (37-39), this may be related to factors other than the Grastofil DP itself. These other factors may include the different chemotherapy regimen with a lower dose of the myelotoxic component doxorubicin in Study KWI-300-104 compared with published studies (50 mg/m^2 in TAC chemotherapy versus 60 mg/m^2 in AT chemotherapy), the difference in tumour stage of the study patients according to the inclusion criteria as well as the patients' self-measurement of body temperature. Nevertheless, the IFN of [redacted]% observed with Grastofil is very similar to the data published in the European public assessment report for the biosimilar filgrastim product Nivestim (1.8% to 2.4% in cycle 1) (24).

Furthermore, the low rate of IFN (3/120; 2.5%), hospitalization (7/12; 5.8%), and IV antibiotic use (4/120; 3.3%) compared with the much higher rate of severe neutropenia ([redacted]; [redacted]%) in cycle 1 is not inconsistent with published data, which showed that a high incidence of severe neutropenia does not always result in development of febrile neutropenia, hospitalization, or use of antibiotics (42, 43). Additional factors independent of the pharmacodynamics of the drug can also influence the occurrence and/or detection of febrile neutropenia.

Overall, the IFN observed in Study KWI-300-104 is not unusual, nor is it significantly different from what has been published for the reference product. Thus, in general, the results of the historically controlled comparison of the efficacy end points under Grastofil and Neupogen support the demonstration of the similarity of efficacy between the two filgrastim medicinal products.

Mobilization of CD34$^+$ Cells: CD34$^+$ cell counts were performed at selected sites for a total of 39 randomly selected patients. In total, three samples were taken from patients in cycle 1: on day 0 (before administration of Grastofil), day 7, and day 9. An increase in CD34$^+$ cell count over baseline was observed on days 7 and 9. The administration of a dosage of 5 mcg/kg/day of Grastofil resulted in increased CD34$^+$ cell counts from 4.57/µL ± 3.33/µL at baseline to 110.67/µL ± 101.18 /µL on cycle 1, day 9 (Table 45). Consistent with results in Study KWI-301-103, broad inter-individual variation in CD34$^+$ mobilization was noted in line with reports in the literature (44, 45), as there are several cellular mechanisms that regulate the mobilization. These mechanisms are likely influenced by various extrinsic and intrinsic factors, including general health and overall disease state (46). The results clearly demonstrated the efficacy of Grastofil during the clinical use of this drug. Furthermore, although comparative data were not available for this trial, based on the results presented earlier from Study KWI-300-103, it is expected that the effect of Grastofil and Neupogen on CD34$^+$ mobilization will be comparable in relevant patient populations.

TABLE 45: STUDY KWI-300-104: CD34+ COUNT IN CYCLE 1 AFTER DAILY SUBCUTANEOUS INJECTION OF 5 MCG/KG BODY WEIGHT GRASTOFIL TO BREAST CANCER PATIENTS (FULL ANALYSIS SET)

End Point		Day 0 (N = 39)	Day 7 (N = 36)	Day 9 (N = 34)
$CD34^+(10^6/L)$	Mean	4.57	[redacted]	110.67
	SD	3.33	[redacted]	101.18
	Minimum	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Maximum	[redacted]	[redacted]	[redacted]

CD34+ = cluster of differentiation 34; SD = standard deviation.
Note: For results based on the intra-individual increase at day 7 and day 9 in $CD34^+$ cell counts, please refer to [redacted].
Source: Common Technical Document 2.7.3, Table 2.7.3-27; Study Report KWI-300-104, Tables 19 and 14.2.12.

Considering the robust comparability data provided for ANC (as presented in this report), together with the available data for $CD34^+$ cells from this study and Study KWI-300-103, it can be concluded that Grastofil and Neupogen demonstrated comparable efficacy, and further suggests that additional data for $CD34^+$ cells will not alter these overall conclusions of efficacy and PD comparability.

Frequency of Culture-Confirmed Infections: One patient had culture-confirmed infections. In this patient, three concomitantly occurring infections were culture-confirmed: cough, stomatitis, and rhinitis.

Intravenous Antibiotic Therapy and Hospitalization: Intravenous antibiotics were used in four patients (3.3%). Febrile neutropenia was the indication for two cases. Leucopenia with neutropenia was the indication for administration of IV antibiotics, whereas sub-febrility during hospitalization for brain metastases was the indication for the administration of IV antibiotics in the fourth patient. All patients were hospitalized and events reported as SAEs. Hospitalization during treatment and follow-up was necessary in eight cases for seven patients (5.8%). The rate of hospitalizations generally corresponded to the number of SAEs. All of the patients who reported SAEs were hospitalized, except for two patients (disease progression and breast cancer recurrent).

Additional Results: Please refer to Table 58 in Appendix 1 for the following results:

- The depth of ANC nadir in cycle 1
- The time to post-nadir ANC recovery (ANC > 1.5×10^9/L) in cycle 1
- The ANC-time profile in cycle 1 (time from the beginning of chemotherapy to the occurrence of ANC nadir).

In summary, although Study KWI-300-104 was designed primarily for the purpose of demonstrating safety, it is believed that sufficient data were available to demonstrate the efficacy of Grastofil in a clinical setting. This is supported by the fact that the mean DSN of 1.4 days with Grastofil in the first cycle of TAC chemotherapy was comparable to a reported DSN of 1.8 days with historical controls of Neupogen following doxorubicin/docetaxel chemotherapy (38), and to a mean DSN of 1.3 days with Neupogen, as reported in the European public assessment report for the biosimilar filgrastim product Nivestim (24) in breast cancer patients following treatment with doxorubicin and docetaxel combination therapy. Furthermore, the ANC profile in chemotherapy cycle 1 was very similar to the profiles published for Neupogen, in spite of the different chemotherapy administered (37-39).

It should be noted that while this study clearly demonstrated the efficacy of Grastofil in cancer patients, the data were not included in the Grastofil product monograph per Health Canada, as the primary objective of the study was safety. Nevertheless, data from this study showed that Grastofil is effective in reducing DSN in cancer patients.

Safety Results

In the phase 3 study in cancer patients, a total of 1,216 TEAEs were reported. A total of 110 out of 120 breast cancer patients (91.7%) reported TEAEs. Of these, 70 (58.3%) patients experienced 252 related TEAEs (Common Technical Document 2.7.4, Table 2.7.4-17). Most TEAEs were described as mild. Three TEAEs resulted in withdrawal from the study, two of which led to fatal outcome due to metastases and disease progression. The third withdrawal due to TEAE was a non-serious TEAE (duodenal ulcer). None of these AEs were considered to be related to the study drug.

The most common TEAE was nausea, with 278 events (22.9%) observed in 64 patients (53.3%), followed by bone pain with 267 events (22.0%) in 80 patients (66.7%). Table 59 in Appendix 1 summarizes the most commonly reported TEAEs (> 5% of patients). As expected in cancer patients undergoing chemotherapy, the most frequently observed **possibly related** TEAE was bone pain, observed in 70 patients (58.3%; Table 60, Appendix 1) (4, 39, 47). Bone pain is further described in detail subsequently.

The (possibly drug-related) AEs were compared with the adverse drug effects listed in the Neupogen product monograph. Bone pain, nausea, injection-site pain, and headache, which were observed with Grastofil treatment, are listed in the Neupogen product monograph and are expected events following treatment with filgrastim products.

A total of 10 SAEs were reported in nine patients (7.5%) during the treatment and safety follow-up periods. An additional SAE was reported during the screening period (this event is recorded as a pre-treatment SAE). Two patients (1.7%) died during the safety follow-up period of approximately five months after the last dose of the study drug due to metastasis and disease progression. Both TEAEs resulting in death were **not considered to be related** to the study drug Grastofil (Study Report KWI-300-104, Appendix 16.3).

Laboratory Parameters: In addition to hematology parameters affected by chemotherapy, particular attention was devoted to the examination of liver transaminases, LDH, and ALP using standard descriptive statistics. There were no individual trends in any biochemistry parameters.

ANC results were presented earlier under efficacy. Nadir ANC below limit of detection was observed in [redacted] patients during the study, as expected for highly myelotoxic chemotherapy. It was followed by recovery in all patients. Thrombocyte count decreased from a mean (SD) of 276.23 ([redacted]) 10^9/L at cycle 1 day 0, reaching its lowest levels from day 6 to day 18 of cycle 1. Values returned to normal by the beginning of each subsequent cycle. None of these cases required treatment. There were no cases of thrombocytopenia.

Three patients experienced abnormal blood chemistry laboratory values that were considered clinically significant. Disease progression in one patient was associated with clinically significant laboratory abnormalities (elevated ALP, GGT, LDH, AST, and ALT). Lab abnormalities observed in two other patients were assessed as clinically significant findings without associated clinical signs or symptoms. One patient

had AST and ALT increases of 3 × upper limit of normal (ULN). The other patient had ALT increased to approximately 10 × ULN and AST and GGT to approximately 6 × ULN.

Vital Signs: No clinically relevant changes were noted for vital signs over the course of the study.

Corrected QT Interval Prolongation: There were [redacted] abnormal ECG findings in [redacted] patients over the course of the study. Two of the findings were assessed as clinically significant (supraventricular and ventricular extrasystole in patient [redacted] and cardiomyopathy in patient [redacted]). Both of these findings were reported as clinically significant following completion of study treatment at week 20, and both were assessed as unrelated to the study drug. Three subjects experienced prolonged corrected QT interval [redacted] after administration of Grastofil, which is not considered to be a known AE of filgrastim. At the time of the trial, these findings were not considered clinically significant, nor related to Grastofil treatment by the trial investigator.

Bone Pain: At first glance, the incidence of bone pain observed in breast cancer patients in this study appeared to be [redacted] than the incidence reported in the Neupogen product monograph in all phase 2 and 3 trials in cancer patients receiving myelosuppressive chemotherapy ([redacted]% versus [redacted]%). As detailed in [redacted] and [redacted] (13, 14), notwithstanding that direct comparison was not available (and indeed, the US-prescribing information for Neupogen indicated that AE rates should not be compared with another drug from another trial due to widely varying conditions [(4)]), a variety of factors could have influenced the incidence and reporting of bone pain between studies. These could include patients' subjective perception of pain; cultural perception or expression of pain; method for collecting bone pain data (e.g., scales used, instruction for recording, spontaneous versus solicited reporting); timing of the assessment and recording of bone pain (e.g., bone pain caused by G-CSF treatment decreases over treatment cycle); and variability in reporting incidence of bone pain; underlying pathophysiological factors (e.g., incidence of bone pain in phase 1 healthy subjects was lower than in phase 3 cancer patients, and was comparable to Neupogen — 24.3% versus 22.9%, respectively); concomitant medications taken by cancer patients (TAC therapy alone was associated with bone pain, as reported by [redacted] of breast cancer patients, according to docetaxel-prescribing information [the pain effect could be additive with filgrastim]).

In specific relation to Neupogen, the population described in the product monograph did not include breast cancer patients on TAC therapy and the method of bone pain data collection was unknown. A recent retrospective analysis measured bone pain in cancer patients receiving chemotherapy in pegfilgrastim clinical trials (48). The analysis included seven studies; within the filgrastim (Neupogen) group, the breast cancer population comprised 72% of the total population. Of note, 79% of the filgrastim (Neupogen) group was also treated with taxane chemotherapy. The results of the retrospective analysis reveal that the incidence of bone pain for the filgrastim (Neupogen) group was 66.1%, consistent with the incidence of bone pain of 66.7% in the Grastofil Study KWI-300-104. The retrospective study also found that the overall incidence of bone pain in patients receiving taxanes compared with those not receiving taxanes was 68.3% and 48.3%, respectively, suggesting a contribution by taxanes to the incidence of bone pain of approximately 20%. Finally, the retrospective analysis also revealed diminishing incidence of bone pain with each progressive cycle of chemotherapy, which is supportive and consistent with other literature reports, and also with the pattern found in Study KWI-300-104. Severe bone pain was reported by [redacted] ([redacted]%) patients, moderate bone pain by [redacted] ([redacted]%) patients, and mild pain by [redacted] ([redacted]%) patients during the study. The remaining [redacted] ([redacted]%) did not report bone pain.

Therefore, considering the totality of the data, including demonstrated comparability of potency and pharmacological effect of Grastofil and Neupogen, it is likely that the higher incidence of bone pain noted in the KWI-300-104 trial for Grastofil, compared with that reported in the product monograph for Neupogen, is an overestimation rather than a true difference in the safety profile of Grastofil and Neupogen. Hence, these differences are not expected to translate into clinically meaningful differences in the overall safety profile of Grastofil compared with Neupogen.

Splenomegaly: Splenomegaly was suspected in one patient who reported mild, possibly related spleen pain in cycle 3 after 14 doses of Grastofil. No clinical sign of splenomegaly was noticed at physical examination, nor in the computerized tomography scan performed a few months later, and no treatment was required. It was not possible to exclude a relationship between the pain described as "spleen pain" and gastric pain; thus, the origin of the symptom could not be ascertained. Furthermore, splenic rupture has been associated with ANCs far above the normal range (49), which was not the case for this patient, who had borderline low ANC.

Allergic Reaction: There was one case of allergic reaction that was considered unrelated to study medication.

Acute Respiratory Distress Syndrome: No cases of deterioration of acute respiratory distress syndrome were observed.

Anemia: Five patients ([redacted]) suffered from anemia and a total of seven events of anemia were noted ([redacted] of all events). None of these events were considered to be related to Grastofil and no action was taken. All cases were resolved at the end of the observation period.

Injection-Site Reactions: Local reactions were reported by [redacted] patients. Pain, warmth, and swelling were reported, while tenderness and erythema were not reported. All reactions were mild, apart from moderate swelling in one patient and severe warmth in another patient. One reaction required treatment.

4.2.11 Summary of Safety

a) Safety Evaluation Plan

Important risks of filgrastim products include splenic rupture, acute respiratory distress syndrome, anemia, serious allergic reactions, injection-site reactions, and immunogenicity. As such, the safety measurements assessed in the studies of Grastofil included the assessment of AEs, laboratory tests, and vital signs throughout the duration of all of the phase 1 studies. Additionally, in study GCSF-SUIN-05SB01-3FA-(5), immunogenicity was included in the safety assessment. All of these safety end points were also included in the phase 3 study in breast cancer patients.

b) Overview of Safety

Healthy Subjects

In the four phase 1 healthy volunteer studies (KWI-300-101, KWI-300-102, KWI-300-103, and GCSF-SUIN-05SB01-3FA-[5]), 235 subjects received at least one dose of the study drug and constituted the safety population. Because Study KWI-300-103 employed a parallel group design, not all 235 subjects were exposed to both Grastofil and Neupogen. A total of 186 subjects were exposed to both Grastofil and Neupogen filgrastim products, including 35 subjects from KWI-300-101, 72 subjects from KWI-300-102 (36 subjects in the 150 mcg cohort and 36 subjects in the 75 mcg cohort), 36 subjects from KWI-300-103, and 43 subjects from GCSF-SUIN-05SB01-3FA-(5).

An integrated data set (pooled analysis) from the four phase 1 studies in healthy subjects was created, irrespective of different routes of administration, dose administered, and dosing schedule. This approach was employed to identify any safety signals associated with treatment of filgrastim not evident in the studies with small number of subjects. Because KWI-300-101, KWI-300-102, and GCSF-SUIN-05SB01-3FA-(5) were crossover studies, the actual study drugs that subjects received during each of the treatment periods was used to pool the treatment groups. Therefore, subjects in the crossover studies are presented in multiple treatment groups for both drugs.

In total, 187 healthy subjects were exposed to Grastofil across the four phase 1 studies. Of these, 118 ( ) experienced TEAEs and had related TEAEs. Similarly, 234 subjects were exposed to Neupogen across the four studies, 131 (60%) subjects experienced 415 TEAEs, and 96 (41%) had 256 related TEAEs (Table 46). subjects in the Grastofil group and two subjects in the Neupogen group experienced TEAEs of severe intensity, but no serious TEAEs occurred. The maximum severity of all TEAEs was similar between the Grastofil-treated and Neupogen-treated groups. No TEAEs resulted in withdrawal of study subjects in the Grastofil-treated group, with the exception of one subject in the Neupogen-treated group, withdrawn due to viral symptoms.

TABLE 46: OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS, INTEGRATED HEALTHY SUBJECTS SET

	Grastofil (N = 187)		Neupogen (N = 234)		Placebo (N = 6)	
	N (%)	E	N (%)	E	N (%)	E
Number of subjects with at least 1 TEAE						
Number of subjects with at least 1 SAE						
Closest relationship of TEAEs[a]						
Related						
Unrelated						
Maximum severity of TEAEs						
Mild						
Moderate						
Severe						
Maximum severity of related TEAEs						
Mild						
Moderate						
Severe						

AE = adverse event; E = number of events; N = number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Notes: If a subject had multiple AEs with different relationship to study drug, only the most closely related event was summarized for the category of interest. If a subject had multiple AEs with different severity, only the most severe event was summarized for the category of interest.
[a] "Related" includes "definitely," "probably," "possibly," and missing relation. "Unrelated" includes "unlikely" and "not related."
Source: Adopted from Common Technical Document 2.7.4, Table 2.7.4-15.

The most common related TEAEs by preferred term were neutrophil count decrease (Grastofil: ; Neupogen: 20.9%), headache (Grastofil: ; Neupogen: 20.9%), and back pain (Grastofil: ; Neupogen: 15.0%). As previously stated, the AE of decreased neutrophil count was not an unexpected AE as it is related to the PD effect of filgrastim (54, 55). The incidence of other TEAEs including fatigue, arthralgia, feeling hot, nausea, bone pain, dyspnea, and pyrexia were found to be similar (all experienced by less than 5% of patients) between Grastofil and Neupogen.

The most common TEAEs observed with Grastofil are also listed as AEs for cancer patients in the prescribing information for Neupogen, including headache, pain (specifically bone pain or skeletal pain), fatigue, nausea, and vomiting. These same AEs have been reported for healthy subjects. For example, as reported by Gascon et al. (17), the most common AEs reported in healthy subjects after administration of filgrastim were musculoskeletal pain, leukocytosis, thrombocytopenia, and headaches. None of the study drug-related TEAEs observed in the phase 1 studies were unexpected and have been previously described following treatment with filgrastim products. There were no deaths and no cases of SAEs in the four phase 1 studies of healthy subjects.

As discussed in Safety Results in Section 4.2.10, KWI-300-104, bone pain is a commonly experienced AE in subjects treated with filgrastim. Across the four phase 1 studies, bone pain was observed in [redacted] of [redacted] ([redacted]%) and [redacted] of [redacted] ([redacted]%) subjects in the Grastofil and Neupogen groups, respectively. Of these, [redacted] of [redacted] ([redacted]%) and [redacted] of [redacted] ([redacted]%) subjects experienced bone pain that was related to the study drug. There were no cases of splenomegaly in either treatment group. A total of three subjects in the Grastofil group experienced five allergic reaction–related AEs. Of these, only the three successive AEs (all of mild severity) experienced by one subject on the 75 mcg dose were considered related to the study drug.

Clinical Laboratory Evaluation: The integrated safety data for healthy subjects also included clinical laboratory parameters. For the parameters of ALT, C-reactive protein, ALP, LDH, and activated partial thromboplastin time, there were no notable differences between Grastofil and Neupogen with respect to changes from baseline to each of the assessed time points (i.e., ≤ 60 hours and > 60 hours). For uric acid, there were no clinically relevant laboratory results across all subjects in the phase 1 studies. For the parameter of D-dimer, clinically relevant results were reported in four (4.5%) subjects in the Neupogen group.

Vital Signs, Physical Findings, and Other Safety Observations: No relevant changes in heart rate or blood pressure were observed across the four studies in healthy subjects.

Overall, the sum of safety data from healthy subjects demonstrated that Grastofil is comparably as safe as Neupogen, with no new safety signals presented across studies KWI-300-101, KWI-300-102, KWI-300-103, and GCSF-SUIN-05SB01-3FA-(5).

Cancer Patients

A total of 120 white female patients with stage IIA, IIB, or IIIA breast cancer without neoadjuvant chemotherapy for breast cancer were enrolled in the phase 3 study in breast cancer patients (KWI-300-104). Overall, 113 patients (94.2%) completed the treatment period and 109 (90.8%) completed the safety follow-up period up to week 48. A total of 1,216 TEAEs were reported. A total of 110 out of 120 breast cancer patients (91.7%) reported TEAEs. Of these, [redacted] subjects experienced [redacted] related TEAEs. Most TEAEs were described as mild. [redacted] TEAEs resulted in withdrawal from the study; none of these AEs were considered to be related to study drug. Further details on safety results from Study KWI-300-104 are provided in Section 4.2.10.

4.3 Pharmacokinetics

PK biosimilarity of Grastofil and Neupogen was demonstrated in the four phase 1 studies after IV single-dose administration of 5 mcg/kg; after subcutaneous administration of single fixed doses of 150 mcg and 300 mcg; and after single and repeated subcutaneous administration of 5 mcg/kg. Results for AUC and C_{max} after intravenous and subcutaneous administration are shown in Table 47. Results for time at

maximum concentration (T_{max}) and half-life ($T_{1/2}$) are shown in Table 63 (ITT) and Table 64 (PP) in Appendix 1.

TABLE 47: SUMMARY OF AUC AND C_{MAX} FOLLOWING INTRAVENOUS OR SUBCUTANEOUS SINGLE OR REPEAT DOSE ADMINISTRATION OF GRASTOFIL OR NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS IN PHASE 1 STUDIES

Study	Parameter	EP[a]	Grastofil		Neupogen		Ratio of Geometric Means [%][b]
			N	Mean (ng/mL × min)	N	Mean (ng/mL × min)	
KWI-300-101	AUC_{0-32}	1	35	22,047.5	35	24,340.8	90.6 (88.7–92.7)[c]
	AUC_{inf}	2		22,075.3 [redacted]		24,366.5 [redacted]	[redacted](88.7–92.7) 90.7[c,d]
KWI-300-102 (150 mcg)	AUC_{0-72}	1	35	3,275.7	35	3,414.6	96.8 (91.0–103.0)
	AUC_{inf}	1		3,282.7 [redacted]		3,419.7 [redacted]	96.8 (91.0–103.0) [redacted]
KWI-300-103	AUC_{0-24} (day 1)	2	35	11,734.8	34	11,839.4	100.2 (90.3–111.1)
	AUC_{ss} (day 4)	2		5,440.8		5,387.6	102.3 (91.1–114.9)
GCSF-SUIN-05SB01-3FA-(5)	AUC_{0-t}	1	43	12,043.2[e]	43[f]	11,542.8[e]	108 (102–114)
					44[g]	11,184.3[e]	110 (104–116)
KWI-300-101	C_{max} (ng/mL)	2	35	103.3	35	111.6	92.5 (90.3–94.7)[c]
KWI-300-102 (150 mcg)		2	35	7.7	35	8.4	94.6 (85.9–104.1)
KWI-300-103		2	35	25.9	34	25.5	102.2 (91.3–114.5)
GCSF-SUIN-05SB01-3FA-(5)		1	43	24.2	43[d]	22.5	110 (101–120)
					44[e]	21.8	111 (102–121)

AUC = area under the curve; AUC_{0-24} = area under the curve from 0 to 24 hours; AUC_{0-32} = area under the curve from 0 to 32 hours; AUC_{0-72} = area under the curve from 0 to 72 hours; AUC_{0-t} = ; AUC_{inf} = area under the curve from 0 extrapolated to infinity; AUC_{ss} = area under the curve at steady-state; CI = confidence interval; C_{max} = peak concentration; EP = end point; EU = European Union; ITT = intention-to-treat; IV = intravenous; min = minimum; PK = pharmacokinetics; PP = per-protocol; $T_{1/2}$ = half-life.

Note: PP population, unless otherwise stated; data for ITT population is shown in Table 65 in Appendix 1.

[a] End point level.

[b] The ratio of geometric means is the ratio (Grastofil/Neupogen) of the inverse transformation of the least squares means.

[c] For the IV data, ratio of geometric means and 90% CIs are presented for the comparison of the PK characteristics (excluding absorption) of the two drugs. Source: Clinical Study Report KWI-300-101, Tables 26–28; Clinical Study Report KWI-300-102, Tables 31–33; Clinical Study Report KWI-300-103, Tables 34, 36, 37; Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Tables 13.1.1, 13.1.2.

[d] AUC_{inf} values were re-calculated using the re-estimated $T_{1/2}$ values obtained using a more appropriate algorithm. (See [redacted] (57).)

[e] Converted from h × pg/mL.

[f] US-licensed Neupogen.

[g] EU-approved Neupogen.

These PK results indicated that Grastofil and Neupogen are pharmacokinetically similar. It is noteworthy that all 90% CIs of AUC and C_{max} were contained within the equivalence margin (in line with the relevant FDA and EMA guidelines (23, 58, 59)). In almost all cases, the 90% CI for these parameters encompassed 100%; however, in two instances, for Study KWI-300-101 and Study GCSF-SUIN-05SB01-3FA-(5), the

90% CI for AUC_t and/or C_{max} did not encompass 100%. This should not be interpreted as clinically relevant, as the probability of having the 90% CI encompass 100% depends not only on the difference between products, but also on the power of the study. It is not uncommon for the 90% CI to not encompass 100% even when two products have a relatively small difference in mean PK. This may be due to the study power being higher than expected, which can be a result of having too many subjects enrolled in the study or the study being well conducted or controlled, leading to lower variability of the data.

4.4 Immunogenicity

Immunogenicity testing was conducted in the phase 1 study GCSF-SUIN-05SB01-3FA-(5) in healthy volunteers, and in the phase 3 Study KWI- 300-104 in breast cancer patients. Anti-drug antibodies were assessed as a three-step procedure: a screening assay, followed by a confirmation assay for the determination of anti–G-CSF antibodies in human serum samples that were identified as being positive in the screening assay, and then a neutralization assay for confirmatory assay positive samples, to detect the neutralizing effect of antibodies.

In study GCSF-SUIN-05SB01-3FA-(5), there were only eight instances of a positive result in the screening assay (for six of the 48 subjects who comprised the ITT population), and all of these screening-positive samples were confirmed as negative in the confirmatory assay (Table 48).

TABLE 48: STUDY GCSF-SUIN-05SB01-3FA-(5): IMMUNOGENICITY RESULTS AT EACH TIME POINT (PER-PROTOCOL POPULATION)

Assay	Period/Time Point	Result	US-Licensed Neupogen (N = 45), n (%)	EU-Approved Neupogen (N = 45) Assay	Grastofil (N = 45) Period/Time Point
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EU = European Union; PP = per-protocol.
[redacted].
Source: Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Section 14.3.5.1.37; Common Technical Document 2.7.4, Table 2.7.4-24.

In Study KWI-300-104, immunogenicity baseline samples were taken before the initiation of each cycle in an immunosuppressed state (when receiving chemotherapy), and thereafter in the safety follow-up phase on weeks 20, 24, 36, and 48 following the first chemotherapy treatment. There were no signs of immunogenicity at any of the sampling time points. Antibodies were detected in the screening antibody assay in four patients, but none of the samples were confirmed as positive on the confirmatory assay.

As committed in its EMA-approved risk management plan, and as part of its pharmacovigilance activities, Apotex has registered with the Severe Chronic Neutropenia International Registry (SCNIR) and

the European Bone Marrow Transplantation Registry for long-term monitoring of Grastofil use in cancer patients enrolled with these registries. As a part of this monitoring, reports and data on suspected immunogenicity events and anti-drug antibody testing will also be collected by the SCNIR for patients using Grastofil. In addition, Apotex will monitor for any suspected immunogenicity-mediated adverse drug reactions reported during the use of Grastofil in the EU by providing a service for anti-drug antibody testing of the patient sample, if deemed necessary by the patient's physician, and the results from the testing will be provided to the physician or registry requesting the testing. The results will also be provided to regulatory agencies as per reporting requirements. This risk management plan is also approved for Canada and Apotex is committed to fulfill the same requirements in Canada.

5. CRITICAL APPRAISAL OF CLINICAL STUDIES

5.1 CADTH Common Drug Review Comments on Internal Validity

The biosimilarity between Grastofil and the reference products (EU-approved Neupogen and US-licensed Neupogen) was evaluated in four studies: KWI-300-101,[3] KWI-300-102,[4] KWI-300-103,[5] and GCSF-SUIN-05SB01-3FA-(5).[6] These studies compared the PK and PD parameters of Grastofil with those of Neupogen in healthy adult volunteers. A fifth, non-comparative study (KWI-300-104) assessed the safety of Grastofil in breast cancer patients undergoing combination chemotherapy.[7]

The eligibility criteria for study participant selection were identical across the four studies in healthy volunteers. Grastofil and Neupogen were administered via intravenous infusion or subcutaneous injection, either as a single or repeated dose. Bioequivalence of the two products was suggested if the lower bound of the 90% CI for the ratio of Grastofil/Neupogen was greater than 80% and the upper bound was less than 125%. In addition, according to the requirements of the EMA, the 95% CIs of the relative mean PD data were calculated and assessed against the predefined equivalence margins of 80% to 125% in post-hoc analyses. The PP population, which was defined as all randomized subjects without any major protocol deviations, was the primary analysis population for efficacy with regard to the PK and PD analyses.

5.1.1 KWI-300-101

Thirty-six participants were randomized to receive a single dose of Grastofil 5 mcg/kg or a single dose of EU-approved Neupogen 5 mcg/kg. After a washout period of at least four weeks, participants received the alternative products. The PK end points included the area under the plasma concentration-time curve (AUC) for filgrastim plasma concentration, maximum plasma concentration (C_{max}) and elimination half-life ($T_{1/2}$). An ANOVA for the parameters AUC_{0-32} (primary efficacy variable), AUC_{inf}, and C_{max} of filgrastim was performed for the comparison between treatment groups. The PD end points included the ANCs at peak (ANC C_{max}) and the AUC of ANC after administration of filgrastim.

Randomization was carried out using sealed envelopes. The method of blinding was considered appropriate and the randomization code was broken only for emergency reasons. Subjects in the Grastofil/Neupogen group were an average of eight years older than those in the Neupogen/Grastofil group; given the relatively small sample size, this imbalance may have been due to chance. The other baseline patient demographic characteristics (such as height, body weight, and BMI) were comparable between the two groups. Because this was a crossover study, the potential for bias from any imbalances in baseline characteristics is likely low. Method of sample size determination was provided and a power of 87% was reported, based on a proposed sample size of 36 participants.

One female subject was excluded from the ITT analysis due to pregnancy. Results from the PP population were similar to those from the ITT population. In post-hoc analyses, the 95% CIs of the ratios (Grastofil/Neupogen) of the geometric means for PD parameters were calculated and assessed against the predefined acceptance intervals of 80% to 125%. All results were enclosed within the intervals.

Overall, KWI-300-101 provides evidence that Grastofil and Neupogen have similar PK/PD and safety profiles in healthy volunteers after a single-dose intravenous infusion. There were no major limitations to the internal validity of this study. The washout period of four weeks was considered adequate based on input from the clinical expert consulted for this review.

5.1.2 KWI-300-102

KWI-300-102 adopted the same eligibility criteria as KWI-300-101. Seventy-three participants were divided into two cohorts. The 36 subjects in the first cohort were randomized to receive either a fixed dose of 150 mcg Grastofil or 150 mcg EU-approved Neupogen; in the second cohort, 37 subjects were randomized to receive a fixed dose of either 75 mcg Grastofil or 75 mcg EU-approved Neupogen. Both Grastofil and Neupogen were administered subcutaneously. After a washout period of four weeks, participants received the alternative product in the same cohort. The primary PD end point was the peak ANC count (C_{max}) for both the 75 mcg and 150 mcg doses. The plasma AUC of filgrastim of the 150 mcg dose was a co-primary PK end point. Other PK parameters such as C_{max} and $T_{1/2}$ of filgrastim in plasma were also evaluated.

The PD/PK biosimilarity was assessed in two cohorts: 150 mcg Grastofil versus 150 mcg Neupogen, and 75 mcg Grastofil versus 75 mcg Neupogen. It was unclear how participants were assigned to the different dose levels. According to the additional information provided by the manufacturer, there were [redacted] regarding how subjects were assigned to either dose.[8] Within each cohort, randomization was carried out using sealed envelopes. The method of blinding was considered appropriate and the randomization code was broken only for emergency reasons. In the higher-dose cohort, in particular, the Grastofil/Neupogen group, subjects were older and had heavier body weights and higher BMIs compared with those in the Neupogen/Grastofil group. Given the relatively small sample size, this imbalance may have been due to chance. Because this was a crossover study, the potential for bias from imbalances in baseline characteristics is likely low. The method of sample size determination was provided and a power of 87% was estimated, based on a proposed sample size of 72.

Results from the PP population were similar to those from the ITT population. In post-hoc analyses, 95% CIs of the ratios (Grastofil/Neupogen) of the geometric means for PD parameters were calculated and assessed against the predefined acceptance intervals of 80% to 125%. The criteria for biosimilarity were met for all investigated PD/PK parameter (within the predefined equivalence limits). In terms of the safety profiles of Grastofil and Neupogen, it is unclear why the lower dose was more frequently associated with AEs than the higher dose. Upon request, it was confirmed by the manufacturer that the data are [redacted] reported (i.e., there was [redacted]).

Overall, KWI-300-102 provides evidence that Grastofil and Neupogen have similar PK/PD in healthy volunteers. There were no major limitations to the internal validity of this study. The washout period of four weeks was considered adequate, based on input from the clinical expert consulted for this review.

5.1.3 KWI-300-103

In this study, 78 participants were randomized to receive 5 mcg/kg of Grastofil per day for four days, 5 mcg/kg of EU-approved Neupogen per day for four days, or placebo. Grastofil, Neupogen, and a

physiological solution of 0.9% sodium chloride were administered subcutaneously. A 1:1 randomization of Grastofil (N = 36) versus Neupogen (N = 36) was performed, and six healthy subjects were randomized to the placebo group for the purpose of obtaining a baseline for the assay of $CD34^+$ cells. The primary PD end point was ANC C_{max} after the last dose of Grastofil or Neupogen. The secondary end points included absolute $CD34^+$ cell count on day 5 after four days filgrastim injection, and filgrastim PK parameters (AUC_{ss}, AUC_{0-24}, and C_{max}) after repeated dose administration.

Randomization was carried out using sealed envelopes. Six healthy subjects, five of whom were female, were randomized to the placebo group. At baseline, the patient demographic characteristics were comparable between the Grastofil group and the Neupogen group. Compared with the active treatment groups, subjects in the placebo group were an average of 7 cm to 8 cm shorter in height, and 9 kg to 10 kg lighter in body weight; the apparent imbalance was possibly due to the small number randomized to this group. The method of blinding was considered appropriate and the randomization code was broken only for emergency reasons. The method of sample size determination was provided and a power of 90% was estimated, based on a proposed sample size of 33 in each active treatment group.

Results from the PP population were similar to those from the ITT population. In post-hoc analyses, the 95% CIs of the ratios (Grastofil/Neupogen) of the geometric means for PD parameters were calculated and assessed against the predefined acceptance intervals of 80% to 125%. The criteria for biosimilarity were met for all investigated PD/PK parameters (within the predefined equivalence limits). It should be noted, however, that the results for $CD34^+$ counts were not subjected to the same equivalence testing against the predefined margin of 80% to 125% that was used for the other PD and PK outcomes; rather, a descriptive analysis was reported in which there was no apparent statistical difference between Grastofil and Neupogen in mean and median values.

Overall, KWI-300-103 provides evidence that Grastofil and Neupogen have similar PK/PD in healthy volunteers after repeat-dose subcutaneous administration of these drugs. There were no major limitations to the internal validity of this study. Results for $CD34^+$ counts were only reported descriptively; therefore, there is some uncertainty as to whether Grastofil and Neupogen are equivalent on this outcome.

5.1.4 GCSF-SUIN-05SB01-3FA-(5)

This was a three-way crossover, active-controlled Canadian study designed to bridge the clinical data between the Grastofil DP manufactured using the commercial-scale process (i.e., the DS intended for the Canadian market) and EU-approved Neupogen. It was also designed to demonstrate similarity between US-licensed Neupogen and EU-approved Neupogen. In this study, 48 participants were randomized to receive a single fixed dose of 300 mcg Grastofil, EU-sourced Neupogen, and US-sourced Neupogen, administered subcutaneously. The sequence of administration was randomly allocated, and the washout period between treatments was four weeks. The primary PD end points were AUC ANC and ANC C_{max} after the single dose of Grastofil or Neupogen. The primary PK end points were the AUC and C_{max} of filgrastim.

Randomization was carried out using a computer-generated randomization scheme. The method of blinding was considered appropriate. Forty-eight subjects were randomized into six dosing sequences. At baseline, patient demographic characteristics varied across these six groups with respect to age, gender, ethnicity, and BMI, likely due to the small number of subjects in each group. Because of the crossover study design, the potential for bias due to unbalanced baseline characteristics is likely low. The method of sample size determination was briefly described, and it indicated that 48 subjects needed to be enrolled. Given the estimated sample size, the level of statistical power was not reported

in the original submission; however, the manufacturer's comments in December 2015 indicated that, based on the minimum number of subjects required to complete the trial (42 subjects), the targeted power was approximately 80%.[9]

Results from the PP population were similar to those from the ITT population. In post-hoc analyses, the 95% CIs of the ratios (Grastofil/Neupogen) of the geometric means for PD parameters were calculated and assessed against the predefined acceptance intervals of 80% to 125%. The criteria for biosimilarity were met for all investigated PD/PK parameters (within the predefined equivalence limits).

Overall, Study GCSF-SUIN-05SB01-3FA(5) provides evidence that the Grastofil produced using the process intended for the Canadian market and Neupogen (EU-approved or US-licensed) have similar PK/PD in healthy volunteers after a single fixed-dose subcutaneous injection of these drugs. There were no major limitations to the internal validity of this study. The washout period of four weeks was considered adequate, based on input from the clinical expert consulted for this review.

5.1.5 **KWI-300-104**

This was a multi-centre, single-group, open-label phase 3 study in breast cancer patients undergoing chemotherapy known to induce neutropenia. The primary objective of this study was to evaluate the safety of Grastofil when used to reduce the duration of neutropenia. The major inclusion criteria were female patients with stage IIA, IIB, or IIIA breast cancer who were suitable for and intended to undergo adjuvant chemotherapy; had a complete surgical resection of the primary breast cancer within the past 60 days; were chemotherapy-naive; and had an ANC $\geq 1.5 \times 10^9$/L and a platelet count of $\geq 100 \times 10^9$/L. In total, 120 patients were enrolled to receive a daily dose of Grastofil 300 mcg or 480 mcg SC, according to body weight. Treatment began on day 2 of every chemotherapy cycle and was continued for up to 14 days, or until post-nadir ANC recovery to normal or near-normal values — whichever occurred first. The treatment period lasted 18 weeks, during which time all eligible patients received six cycles of TAC chemotherapy (docetaxel, doxorubicin, and cyclophosphamide). At the end of the TAC regimen, patients were followed for 30 weeks. The primary safety end point (also the primary study end point) was the incidence of AEs (all severe and serious) classified by body system, preferred term, frequency, and relationship to the study drug. Immunogenicity was another key safety end point. The main efficacy end point was DSN in cycle 1. $CD34^+$ cell mobilization was another key secondary end point. PK was not assessed in this study. The safety analysis was performed based on the safety analysis subset, which was the same as the FAS. The efficacy analysis was performed upon the FAS and PP population. The investigators also justified the sample size used in this study, indicating that 100 patients was considered adequate to detect whether the common AEs occurred to a similar extent as in previous publications and to detect any other AEs occurring with a frequency of more than 3%.

This was an open-label, single-group, non-comparative study; therefore, it provides no direct information as to whether the efficacy and safety of Grastofil is similar to Neupogen in patients with cancer. Although the data for Grastofil was compared with the published data for Neupogen and other filgrastim products, interpretation of such informal indirect comparisons is limited by potential differences between KWI-300-104 and other filgrastim studies (e.g., in chemotherapy regimen, baseline characteristics, tumour stage).

5.2 CADTH Common Drug Review Comments on External Validity

Of the five included studies, four were single-centre randomized controlled studies conducted in Europe or Canada. The number of randomized subjects ranged from 36 to 78. The majority of subjects in all studies were Caucasian. The studied dose of G-CSF reflects the most commonly used dose (5 mcg/kg) in

clinical practice. The four studies directly comparing Grastofil and Neupogen recruited healthy volunteers aged 18 to 55 years. While this population is not directly relevant to patients that will be treated with Grastofil in clinical practice, it appears reasonable to generalize the results from the comparative studies in healthy subjects to the target patient populations (see 6.4 CDR Comments on Extrapolation for further discussion).

Study KWI-300-104 recruited a clinically relevant population, breast cancer patients undergoing myelosuppressive chemotherapy, from multiple centres in Europe and Canada. All patients were Caucasians. According to the clinical expert consulted for this review, the pharmacokinetic and clinical results from Caucasians can be generalized to non-Caucasian patients. The TAC chemotherapy regimen is a typical one for this population. While the safety outcomes assessed in KWI-300-104 are of direct clinical relevance, the efficacy outcomes of ANC and DSN are surrogates for the clinical outcome of interest, febrile neutropenia. Febrile neutropenia was infrequent, occurring in approximately 2% of patients in each treatment group.

The data on $CD34^+$ counts from the multi-dose Study KWI-300-103 are relevant to the use of Grastofil for mobilization of PBPCs in order to accelerate hematopoietic recovery after myelosuppressive or myeloablative chemotherapy, as this is the main surrogate used in this procedure. There are no data for $CD34^+$ response in patients requiring harvesting of PBPCs; however, similar to the use of healthy volunteers to confirm the similarity of ANC response, substantive differences between Grastofil and Neupogen are unlikely based on the results from healthy subjects. However, as noted earlier under Internal Validity (Section 5.1), results for $CD34^+$ counts were only reported descriptively in Study KWI-300-103; therefore, the equivalence of Grastofil and Neupogen on this outcome was not demonstrated, as it was for ANC.

Overall, there were no major concerns with generalizability of the available clinical studies to the Canadian clinical context. The lack of direct comparative data for Grastofil and Neupogen in patients with cancer and other conditions for which Grastofil is indicated represents a limitation, particularly with respect to safety. Another limitation is the lack of data for Grastofil in children.

6. EXTRAPOLATION OF INDICATIONS (MANUFACTURER-SUBMITTED INFORMATION)

6.1 Rationale for Extrapolation

The efficacy of filgrastim in the treatment of neutropenia is directly related to its biological effects, as it acts selectively on the lines of the neutrophil lineage. It is well documented that G-CSF exerts its effect via binding to the G-CSF receptor, leading to activation of several distinct downstream intracellular signalling cascades. This ultimately leads to transcriptional changes that affect cell survival, migration, differentiation and, most importantly, proliferation of neutrophils (i.e., granulopoiesis) (61-64). As described subsequently, although the pathophysiological factors responsible for neutropenia may vary in the stated indications (whether due to myeloablative or myelosuppressive chemotherapy, induction or consolidation chemotherapy, or concomitant antimicrobial therapy in the case of HIV/AIDS), the pathophysiological consequence of neutropenia is very similar. Common to all these conditions is the increased risk of infection due to potentially life-threatening bacterial infections; the medical need to shorten this period of risk; and the fact that treatment efficacy, and hence patient response, is measured by the ANC, regardless of underlying pathophysiological factors (excluding PBPC mobilization). Indeed, the EMA recognizes ANC as a surrogate marker for the efficacy of filgrastim medicinal products, as the relationship between dose and exposure to the product and this surrogate marker is well known and established. Furthermore, in accordance with the dosage and administration guidelines for Neupogen, for each of these indications, Neupogen can be titrated against the neutrophil response. In addition, the overall favourable safety and tolerability of filgrastim facilitates response-driven treatment in a clinical setting, while also lending support to the justifiable extrapolation of indications.

6.1.1 Myelosuppressive Chemotherapy; Acute Myeloid Leukemia; Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

Most chemotherapies target actively dividing cells (both tumorous and non-tumorous) by disrupting various processes within the cell cycle. It is well known that these therapies have the ability to induce myelosuppression (i.e., anemia, thrombocytopenia, and neutropenia) and that G-CSF is used to reduce the severity and duration of chemotherapy-induced neutropenia (65, 66).

6.1.2 Severe Chronic Neutropenia

Severe chronic neutropenia (SCN) includes congenital, cyclic, or idiopathic neutropenia. Both congenital and cyclic neutropenia are genetic disorders that negatively impact the neutrophils' function in eliminating pathogens (67, 68). Idiopathic neutropenia, which has also been associated with genetic mutation (69), is defined as any persistent, unexplained reduction in the number of ANCs below the lower limit of the normal range. Regardless of the cause, treatment of SCN involves the stimulation of neutrophil product.

6.1.3 HIV

The occurrence of neutropenia is common in patients with HIV. While the causes may vary, it is considered an independent risk factor for bacterial infections, which can also complicate the use of myelosuppressive antimicrobial chemotherapy in such patients. It has been reported that the antimetabolite action and resultant decreased neutrophil count associated with ganciclovir (a drug used to treat or prevent cytomegalovirus infection in some patients with HIV infection) is similar to that of some anticancer chemotherapies (70, 71).

6.1.4 Mobilization of Peripheral Blood Progenitor Cell Collection and Therapy

The mechanism of mobilizing hematopoietic stem/progenitor cells (HSPCs) with G-CSF has been extensively studied. Available studies suggest G-CSF acts on the G-CSF receptors expressed on HSPCs (including hematopoietic stem cells) that, in turn, leads to HSPC mobilization (46, 72). Hence, the potency and effect of G-CSF at the G-CSF receptor is suggested to be the same for both ANC and PBPC mobilization, as measured by $CD34^+$ count, the most commonly used surrogate for measurement of human progenitor cells (31).

Consistent with the mechanism of action of filgrastim on ANC, the mechanism of action of filgrastim on PBPC mobilization is the same in healthy subjects and in patients, as evidenced by its clinical use in both healthy stem cell donors and in cancer patients. From a clinical perspective, there is substantial experience in the assessment of the mobilization of PBPCs in both healthy and diseased population sets (46, 73). Filgrastim use in each of these population sets has been studied in regard to dosage optimization. Regardless of the various confounding pathophysiological factors in patient populations, the response to filgrastim treatment for PBPC mobilization is always measured by $CD34^+$ count. Thus, considering the demonstrated potency of Grastofil and Neupogen at the site of action, the similarity of response of Grastofil and Neupogen in mobilizing $CD34^+$ cells suggests that, clinically, both filgrastim medicinal products are expected to elicit a comparable PD effect in PBPC mobilization, thereby supporting the extrapolation of indications for Grastofil for the treatment of *cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation*, and *cancer patients undergoing PBPC collection and therapy.*

6.1.5 Justification of Extrapolation

a) Clinical Experience

There has been more than 25 years of clinical experience with Neupogen; as such, extensive clinical experience with filgrastim exists from both an efficacy and safety perspective. Available evidence suggests that filgrastim has a consistent and predictable pharmacological profile when administered subcutaneously or intravenously over a wide dose range, which is a consequence of filgrastim's selectivity and specificity for its site of action, the G-CSF receptor (61, 62, 64). It is expected that Grastofil will be equally efficacious and safe, based on the demonstrated biosimilarity with Neupogen.

b) Analytical Similarity and Non-clinical Comparability

A series of physiochemical and biologic assays demonstrated comparability in the primary and higher-order structures. On a receptor level, Grastofil exhibited similar binding affinity and kinetics as Neupogen to the G-CSF receptor. Grastofil and Neupogen also showed highly comparable effects on the proliferation of the NFS-60 cell line in the comparative in vitro bioassay. These results are highlighted in Section 4.1. Overall, these findings are in line with the observed PD effect of ANC proliferation and support the biosimilarity between Grastofil and Neupogen.

c) Pharmacokinetics and Pharmacodynamics Comparability

Results from the four comparative phase 1 PK/PD studies showed that the 90% CIs for the PK end point parameters for Grastofil (C_{max} and AUC) were fully contained within the predefined equivalence margin. Similarly, in these studies, the more stringent 95% CIs of the ANC PD end-point parameters (C_{max} and AUC) were fully contained within the accepted equivalence margin. The conclusion of PK and PD comparability between Grastofil and Neupogen was therefore based on the highly similar results in each of these studies conducted at various sensitive dose levels and different routes of administration (SC and IV) in the most sensitive population (healthy subjects). As such, PD comparability between these

products is expected not only at the assessed doses of between 1 mcg/kg and 5 mcg/kg, but also across all indicated doses for Neupogen, as further supported and elaborated upon in the response below.

d) Clinical Efficacy of Grastofil

Efficacy data from the phase 3 single-group safety study in breast cancer patients are also supportive of extrapolation. In particular, the assessment of the DSN for Grastofil found in this study, along with that for Neupogen published in the literature, support their comparability in the treatment of severe neutropenia, as the DSN for Grastofil was similar to the DSN for Neupogen (as summarized in Table 43). In addition, from the PD perspective, $CD34^+$ data from studies KWI-300-103 and KWI-300-104 demonstrated that Grastofil was effective at mobilizing $CD34^+$ cells. In Study KWI-300-103, there was comparable mobilization of $CD34^+$ cells at day 5, compared with baseline, between Grastofil and Neupogen; a robust 10-fold increase relative to the placebo group was observed, demonstrating excellent signal-over-noise ratio (Table 27). Similarly, in Study KWI-300-104, Grastofil at 5 mcg/kg/day increased $CD34^+$ cell count from 4.57/µL ± 3.33/µL at baseline to 110.67/µL ± 101.18/µL on day 9 of cycle 1, clearly demonstrating its efficacy. Although comparative data were not available, based on the aforementioned results, and the fact that the mechanism of action for recombinant filgrastim is fundamentally the same in healthy volunteers and neutropenic patients, it is expected that the effect of Grastofil and Neupogen on $CD34^+$ mobilization will also be comparable in a patient population.

e) Posology

Following the concept of biosimilarity, the recommended doses of Grastofil are based on the approved doses of the reference product, Neupogen. This is justified by the highly comparable biosimilarity of Grastofil and Neupogen that was demonstrated in four studies in healthy volunteers. In line with the biosimilarity concept, no formal dose-finding studies with Grastofil were conducted. For patients being treated with chemotherapy for cancer, the dose of 5 mcg/kg/day (based on actual body weight) for Grastofil was chosen based on the recommended dose for Neupogen and the highly comparable PK/PD properties of Grastofil and Neupogen after SC and IV administration demonstrated in the studies in healthy volunteers. Indeed, as stated in the EMA's Assessment Report for Grastofil (p. 87), "PK similarity between (Grastofil) and Neupogen at and around the main clinical dose (5 mcg/kg) has been convincingly demonstrated."(5)

The 5 mcg/kg/day (tested SC or IV) dose is also recommended after PBPC transplantation (SC or IV) and for the treatment of idiopathic or cyclic neutropenia (SC)(15). The lower dose of 1 mcg/kg/day (SC) for the treatment of HIV corresponded to the tested dose of 75 mcg (SC). In contrast, although the recommended dose for treating congenital neutropenia is 12 mcg/kg/day (SC), information from the SCNIR showed the actual median doses of G-CSF used in practice were approximately 6 mcg/kg/day for SCN (which includes congenital neutropenia) and approximately 4 mcg/kg/day for Shwachman-Diamond syndrome (which includes neutropenia as a symptom)(75) and thus comparable to indications ranging from chemotherapy-induced neutropenia in cancer patients, or mobilization of progenitor cells in healthy volunteers. Indeed, in a handbook published by the SCNIR (which contains Canadian members), the recommended dose for most patients with SCN was 5 mcg/kg/day to 20 mcg/kg/day (76). Finally, although higher doses (as used in PBPC mobilization and myeloablative therapy followed by bone marrow transplantation) were not tested, based on analyses of linearity of dose-response (data not presented), the PD/efficacy of Grastofil — and, as such, equivalence in PD response for Grastofil and Neupogen — is expected across all indicated doses. This was affirmed by the recent approval of Grastofil by the EMA, as well as affirmation by Health Canada that the NDS was considered approvable for all indications.

f) Reduction of Neutropenia in Special Population (Pediatric)

Although there are no data on the efficacy and safety of Grastofil in children, limited experience with Neupogen indicates no overall differences in children or in elderly patients when compared with adults aged 18 to 65 years, and no effects on overall development and growth. Furthermore, based on the extensive data and clinical history for Neupogen and filgrastim medicinal products, the extrapolation of indications of Neupogen is also justified in a pediatric population.

For the extrapolation of indications to a pediatric population (e.g., cancer patients receiving myelosuppressive chemotherapy requiring filgrastim at a dose of 5 mcg/kg/day SC), some important considerations include aspects of clinical practice and dosing of the patient population, such as clear and legible gradations, reliability of volume delivery, and the clear instructions on dose measuring or adjustment from a full syringe. While Neupogen syringes have 1/5 graduations between 0.1 and 0.5 mL, the markings for the graduated Grastofil syringes have 1/40 graduations, with major graduations of 0.1 mL to 1.0 mL, and minor graduations of 0.025 mL. In fact the addition of 1/40 gradations will allow for accuracy of dosing of multiples of 15µg of Grastofil for the 300 µg/0.5 mL, which is more accurate than the dosing accuracy that can be achieved by Neupogen based on graduations of 0.1 mL (i.e., increments of 60 µg).

6.2 Health Canada's Conclusion on Extrapolation

As per the Health Canada Biologics Safety and Efficacy Assessment Report (Indication Extrapolation, p. 32):

> Based on thorough assessments and internal discussions, a justification has been made that suggests that extrapolation of indications, doses, and routes of administration in adults for which the Canadian reference product are licensed could be granted for Apo-Filgrastim based on the following considerations:
>
> - Filgrastim is a relatively simple and small protein molecule biologic product.
> - Mechanism of action: The biological activity of G-CSF is initiated by the binding of G-CSF to the G-CSF receptor on myeloid progenitor cells and mature neutrophils.
>   - ANC in blood is a relevant and acceptable PD marker for neutropenia.
>   - Hematopoietic stem cells are identified by the presence of the cluster of differentiation protein 34 (CD34) marker on their surface. $CD34^+$ cell count is a relevant and acceptable PD marker for mobilization of hematopoietic stem cells.
> - Similarity between Apo-Filgrastim and the reference product has been demonstrated:
>   - Demonstrated highly similar to the reference within the limits of the analytical methods used for characterization (primary, secondary, and tertiary structures, impurity, and biological activity) and the same final formulation.
>   - Demonstrated similarity of PK and PD parameters to the reference in normal healthy subjects.
> - Up to date, there have been no significant new safety signals that have been identified with clinical studies of Grastofil compared with the reference product.
> - Clinical experience with the reference product with dose range used for both IV and SC routes of administration cross all indications.
> - Proper labelling and adequate post-market commitment for long-term safety monitoring (e.g., immunogenicity) in large and real-world patient populations are required.

6.3 International Regulatory Conclusions on Extrapolation

The EMA's CHMP assessment report has approved Grastofil for multiple indications (p. 88), specifically for:

- Reduction in the duration of neutropenia and the IFN in adult patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes), and for the reduction in the duration of neutropenia in adult patients undergoing myeloablative therapy followed by bone marrow transplantation who are considered to be at increased risk of prolonged severe neutropenia
- The mobilization of PBPCs in adults
- Adult patients with severe congenital, cyclic, or idiopathic neutropenia with an ANC of ≤ 0.5×10^9/L, and a history of severe or recurrent infections, long-term administration of Grastofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events
- The treatment of persistent neutropenia (ANC ≤ 1.0×10^9/L) in adults with advanced HIV infection in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Grastofil has not yet been approved by the FDA or the Australian Therapeutic Goods Administration.

6.4 CADTH Common Drug Review Comments on Extrapolation

The reference product, Neupogen, has six indications approved in Canada: cancer patients receiving myelosuppressive chemotherapy; patients with acute myeloid leukemia; cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation; cancer patients undergoing PBPC collection and therapy; patients with SCN; and patients with HIV infection. Health Canada granted approval to Grastofil for all six indications in December 2015. Clinical trial data are available only for the first indication — i.e., cancer patients receiving myelosuppressive chemotherapy (KWI-300-104); this study did not directly compare Grastofil with Neupogen, although the safety and efficacy were concluded by the authors to be similar to Neupogen, based on comparisons with published literature.

The approval of all six indications is based largely on the extrapolation of the four comparative studies in healthy subjects that demonstrated similar PK and PD properties of Grastofil and Neupogen. According to the manufacturer, healthy subjects represent the most sensitive population in which to identify differences between G-CSF products. Although the development of neutropenia can be attributed to various pathophysiological factors, the clinical consequences of neutropenia are similar, and treatment effects and patient response are measured by ANC — regardless of the underlying cause of neutropenia. Furthermore, Neupogen has been available in the market for more than two decades and its clinical benefits and risks have been well established in patients with neutropenia. The mechanism of action and the pharmacological properties of recombinant G-CSFs are reported to be the same in healthy subjects and in patients with neutropenia (regardless of the underlying cause), thereby supporting the extrapolation of the biosimilarity between Grastofil and Neupogen observed in studies of healthy subjects to patients. Furthermore, the sensitivity and relevance of healthy subjects for the verification of PK and PD similarity of G-CSF products have been accepted by the EMA and the FDA.[10-12] The clinical expert consulted for this review also supported the view that it is reasonable to conduct comparative biosimilarity studies in healthy volunteers.

Similar to the effects on ANC, the effects of repeat-dose Grastofil and Neupogen on $CD34^+$ counts in healthy volunteers in Study KWI-300-103 can likely be extrapolated to cancer patients requiring collection of PBPCs, although these data arise from only one study, which did not employ the Grastofil derived from the process that will be used to supply the Canadian market. In the bridging study (GCSF-SUIN-05SB01-3FA-[5]), similarity between the Grastofil produced with the process intended for the

Canadian market and the EU-approved Neupogen used in other phase 1 trials was demonstrated; therefore, it is likely that the Grastofil produced with the process intended for the Canadian market will have similar effects on $CD34^+$ counts in healthy volunteers and cancer patients. Furthermore, results for $CD34^+$ counts were only reported descriptively in Study KWI-300-103; therefore, equivalence of Grastofil and Neupogen on this outcome was not demonstrated, as it was for ANC. It is also noteworthy that in some indications (i.e., in PBPC mobilization and for patients undergoing myeloablative therapy), higher doses of filgrastim than those studied (i.e., 5 mcg/kg) may be required. Analyses on the linearity of the dose–effect relationship conducted by the manufacturer as part of the regulatory filing supported extrapolation of the findings from the available studies to higher doses (data not shown); nevertheless, there is a lack of specific data on the comparability of Grastofil and Neupogen at higher doses with respect to $CD34^+$ counts. Given the similar PD and PK data between Grastofil and Neupogen, and the expected linearity of filgrastim biosimilars at higher doses, which was supported by data in the literature (dose linearity with Neupogen at higher doses of up to 10 mcg/kg/day), the totality of the evidence suggests that higher doses of Grastofil and Neupogen will likely have similar effects on $CD34^+$ counts.[9]

Although, according to the manufacturer, there are no data on the efficacy, safety, or PK profile of Grastofil in children, experience with Neupogen indicates no overall differences between children and adults. Therefore, the extrapolation to Grastofil of the indications for Neupogen is likely reasonable for the pediatric population although, unlike the adult population, there is no direct supportive evidence.

Grastofil and Neupogen demonstrated comparable safety in the studies of healthy subjects, and the observed adverse events were largely those that are known to be associated with filgrastim. Despite the apparent PD and PK similarity of the two products, it is uncertain to what extent the safety data from healthy subjects can be extrapolated to patients, as the risk of AEs may differ. Furthermore, the total integrated safety population in the studies of healthy subjects comprised only 186 individuals exposed to both products; hence, rarer AEs associated with one or both of Grastofil and Neupogen would not necessarily be observed. Therefore, cumulative data from post-marketing surveillance and clinical experience over time will be important to verify the safety profile of Grastofil.

7. COST COMPARISON (MANUFACTURER-SUBMITTED INFORMATION)

The Grastofil 300 mcg/0.5 mL PFS DP is being submitted at a 25% lower price ($144.3135) relative to the current Ontario Drug Benefit listed price of Neupogen 300 mcg/1 mL vial, which is at $192.4180. Consequently, the 25% cost differential equates to savings of $48.1045 per 300 mcg (PFS or vial).

It should be noted that the full contents of vials or PFSs might not be used, depending on patients' weights. However, as both Grastofil and Neupogen are single-use only, the manufacturer rounded up the number of vials or PFSs to calculate the "average drug cost" per indication (this approach was validated by CDR reviewers).

Across Canada, for all indications, the proportion of sales of the Neupogen 300 mcg/1 mL vial is eight times higher than the sales of Neupogen 480 mcg/1.6 mL (based on IMS Brogan claims data MAT ending March 2015).

TABLE 49: COST COMPARISON OF GRASTOFIL AND NEUPOGEN FOR CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY

Drug/Comparator	Strength	Dosage Form	Price ($)[a,b]	Recommended Dose[c]	Average Drug Cost[d] ($)
Grastofil	300 mcg/0.5 mL PFS	Sterile solution for injection	144.3135	5 mcg/kg/day	5,050.97[e]
Neupogen	300 mcg/1 mL vial		192.4180		6,734.63[e]
	480 mcg/1.6 mL vial		307.8690		10,775.42[f]

ODB = Ontario Drug Benefit; PFS = pre-filled syringe.
[a] Transparent price.
[b] ODB Formulary/Comparative Drug Index, effective from July 29, 2015.
[c] Grastofil and Neupogen product monographs.
[d] For a patient receiving 5 chemotherapy cycles with 7 injections per cycle.
[e] Based on ODB reimbursement criteria for a patient weighing less than 90 kg, the maximum reimbursement coverage is 300 mcg per day.
[f] Based on ODB reimbursement criteria for a patient weighing 90 kg or more, the maximum reimbursement coverage is 480 mcg per day.

TABLE 50: COST COMPARISON OF GRASTOFIL AND NEUPOGEN FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA

Drug/Comparator	Strength	Dosage Form	Price ($)[a,b]	Recommended Dose[c]	Average Drug Cost[d] ($)
Grastofil	300 mcg/0.5 mL PFS	Sterile solution for injection	144.3135	5 mcg/kg/day	3,030.58[e]
Neupogen	300 mcg/1 mL vial		192.4180		4,040.78[e]
	480 mcg/1.6 mL vial		307.8690		6,465.25[f]

ODB = Ontario Drug Benefit; PFS = pre-filled syringe.
[a] Transparent price for Grastofil.
[b] Neupogen price from ODB Formulary/Comparative Drug Index, effective from July 29, 2015.
[c] Considering an induction dose and a consolidation dose of 5 mcg/kg/day.
[d] For a patient receiving 21 days of treatment (80).
[e] Based on ODB reimbursement criteria for a patient weighing less than 90 kg, the maximum reimbursement coverage is 300 mcg per day. This is in line with the Sunnybrook guideline indicating the use of one vial of 300 mcg for patients < 85 kg.
[f] Based on ODB reimbursement criteria for a patient weighing 90 kg or more, the maximum reimbursement coverage is 480 mcg per day. This is in line with the Sunnybrook guideline indicating the use of one vial of 480 mcg for patients > 85 kg.

TABLE 51: COST COMPARISON OF GRASTOFIL AND NEUPOGEN FOR CANCER PATIENTS RECEIVING MYELOABLATIVE CHEMOTHERAPY FOLLOWED BY BONE MARROW TRANSPLANTATION

Drug/ Comparator	Strength	Dosage Form	Price ($)[a,b]	Recommended Dose[c]	Average Drug Cost[d] ($)
Grastofil	300 mcg/0.5 mL PFS	Sterile solution for injection	144.3135	10 mcg/kg/day	6,061.17[e]
Neupogen	300 mcg/1 mL vial		192.4180		8,081.56[f]
	480 mcg/1.6 mL vial		307.8690		8,620.33[g]
	300 mcg/1 mL vial and 480 mcg/1.6 mL vial		192.4180 and 307.8690		7,004.02[h]

PFS = pre-filled syringe.
[a] Transparent price for Grastofil.
[b] Neupogen price from Ontario Drug Benefit Formulary/Comparative Drug Index, effective from July 29, 2015.
[c] Grastofil and Neupogen product monographs.
[d] For a patient weighing 70 kg receiving a dose of 10 mcg/kg/day for 14 days.(81)
[e] Three × 300 mcg/0.5 mL PFSs per day.
[f] Three × 300 mcg/1 mL vials per day.
[g] Two × 480 mcg/1.6 mL vials per day.
[h] One × 300 mcg/1 mL vial plus 1 × 480 mcg/1.6 mL vial per day.

TABLE 52: COST COMPARISON OF GRASTOFIL AND NEUPOGEN FOR CANCER PATIENTS UNDERGOING PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY

Drug/ Comparator	Strength	Dosage Form	Price ($)[a,b]	Recommended Dose[c]	Average Drug Cost[d] ($)
Grastofil	300 mcg/0.5 mL PFS	Sterile Solution for Injection	144.3135	10 mcg/kg/day	3,030.58[e]
Neupogen	300 mcg/1 mL vial		192.4180		4,040.78[f]
	480 mcg/1.6 mL vial		307.8690		4,310.17[g]
	300 mcg/1 mL vial and 480 mcg/1.6 mL vial		144.3135 and 230.9017		3,502.01[h]

PFS = pre-filled syringe.
[a] Transparent price for Grastofil.
[b] Neupogen price from Ontario Drug Benefit Formulary/Comparative Drug Index, effective from July 29, 2015.
[c] Grastofil and Neupogen product monographs.
[d] For a patient weighing 70 kg, receiving a dose of 10 mcg/kg per day for 7 days.
[e] Three × 300 mcg/0.5 mL PFSs per day.
[f] Three × 300 mcg/1 mL vials per day.
[g] Two × 480 mcg/1.6 mL vials per day.
[h] One × 300 mcg/1 mL vial plus 1 × 480 mcg/1.6 mL vial per day.

TABLE 53: COST COMPARISON OF GRASTOFIL AND NEUPOGEN FOR PATIENTS WITH SEVERE CHRONIC NEUTROPENIA

Drug/ Comparator	Strength	Dosage Form	Price ($)[a,b]	Recommended Dose[c]	Average Drug Cost ($)[d]
Grastofil	300 mcg/0.5 mL PFS	Sterile solution for injection	144.3135	Congenital neutropenia: 6 mcg/kg/day Idiopathic neutropenia: 1.2 mcg/ kg/day Cyclic neutropenia: 2.1 mcg/kg/day	144.31
Neupogen	300 mcg/1 mL vial		192.4180		192.42
	480 mcg/1.6 mL vial		307.8690		307.87

PFS = pre-filled syringe; SCN = severe chronic neutropenia.
[a] Transparent price for Grastofil.
[b] Neupogen price from Ontario Drug Benefit Formulary/Comparative Drug Index, effective from July 29, 2015.
[c] Based on the SCN post-marketing surveillance study stated in Neupogen product monograph.
[d] Cost per day per patient. Considering an average weight of 10 kg for congenital neutropenia and 70 kg for idiopathic and cyclic neutropenia, no patient will use more than 1 vial or 1 PFS of 300 mcg per day based on the assumed dose/weight combinations across the SCN indications. The inclusion of the cost for the 480 mcg vial is for illustrative purpose only.

TABLE 54: COST COMPARISON OF GRASTOFIL AND NEUPOGEN FOR PATIENTS WITH HIV INFECTION

Drug/ Comparator	Strength	Dosage Form	Price ($)[a,b]	Recommended Dose[c]	Average Drug Cost ($)[d]
Grastofil	300 mcg/0.5 mL PFS	Sterile solution for injection	144.3135	1 mcg/kg/day or 300 mcg 3 times per week	432.94
Neupogen	300 mcg/1 mL vial		192.4180		577.25
	480 mcg/1.6 mL vial		307.8690		923.61

PFS = pre-filled syringe.
[a] Transparent price.
[b] Ontario Drug Benefit Formulary/Comparative Drug Index, effective from July 29, 2015.
[c] Grastofil and Neupogen product monograph.
[d] Cost per week per patient. Assume patient uses 300 mcg for 3 injections per week. Based on the recommended dose stated in the Grastofil and Neupogen product monographs, no patient will use more than 1 vial or 1 PFS of 300 mcg per injection. The inclusion of the cost for the 480 mcg vial is for illustrative purpose only.

7.1 CDR Reviewers' Comments Regarding Cost Information

7.1.1 Summary of the Manufacturer's Analysis

Subsequent-entry filgrastim (Grastofil) is available in 300 mcg/0.5 mL single-use pre-filled syringes for injection at a manufacturer-submitted price of $144.3135. The manufacturer submitted a cost comparison assessment of Grastofil versus Neupogen for the six indications under review, summarized in Table 55. This comparison focuses on the Grastofil 300 mcg/0.5 mL dose versus the Neupogen 300 mcg/1 mL dose. Neupogen is currently available as single-use vials of 300 mcg/1 mL, and also 480 mcg/1.6 mL, priced at $192.4180 and $307.8690, respectively, according to the Ontario Drug Benefit Formulary (November 2015). The pre-filled syringe format of Neupogen is currently not available in Canada. According to the manufacturer's cost comparison, the drug cost of Grastofil 300 mcg/0.5 mL is 25% less than Neupogen 300 mcg/1 mL when used for all of the indications under review presented in Table 55. Details of the methods, assumptions (such as patient weight) and sources of evidence used to calculate the cost of compared drugs are presented earlier in this section.

TABLE 55: SUMMARY OF MANUFACTURER'S COST COMPARISON

Indication	Dosage	Treatment Length	Cost of Grastofil ($)	Cost of Neupogen ($)	Cost Difference ($)
Cancer patients receiving myelosuppressive chemotherapy (based on use of 300 mcg per day)	5 mcg/kg/day	For a patient receiving 5 chemotherapy cycles with 7 once-daily injections of filgrastim per cycle	5,050.97	6,734.63	1,683.66 per course of treatment
Patients with acute myeloid leukemia (based on use of 300 mcg per day)	5 mcg/kg/day	21 days	3,030.58	4,040.78	1,010.20 per course of treatment
Cancer patients receiving myeloablative chemotherapy followed by bone marrow	10 mcg/kg/day	14 days	6,061.17	8,081.56	2,020.39 per course of treatment

Indication	Dosage	Treatment Length	Cost of Grastofil ($)	Cost of Neupogen ($)	Cost Difference ($)
transplantation (based on use of 3 × 300 mcg per day)					
Cancer patients undergoing peripheral blood progenitor cell collection and therapy (based on use of 3 × 300 mcg per day)	10 mcg/kg/day	7 days	3,030.58	4,040.78	1,010.20 per course of treatment
Patients with severe chronic neutropenia (based on use of 300 mcg per day)	Congenital neutropenia: 6 mcg/kg/ day Idiopathic neutropenia: 1.2 mcg/ kg/day Cyclic neutropenia: 2.1 mcg/kg/day	Cost per day per patient	144.31	192.42	48.11 daily
Patients with HIV infection (based on use of 300 mcg per day)	1 mcg/kg/day or 300 mcg 3 times per week	Cost per week per patient	432.94	577.25	144.31 weekly

7.1.2 CADTH Common Drug Review Assessment of the Manufacturer's Cost Comparison

- The methods used by the manufacturer for drug cost calculations regarding dosing regimens were found to be appropriate by CDR and the clinical expert involved in this review.
- The use of Grastofil is associated with 25% lower drug costs when compared with the Ontario Drug Benefit Formulary price of Neupogen for all indicated usages and available strengths.

7.1.3 Issues for Consideration

- The clinical expert indicated there are no anticipated difficulties or disadvantages in switching from Neupogen to Grastofil in patients currently receiving Neupogen. This would lead to savings for drug plans.
- The use of PFSs with Grastofil in place of vials with Neupogen may lead to savings in nursing time and related costs, as patients can self-inject with less need for supervision or instructions.
- The manufacturer's cost comparison used the Ontario Drug Benefit list price for Neupogen and expected cost savings may vary between the participating drug plans. In particular, the use of Grastofil instead of Neupogen may be associated with more notable cost savings in Saskatchewan where the list price for Neupogen is priced at $297.380 per 300 mcg/1 mL vial, which is $104.962 more than the price listed on the Ontario Drug Benefit Formulary.
- Projected savings do not account for any confidential pricing of Neupogen.
- The dosage of filgrastim is based on the patient's weight. Grastofil and Neupogen share the same dosing regimen strategies, and variations in a patient's weight would not affect the relative cost difference between the drugs.
- Some of the indications for filgrastim are chronic in nature, such as SCN and HIV infection. The relative costs of Grastofil and Neupogen are not expected to vary with the longer time horizon of treatment associated with these conditions, although absolute savings may become substantial, especially since daily treatment is indicated for these conditions.

7.2 Conclusion

At the manufacturer's submitted transparent price for Grastofil, the treatment cost for Grastofil is 25% lower than the reference filgrastim — Neupogen — when using the Ontario Drug Benefit list price for Neupogen. This holds for all reviewed indications of usage.

8. DISCUSSION

Patients with neutropenia have unusually low levels of neutrophils in the body and are susceptible to infections, which can be life-threatening.[13] Possible causes of neutropenia include congenital disorders, cancer, or other diseases that damage bone marrow, and chemotherapy.[14] Filgrastim has been recommended in various clinical practice guidelines as one of the treatment options for neutropenia.[15,16] Neupogen (filgrastim) has been approved and marketed in Canada since the 1990s.[17] Grastofil is the first SEB of filgrastim that will be available on the Canadian market. The "subsequent entry biologic" designation is used by Health Canada to describe a biologic drug that enters the market subsequent to a version previously authorized in Canada.[18] While such products may provide a potentially cost-effective treatment option for patients, the molecular complexity of biologics compared with other drugs requires close scrutiny of their pharmacokinetics, efficacy, safety, and immunogenicity. There are also concerns surrounding interchangeability and the need for ongoing post-marketing surveillance.[18,19] The automatic substitution of an SEB by dispensing pharmacies, as is done with non-biologics, is not recommended by Health Canada.

Filgrastim (Neupogen) has been used in clinical practice for more than two decades and has a demonstrated efficacy and safety profile in treating neutropenia. The phase 1 pharmacological studies (KWI-300-101, KWI-300-102, KWI-300-103, and GCSF-SUIN-05SB01-3FA) in healthy volunteers provided sufficient evidence that Grastofil is comparable to Neupogen in terms of PD and PK parameters upon administration of single and multiple doses. Healthy subjects are considered the most G-CSF–responsive population, and are accepted by regulators for demonstrating biosimilarity of filgrastim SEBs. In addition, data were available from one single-group phase 3 study in breast cancer patients undergoing myelosuppressive chemotherapy. In this study, the safety and efficacy of Grastofil appeared to be similar to that of Neupogen, based on data reported in the literature; however, the interpretability of this study is limited by the lack of a comparator group. There were no studies of Grastofil in patients falling under the other five indications submitted by the manufacturer; therefore, these indications were approved largely on the basis of the comparative studies of Grastofil in healthy subjects.

Overall, it appears reasonable to extrapolate the comparative PK and PD data (and, consequently, the comparative efficacy in terms of ANC levels) for Grastofil and Neupogen across the six submitted indications. Results for $CD34^+$ counts were only reported descriptively in Study KWI-300-103; although the data provided from this study do not suggest a significant difference in $CD34^+$ response, equivalence of Grastofil and Neupogen on this outcome was not demonstrated, as it was for ANC. Perhaps the area of greatest uncertainty in extrapolating the evidence from available trials of Grastofil versus Neupogen is safety, because there were no comparative studies in indicated populations of patients, and the total safety population of healthy subjects exposed to both Grastofil and Neupogen was relatively small. Adverse effects of biologics may be caused through mechanisms other than the main pharmacological effect — i.e., stimulation of G-CSF receptor in the case of filgrastim — which can make them difficult to predict. AEs due to immunogenicity are of particular concern in evaluating biosimilars,[20] although the only comparative study (GCSF-SUIN-05SB01-3FA-[5]) of Grastofil versus Neupogen assessing this outcome identified no confirmed cases of immunogenicity in healthy volunteers. Nevertheless, it will be

important to evaluate accumulated post-marketing data and clinical experience over time to verify the safety of Grastofil. In this submission, the manufacturer has indicated a commitment to post-marketing surveillance activities to verify the safety of Grastofil, for example, registration with neutropenia and bone marrow transplantation registries to detect immunogenicity and anti-drug antibodies.

8.1 Potential Place in Therapy

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Grastofil is a SEB product to the reference product, recombinant human G-CSF (Neupogen). It has been approval by Health Canada for all six indications granted for the reference product. The submitter has not requested any new or expanded indications beyond those for Neupogen; hence, there are no clinical unmet or suboptimally met needs for the population in question that Grastofil will address. The dosing of Grastofil is not different from Neupogen.

The American Society of Clinical Oncology recently published an update to the 2006 guidelines for the use of white blood cell growth factors in which biosimilars are acknowledged and not differentiated from Neupogen.[21] The submitter has, however, suggested that the introduction of Grastofil may lead to economic savings for both payers and patients, given the proposed pricing. Grastofil also differs from Neupogen in that it includes the PFS format and a longer period of stability at room temperature. Based on the available PK and PD data, there are no apparent barriers to the use of Grastofil in place of Neupogen for any of the indications, although no safety or efficacy data have been submitted for patients with acute myeloid leukemia, patients receiving myeloablative chemotherapy followed by bone marrow transplantation, cancer patients undergoing PBPC collection, patients with SCN, or patients with HIV infection.

9. CONCLUSIONS

The reviewed studies demonstrated biosimilarity in PD and PK parameters between Grastofil and Neupogen in healthy subjects. Extrapolation of these results to relevant patient populations, along with the demonstrated similarity in the physicochemical and quality characteristics of Grastofil and Neupogen, formed the basis for the six approved indications for Grastofil. With respect to efficacy, the data for biosimilarity were strongest for ANC, while equivalence was not statistically tested for $CD34^+$ counts. The safety profile of Grastofil appeared similar to Neupogen. However, given the small total sample size of the studies, and the lack of head-to-head studies in the types of patients that will receive Grastofil in clinical practice, comparative safety remains somewhat uncertain. Hence, cumulative post-marketing surveillance data over time will be important to verify safety. The only study of Grastofil in a relevant patient population (i.e., breast cancer patients) was uncontrolled and provided no direct information on comparative efficacy and safety, although comparisons with prior studies of Neupogen did not suggest important differences.

APPENDIX 1: ADDITIONAL DATA

TABLE 56: STUDY KWI-300-103: ANC $C_{MAX,24H}$ AFTER A SINGLE SC INJECTION OF 5 MCG/KG GRASTOFIL OR NEUPOGEN (PP AND ITT POPULATIONS)

End Point		Grastofil	Neupogen	Placebo	Ratio of Geometric Means [%]	95% CI [%]	*P* > [t]
PP Population							
ANC $C_{max,24h}$ (cells × 10^9)	N	35	34	6	96.17	87.58 to 105.61	0.4081
	Mean	21.04	21.96	5.34			
	SD	3.68	4.62	1.87			
	Minimum	13.07	13.79	4.25			
	Median	21.09	22.05	4.62			
	Maximum	26.01	34.85	9.05			
ITT Population							
ANC $C_{max,24h}$ (cells × 10^9)	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]			
	SD	[redacted]	[redacted]	[redacted]			
	Minimum	[redacted]	[redacted]	[redacted]			
	Median	[redacted]	[redacted]	[redacted]			
	Maximum	[redacted]	[redacted]	[redacted]			

ANC = absolute neutrophil count; CI = confidence interval; $C_{max,24h}$ = maximum concentration at 24 hours; ITT = intention-to-treat; PP = per-protocol; SC = subcutaneous; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3-13 and 2.7.3-15; Clinical Attachment 1, p. 24, 30.

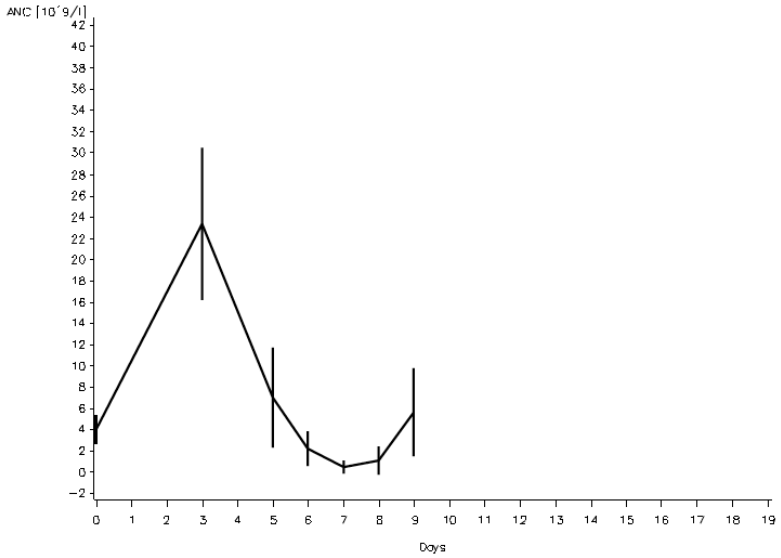
TABLE 57: STUDY KWI-300-103: ANC AUC_{0-24} AFTER A SINGLE SC INJECTION OF 5 MCG/KG GRASTOFIL OR NEUPOGEN (PP AND ITT POPULATIONS)

End Point		Grastofil	Neupogen	Placebo	Ratio of Geometric Means [%]	95% CI [%]	*P* > [t]
PP Population							
ANC AUC_{0-24} (cells × 10^9*min/L)	N	35	34	6	[redacted]	[redacted]	[redacted]
	Mean	22,974.9	23,873.8	5,502.2			
	SD	3,878.1	4,679.4	781.0			
	Minimum	14,321.4	16,167.1	4,622.8			
	Median	22,781.9	23,422.1	5,492.7			
	Maximum	28,634.7	38,997.2	6,410.5			

End Point		Grastofil	Neupogen	Placebo	Ratio of Geometric Means [%]	95% CI [%]	*P* > [t]
ITT Population							
ANC AUC_{0-24} (cells × 10^9*min/L)	N	36	36	6	[redacted]	[redacted]	[redacted]
	Mean	23,083.5	24,177.0	5,502.2			
	SD	3,877.5	4,717.4	781.0			
	Minimum	14,321.4	16,167.1	4,622.8			
	Median	22,842.6	23,735.3	5,492.7			
	Maximum	28,634.7	38,997.2	6,410.5			

AUC_{0-24} = area under the curve from 0 to 24 hours; ANC = absolute neutrophil count; CI = confidence interval; $C_{max,24h}$ = maximum concentration at 24 hours; ITT = intention-to-treat; PP = per-protocol; SC = subcutaneous; SD = standard deviation.
Source: Common Technical Document 2.7.3, Tables 2.7.3-13 and 2.7.3-15; Clinical Attachment 1, p. 21 and 27.

TABLE 58: STUDY KWI-300-104: RESULTS FOR OTHER SECONDARY EFFICACY OUTCOMES IN BREAST CANCER PATIENTS TREATED WITH GRASTOFIL

End Point	Results
Depth of ANC nadir in cycle 1	The mean ANC nadir of 0.37 × 109/L was recorded on mean (SD) day 7.20 (0.64) of chemotherapy cycle 1
Time (number of days) to the post nadir ANC recovery (ANC >1.5 × 10^9/L) in cycle 1, relative to chemotherapy administration	Recovery occurred after a median of 9 and a mean (SD) of 9.11 (1.32) days
ANC-time profile in cycle 1 (Time from the beginning of chemotherapy to the occurrence of ANC nadir)	Severe neutropenia occurred most frequently on day 7 of cycle 1, with the day of onset ranging from day 5 to day 9. The following figure displays the ANC-time profile in cycle 1. Absolute neutrophil count peaked at day 3 with a mean (SD) count of 22.73 (7.18) and maximum of 41.80 × 10^9/L. **Absolute Neutrophil Count–Time Profile in Cycle 1 (Mean ± SD)** **Full Analysis Set** 

ANC = absolute neutrophil count; SD = standard deviation.
Source: Common Technical Document 2.7.3, Section 2.5, Clinical Study Report KWI-300-104.

TABLE 59: STUDY KWI-300-104: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS ACCORDING TO SYSTEM ORGAN CLASS > 5% (CANCER PATIENTS SET)

System Organ Class	MedDRA Preferred Term	Number of Patients (%)	Number of Events (%)
All events		120 (100.0)	1,216 (100.0)
Ear and labyrinth disorders	Vertigo	11 (9.17)	36 (2.96)
Gastrointestinal disorders	Abdominal pain	6 (5.00)	7 (0.58)
	Abdominal pain upper	7 (5.83)	14 (1.15)
	Diarrhea	22 (18.33)	36 (2.96)
	Dyspepsia	7 (5.83)	17 (1.40)
	Nausea	64 (53.33)	278 (22.86)
	Vomiting	12 (10.00)	21 (1.73)
General disorders and administration site conditions	Asthenia	6 (5.00)	20 (1.64)
	Fatigue	24 (20.00)	60 (4.93)
	Pyrexia	7 (5.83)	13 (1.07)
Metabolism and nutrition disorders	Anorexia	6 (5.00)	12 (0.99)
Musculoskeletal and connective tissue disorders	Bone pain	80 (66.67)	267 (21.96)
Nervous system disorders	Dizziness	16 (13.33)	59 (4.85)
	Headache	29 (24.17)	84 (6.91)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	9 (7.50)	9 (0.74)
Skin and subcutaneous tissue disorders	Alopecia	36 (30.00)	36 (2.96)

MedDRA = Medical Dictionary for Regulatory Activities.
Source: Common Technical Document 2.7.4, Table 2.7.4-18; Study Report KWI-300-104, Table 24.

TABLE 60: STUDY KWI-300-104: SUMMARY OF POSSIBLY RELATED TREATMENT-EMERGENT ADVERSE EVENTS ACCORDING TO SYSTEM ORGAN CLASS (CANCER PATIENTS SET)

		Patients	Events
Total number of subjects		120 (100.00)	
Total number of subjects with possibly related TEAEs		70 (58.33)	252
System Organ Class	**MedDRA Preferred Term**	**N (%)**	**Number of Events**
Musculoskeletal and connective tissue disorders	Bone pain	70 (58.33)	228
Gastrointestinal disorders	Nausea	4 (3.33)	6
	Abdominal pain	1 (0.83)	1
General disorders and administration site conditions	Injection-site reaction	4 (3.33)	4
	Injection-site pain	2 (1.67)	4
	Injection-site pruritus	1 (0.83)	1
	Pyrexia	1 (0.83)	3
Nervous system disorders	Headache	3 (2.50)	3
	Dizziness	2 (1.67)	2

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Common Technical Document 2.7.4, Table 2.7.4-19; Study Report KWI-300-104, Tables 14.3.1.8-14.3.1.10.

TABLE 61: SUMMARY OF ANC PARAMETERS (C_{MAX} AND AUC) IN SUBCUTANEOUS PK/PD CLINICAL STUDIES COMPARING G-CSF SUBSEQUENT ENTRY BIOLOGIC TEST PRODUCTS AND NEUPOGEN

Test Product (Study)	Dose (mcg/kg)	N	C_{max} (SD) (Cells × 10^9/L) Neupogen	N	C_{max} (SD) (Cells × 10^9/L) Test	C_{max} PE (95% CI)	N	AUC_{0-96} (SD) (Cells × 10^9*h/L) Neupogen	N	AUC_{0-96} (SD) (Cells × 10^9*h/L) Test	AUC PE (95% CI)
Zarzio (Hexal) (EP06-105)	1	23[a]	20 (4)	23[a]	20 (4)	100 (94 to 105)	23[a]	725 (133)[b]	23[a]	741 (125)[b]	102 (97 to 108)
Zarzio (Hexal) (EP06-103)	2.5	28[c]	20 (4)	28[c]	20 (5)	104 (97 to 111)	NA		NA		NA
	5	27[d]	23 (6)	27[d]	22 (4)	100 (95 to 105)	NA		NA		NA
Tevagrastim (XM02-01-LT)	5	27[e]	23 (3)	25[e]	22 (3)	99 (93 to 105)[f]	27[e]	902 (144)	25[e]	902 (119)	100 (97 to 103)[f]
Tevagrastim (XM02-05-DE)	5	33[g]	21 (1.3)[h]	33[g]	23 (1.3)[h]	107 (102 to 113)[f]	33[g]	983 (1.3)[h]	33[g]	957 (1.4)[h]	98 (86 to 110)[f]
Zarzio (Hexal) (EP06-101)	10	32[i]	24 (8)	32[i]	24 (8)	98 (91 to 105)	NA		NA		NA
Tevagrastim (XM02-01-LT)	10	27[j]	26 (6)	27[j]	26 (7)	99 (94 to 106)[n]	27[j]	1,188 (202)	27[j]	1,200 (205)	101 (96 to 106)[n]
Tevagrastim (XM02-05-DE)	10	30[k]	27 (1.3)[h]	30[k]	27 (1.3)[h]	100 (95 to 104)[n]	30[k]	1,245 (1.6)[h]	30[k]	1,306 (1.4)[h]	105 (89 to 124)[n]
Nivestim (GCF061)	10	26[l]	23 (14–37)[m]	26[l]	23 (17–34)[m]	104 (97 to 112)[n]	26[l]	1,300 (732–2,031)[m,n]	26[l]	1,334 (954–2,169)[m,n]	103 (98 to 107)[n]
Grastofil (KWI-300-102)[o]	Approx. 1 (75 mcg)	36	[redacted]	37	[redacted]	92 (87 to 97)	36	[redacted][p]	36	[redacted][p]	95 (91 to 99)
	Approx. 2 (150 mcg)	36	[redacted]	36	[redacted]	96 (91 to 102)	36	[redacted][p]	35	[redacted][p]	98 (93 to

Test Product (Study)	Dose (mcg/kg)	N	C_{max} (SD) (Cells × 10^9/L) Neupogen	N	C_{max} (SD) (Cells × 10^9/L) Test	C_{max} PE (95% CI)	N	AUC_{0-96} (SD) (Cells × 10^9*h/L) Neupogen	N	AUC_{0-96} (SD) (Cells × 10^9*h/L) Test	AUC PE (95% CI)
											123)
Grastofil (GCSF-SUIN-05SB01-3FA-[5])[o]	Approx. 4 (300 mcg)	45	[redacted][q]	43	[redacted]	103 (98 to 109)[q]	45	[redacted][q]	43	[redacted]	103 (99 to 107)[q]
		45	[redacted][r]			100 (95 to 106)[r]	45	[redacted][r]			100 (96 to 104)[r]

ANC = absolute neutrophil count; approx. = approximately; AUC = area under the curve; AUC_{0-72} = area under the curve from 0 to 72 hours; AUC_{0-96} = area under the curve from 0 to 96 hours; $AUEC_{0-120h}$ = Area under the effect-time curve between 0 and 120 hours; $AUEC_{0-tlast}$ = Area under the effect-time curve between 0 and the last measured time point; CI = confidence interval; C_{max} = peak concentration; EU = European Union; G-CSF = granulocyte-colony stimulating factor; ITT = intention-to-treat; NA = not applicable; PD = pharmacodynamics; PE = pharmacoeconomic; PK = pharmacokinetics; SC = subcutaneous; SD = standard deviation.
Note: ANC results of C_{max} and AUC are expressed as geometric mean [SD].
[a] Twenty-four subjects were enrolled and completed the two-way crossover study, but only 23 subjects were eligible for PD analysis.
[b] $AUEC_{0-120h}$.
[c] Twenty-eight subjects were enrolled and completed the 2.5 mcg/kg dose group in the two-way crossover study and all were eligible for PD analysis.
[d] Twenty-eight subjects were enrolled and 27 subjects completed the 5 mcg/kg dose group in the two-way crossover study and were eligible for PD analysis.
[e] Twenty-eight subjects were enrolled and 24 subjects completed the 5 mcg/kg dose group in the two-way crossover study but 25 and 27 subjects had sufficient data for PD analysis in the test (Grastofil) and Neupogen groups, respectively.
[f] The 95% CIs are calculated based on the 90% CI given in the publications.
[g] Thirty-six subjects were enrolled and 35 subjects completed the 5 mcg/kg dose group in the two-way crossover study but only 33 subjects had sufficient data for PD analysis.
[h] Geometric SD.
[i] Forty subjects were enrolled and 32 subjects completed the two-way crossover study and were eligible for PD analysis.
[j] Twenty-eight subjects enrolled and 27 subjects completed the 10 mcg/kg dose group in the two-way crossover study and these 27 subjects had sufficient data for PD analysis in both the test (Grastofil) and Neupogen groups.
[k] Thirty-six subjects were enrolled and 34 subjects completed the 10 mcg/kg dose group in the two-way crossover study but only 30 subjects had sufficient data for PD analysis.
[l] Twenty-six subjects were enrolled into the SC portion of the two-way crossover study and all subjects were included in the main PD population.
[m] Range.
[n] $AUEC_{0-tlast}$ (Last time point not provided in the literature; it is at least 120 hours according to the graphs in the publication.)
[o] ITT population data.
[p] Reported as ANC AUC_{0-72} (cells × 10^9*min/L).
[q] Versus EU-approved Neupogen.
[r] Versus US-licensed Neupogen.
[s] Mean dose calculated from individual body weight.
Source: Response to [redacted] (20); Table 16, Table 17, Table 18, and Table 19.

TABLE 62: SUMMARY OF ANC PARAMETERS (C_{MAX} AND AUEC) IN CLINICAL STUDIES COMPARING G-CSF SUBSEQUENT ENTRY BIOLOGIC TEST PRODUCTS AND NEUPOGEN FOLLOWING MULTIPLE DOSES

Test Product (Study)	Dose (mcg/kg)	N	C_{max} (SD) (Cells × 10^9/L) Neupogen	N	C_{max} (SD) (Cells × 10^9/L) Test	C_{max} PE (95% CI)	N	AUC_{0-216} (Cells × 10^9*h/L) Neupogen	N	AUC_{0-216} (Cells × 10^9*h/L) Test	AUC PE (95% CI)
Zarzio (Hexal) (EP06-103)	2.5 × 7 days	28[a]	40 (9)	28[a]	39 (10)	98 (93 to 102)	28[a]	4,135 (951)	28[a]	4,224 (1,048)	102 (99 to 105)
Nivestim (GCF062)	5 × 5 days	24[b]	36 (18–58)[c]	24[b]	36 (24–52)[c]	101 (94 to 108)[d]	24[b]	1,660[e] (696–2,535)[c]	24[b]	1,633[e] (918–2,633)[c]	98 (91 to 106)[d]
Zarzio (Hexal) (EP06-103)	5 × 7 days	27[f]	58 (12)	27[f]	56 (12)	97 (93 to 101)	27[f]	5,177 (1,087)	27[f]	5,192 (1,250)	101 (98 to 103)
Zarzio (Hexal) (EP06-101)	10 × 7 days	32[g]	73 (35)	32[g]	71 (27)	97 (88 to 107)	32[g]	6,515 (1,839)	32[g]	6,475 (1,458)	99 (96 to 103)
Nivestim (GCF062)	10 × 5 days	23[h]	47 (25–66)[c]	23[h]	46 (31–70)[c]	98 (94 to 102)[d]	23[j]	2,249[e] (1,099–3,970)[c]	23[h]	2,170[e] (1,091–3,341)[c]	97 (92 to 102)[d]
Grastofil (KWI-300-103)	5 × 4 days	34	32 (8)[d]	35	31 (6)[d]	95 (86 to 106)	34	11,9436 (20,700)[j]	35	114,232 (19,349)[j]	96 (88 to 104)

ANC = absolute neutrophil count; AUC = area under the curve; AUC_{0-96} = area under the curve from 0 to 96 hours; AUC_{0-216} = area under the curve from 0 to 216 hours;AUEC = area under the effect-time curve; CI = confidence interval; C_{max} = peak concentration; G-CSF = granulocyte-colony stimulating factor; PD = pharmacodynamics; PE = pharmacoeconomic; PP = per-protocol; SD = standard deviation.

Note: ANC results of C_{max} and AUEC are expressed as geometric mean [SD].

[a] Twenty-eight subjects enrolled and completed the 2.5 mcg/kg dose group in the two-way crossover study and all were eligible for PD analysis.

[b] Twenty-four subjects were enrolled and completed the 5 mcg/kg dose group in the two-way crossover study and were included in the PD analysis.

[c] Range.

[d] The 95% CIs are calculated based on the 90% CI given in the publications.

[e] $AUEC_{0-120h}$.

[f] Twenty-eight subjects enrolled and 27 subjects completed the 5 mcg/kg dose group in the two-way crossover study and were eligible for PD analysis.

[g] Forty subjects enrolled and 32 subjects completed the two-way crossover study and were eligible for PD analysis.

[h] Twenty-six subjects were enrolled but only 23 subjects completed the 10 mcg/kg dose group in the two-way crossover study and were included in the PD analysis.

[i] $C_{max,ss}$ (PP data).

[j] ANC AUC_{0-96h} (PP data).

Source: Response to [redacted] (20). Table 25, Table 26.

TABLE 63: SUMMARY OF MEAN (SD) T_{MAX} AND $T_{1/2}$ FOLLOWING INTRAVENOUS OR SUBCUTANEOUS SINGLE OR REPEAT DOSE ADMINISTRATION OF GRASTOFIL OR NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS IN PHASE 1 STUDIES (ITT POPULATION)

	T_{max} (Minimum)				$T_{1/2}$ (Maximum)			
	Grastofil		Neupogen		Grastofil		Neupogen	
KWI-300-101, mcg/kg, IV	35	16.3 (9.1)	36	16.1 (5.5)	35	168.5 (13.5)	36	165.5 (13.0)
KWI-300-102, 150 mcg, SC	36	278.3 (41.0)	36	283.3 (53.4)	36	328.4 (95.3)	36	309.3 (87.1)
KWI-300-103, 5 mcg/kg, SC, day 1	36	299.2 (36.2)	36	305.8 (32.7)	36	162.2 (15.6)	36	162.2 (19.4)
GCSF-SUIN-05SB01-3FA-(5), 300 mcg SC[a]	43	300	43	300[b]	43	430.2	43	457.2[b]
			44	300[c]			44	438.0[c]

EU = European Union; ITT = intention-to-treat; IV = intravenous; PP = per-protocol; SC = subcutaneous; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time at maximum concentration.
[a] PP population data only.
[b] US-licensed Neupogen.
[c] EU-approved Neupogen.
Source: Clinical Study Report KWI-300-101, Tables 105–106; Clinical Study Report KWI-300-102, Tables 118–119; Clinical Study Report KWI-300-103, Tables 132–133; Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Tables 13.1.1, 13.1.2.

TABLE 64: SUMMARY OF MEAN (SD) T_{MAX} AND $T_{1/2}$ FOLLOWING INTRAVENOUS OR SUBCUTANEOUS SINGLE OR REPEAT DOSE ADMINISTRATION OF GRASTOFIL OR NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS IN PHASE 1 STUDIES (PP POPULATION)

	T_{max} (Minimum)				$T_{1/2}$ (Maximum)			
	Grastofil		Neupogen		Grastofil		Neupogen	
KWI-300-101, 5 mcg/kg, IV	35	16.3 (9.1)	35	16.0 (5.5)	35	168.5 (13.5) [redacted][a]	35	165.3 (13.1) [redacted][c]
KWI-300-102, 150 mcg, SC	35	278.6 (41.5)	35	283.7 (54.1)	35	[redacted]	35	[redacted]
KWI-300-103, 5 mcg/kg, SC, day 1	35	297.4 (35.2)	34	307.1 (33.1)	35	[redacted]	34	[redacted]
GCSF-SUIN-05SB01-3FA-(5), 300 mcg SC	43	300	43	300[b]	43	430.2	43	457.2[b]
			44	300[c]			44	438.0[c]

EU = European Union; IV = intravenous; PP = per-protocol; SC = subcutaneous; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time at maximum concentration.
[a] $T_{1/2}$ (min) values were re-estimated using a more appropriate algorithm (see [redacted] (57)).
[b] US-licensed Neupogen.
[c] EU-approved Neupogen.
Source: Clinical Study Report KWI-300-101, Tables 29–30; Clinical Study Report KWI-300-102, Tables 34–35; Clinical Study Report KWI-300-103, Tables 38–39; Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Tables 13.1.1, 13.1.2.

TABLE 65: SUMMARY OF AUC AND C_{MAX} FOLLOWING INTRAVENOUS OR SUBCUTANEOUS SINGLE OR REPEAT DOSE ADMINISTRATION OF GRASTOFIL OR NEUPOGEN TO HEALTHY MALE AND FEMALE VOLUNTEERS IN PHASE 1 STUDIES (ITT POPULATION)

Study	Parameters	EP[a]	Grastofil		Neupogen		Ratio of Geometric Means (90% CI) (%)[b]
			N	Mean (ng/mL*min)	N	Mean (ng/mL*min)	
KWI-300-101	AUC_{0-32}	1	35	22,047.5	36	24,366.8	90.6 (88.7 to 92.7)[c]
	AUC_{inf}	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KWI-300-102 (150 mcg)	AUC_{0-72}	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AUC_{inf}	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KWI-300-103	AUC_{0-24} (day 1)	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AUC_{ss} (day 4)	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCSF-SUIN-05SB01-3FA-(5)[d]	AUC_{0-t}	1	43	12,043.2[e]	43[f]	11,542.8[e]	108 (102 to 114)
					44[g]	11,184.3[e]	110 (104 to 116)
KWI-300-101	C_{max} (ng/mL)	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KWI-300-102 (150 mcg)		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KWI-300-103		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCSF-SUIN-05SB01-3FA-(5)[d]		1	43	24.2	43[f]	22.5	110 (101 to 120)
					44[g]	21.8	111 (102 to 121)

AUC = area under the curve; AUC_{0-24} = area under the curve from 0 to 24 hours; AUC_{0-32} = area under the curve from 0 to 32 hours; AUC_{0-72} = area under the curve from 0 to 72 hours; AUC_{0-ss} = area under the curve at steady-state; AUC_{0-t} = Area under the curve from 0 to time t; AUC_{inf} = area under the curve from 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum concentration; EP = end point; ITT = intention-to-treat; min = minute; PK = pharmacokinetics; PP = per-protocol.

[a] End point level.

[b] The ratio of geometric means is the ratio (Grastofil/Neupogen) of the inverse transformation of the least squares means.

[c] For the IV data, ratio of geometric means and 90% CIs are presented for the comparison of the PK characteristics (excluding absorption) of the two drugs.

[d] PP data only.

[e] Converted from h*pg/mL.

[f] US-licensed Neupogen.

[g] EU-approved Neupogen.

Source: Clinical Study Report KWI-300-101, Tables 102–104; Clinical Study Report KWI-300-102, Tables 115–117; Clinical Study Report KWI-300-103, Tables 129, 131, 136; Clinical Study Report GCSF-SUIN-05SB01-3FA-(5), Tables 13.1.1, 13.1.2.

APPENDIX 2: DRUG PLAN LISTING STATUS FOR REFERENCE PRODUCT

For each indication that is approved by Health Canada for the subsequent biologic entry (or likely to be approved, in the case of a submission filed on a pre–Notice of Compliance basis), please provide the publicly available listing status and criteria for the reference product. CADTH may update the information provided by the manufacturer with new information provided by the CDR-participating drug plans, as required.

Step 1: Use the following abbreviations to complete the table. Use a separate row for each indication and add more rows if necessary.

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review
–	Information not available

TABLE 66: LISTING STATUS FOR NEUPOGEN

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Cancer patients receiving myelosuppressive chemotherapy	RES[a]	RES	RES[b]	RES[c]	RES	RES	RES[d]	RES	RES	RES	FB	FB	FB	RES
Patients with acute myeloid leukemia	RES[a]	RES	RES[b]	EX[c]	RES	–	RES[d]	–	EX	RES	FB	FB	FB	RES
Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation	RES[a]	–	RES[b]	EX[c]	RES	RES	–	–	EX	RES	FB	FB	FB	RES
Cancer patients undergoing peripheral blood progenitor cell collection and therapy	RES[a]	RES	–	EX[c]	RES	RES	RES[d]	RES	EX	RES	FB	FB	FB	RES
Patients with severe chronic neutropenia	RES[a]	RES	RES	EX[c]	EX	RES	EX[d,e]	EX[e]	EX[e]	EX	FB	FB	FB	RES
Patients with HIV infection	RES[f]	–	RES	RES	RES	RES	EX[d,e]	EX[e]	EX[e]	EX	FB	FB	FB	RES

AB = Alberta; BC = British Columbia; CDR = CADTH Common Drug Review; DND = Department of National Defence; EX = exceptional status, coverage determined on a case-by-case basis; FB = full benefit; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

[a] BC Cancer Agency.
[b] Saskatchewan Cancer Agency.
[c] CancerCare Manitoba.
[d] Cancer Care Nova Scotia.
[e] Ccovered only if the patient is undergoing cancer treatment.
[f] BC Centre for Excellence in HIV/AIDS.

Note: Although Table 66 lists the Health Canada–approved indications as stated in the Neupogen product monograph, each of the drug plans below have their own specific criteria (especially those related to oncology-supportive indications). Therefore, they may not completely match the criteria in the product monograph, nor do they provide the criteria on publicly available websites. Some of the aforementioned listing statuses were determined based on telephone conversations with formulary staffs.

Step 2: For all restricted benefit entries, please state the criteria used by each drug plan. Use a separate table for each indication and add or delete rows as necessary.

TABLE 67: RESTRICTED BENEFIT CRITERIA FOR NEUPOGEN FOR CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY

Drug Plan	Criteria for Restricted Benefit
BC	For rescue of prolonged febrile neutropenia following chemotherapy To prevent neutropenia, which interferes with delivery of standard doses of adjuvant chemotherapy in potentially curative chemotherapy regimens meeting the following criteria: • ≥ Second cycle of adjuvant chemotherapy • Potentially curative regimen
AB	In patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs with curative intent, to decrease the incidence of infection as manifested by febrile neutropenia Coverage cannot be considered for palliative patients

SK	Filgrastim (G-CSF) is approved to prevent or mitigate neutropenic complications resulting from cancer treatment according to the following indications:
	• Primary prophylaxis in patients receiving an SCA-approved regimen where the documented or expected incidence of febrile neutropenia is 20% or higher. This includes the approved use of G-CSF for primary prophylaxis in patients who are:
	  • Age 65 and older receiving CHOP or R-CHOP for diffuse large B cell lymphoma or follicular Grade 3 lymphoma
	  • Age 65 and older receiving a docetaxel-based regimen in the adjuvant or neoadjuvant setting for breast cancer
	  • Receiving the docetaxel-carboplatin-trastuzumab regimen (any age) for HER2-positive breast cancer
	  • Younger than age 65 receiving a docetaxel-based regimen in the adjuvant or neoadjuvant setting for breast cancer when primary prophylaxis with ciprofloxacin cannot be given
	• Secondary prophylaxis in patients receiving curative therapy following a dose delay due to neutropenia or an episode of febrile neutropenia and where further treatment delays and/or dose reductions may result in inferior outcomes

MB	**Febrile Neutropenia** G-CSF (filgrastim) is a commonly used treatment in patients for secondary prophylaxis for febrile neutropenia. Secondary prophylaxis: • Treatment is given after development of febrile neutropenia to prevent recurrences • It may also be used if the ability to continue to administer the treatment without delay is impaired due to prolonged myelosuppression between cycles Primary prophylaxis: • Treatment is given to prevent the development of the complication with no previous occurrence

Drug Plan	Criteria for Restricted Benefit
	• ASCO guidelines suggest it be used only in regimens with a > 20% risk of febrile neutropenia • Colorectal cancer treatments generally are not highly myelosuppressive, and primary prophylaxis is not recommended **Filgrastim Use** Secondary prophylaxis only
ON	Prophylaxis of febrile neutropenia for patients receiving chemotherapy with curative intent as follows: • Primary G-CSF prophylaxis: Patients with cancer receiving a curative chemotherapy who are expected to have incidence of febrile neutropenia of ≥ 20% (e.g., due to highly myelosuppressive regimen, patient co-morbidities, pre-existing severe neutropenia, etc.) • Secondary G-CSF prophylaxis: For secondary prophylaxis of febrile neutropenia (i.e., patient has experienced an episode of sepsis or febrile neutropenia, or neutropenia such that treatment has had to be delayed for at least one week) for patients with cancer receiving a curative chemotherapy. Note: Reimbursement is limited to the duration of chemotherapy and to prescriptions written by an oncologist or hematologist. Dosage restriction: • Patient's weight is less than 90 kg: 300 mcg (note: 480 mcg dose may be considered for patients weighing less than 90 kg who are unable to achieve an adequate response from 300 mcg) • Patient's weight is 90 kg or more: 480 mcg **Exclusion Criteria** Patients with non-curative cancer receiving chemotherapy with palliative intent are NOT eligible for either primary or secondary G-CSF prophylaxis. Requests for Neupogen for febrile neutropenia for non-curative disease may be considered through EAP on a case-by-case basis. Please provide appropriate and adequate details in the request submission for a full assessment.

NB	**1. Use for Chemotherapy Support**
	
	a) Primary prophylaxis:
	• For use in previously untreated patients receiving a moderate to severely myelosuppressive chemotherapy regimen (i.e., ≥ 40% incidence of febrile neutropenia). Febrile neutropenia is defined as a temperature ≥ 38.5^{o}C or > 38^{o}C three times in a 24-hour period, and neutropenia with an ANC of < 0.5 × 10^{9}/L
	
	b) Secondary prophylaxis:
	• For use in patients receiving myelosuppressive chemotherapy who have experienced an episode of febrile neutropenia, neutropenic sepsis, or profound neutropenia in a previous cycle of chemotherapy, OR
	• For use in patients who have experienced a dose reduction or treatment delay longer than one week due to neutropenia
	
	c) Dosing for chemotherapy support:
	• The manufacturer recommends an initial dose of 5 mcg/kg/day. When dose-scavenging techniques are not available, the following recommendations are suggested:
	  • Patients weighing ≤ 70 kg, use 1 mL vial (300 mcg), DIN 01968017
	  • patients weighing > 70 kg, use 1.6 mL vial (480 mcg), PIN 00999001

Drug Plan	Criteria for Restricted Benefit
NS	**Cancer Care Nova Scotia** Primary use: • For the primary prevention of FN in patients receiving approved myelosuppressive chemotherapy regimens when the documented risk of FN without G-CSF is ≥ 20%. Prophylactic use of G-CSF could be considered in patients ≥ 65 years old with diffuse large B cell lymphoma when treated with CHOP-like regimens with the intent to improve overall survival. Secondary line: • For secondary prevention of FN (to reduce subsequent episodes of FN) in patients receiving myelosuppressive chemotherapy who experienced FN, neutropenic sepsis, or profound neutropenia (ANC < 0.5×10^9/L) in a prior cycle of myelosuppressive chemotherapy (for which primary prophylaxis was not received), a dose reduction or delay may be a reasonable alternative unless it was felt to compromise treatment outcome.
PE	**PEI Pharmacare High-Cost (M) and Catastrophic Drug (Q) Programs** **Chemotherapy Support** a) For use in patients treated with curative intent, where maintaining maximal dose intensity is likely to improve the cure rate, and where the risk of neutropenic fever is greater than 20%. b) For use in patients treated with curative intent, after an episode of neutropenic fever or where treatment is delayed beyond one week due to neutropenia. Neutropenic fever is defined as a body temperature of ≥ 38.5°C (as a single measurement) or > 38°C three times in a 24-hour period, and neutropenia with an ANC < 0.5×10^9/L. Must be requested and prescribed by a specialist in hematology or medical oncology. The manufacturer recommends an initial dose of 5 mcg/kg/day. The dosage can be rounded off to 300 mcg or 480 mcg to avoid wastage. When dose-scavenging techniques are not available, the following recommendations are suggested: • Patients ≤ 70 kg: use 1 mL vial (300 mcg) • Patients > 70 kg: use 1.6 mL vial (480 mcg). Coverage will be limited to a maximum of three months. Coverage beyond this will require completion and submission of a new Special Authorization form. The request for coverage must be made and the medication prescribed by a specialist in hematology or medical oncology, or a general practitioner acting under the direction of those specialists, using the Special Authorization Request for Coverage of High-Cost Cancer Drugs available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms. Patients must also apply for coverage by the High-Cost Drug Program. The patient application is available from the Drug Programs Office or online at http://healthpei.ca/pharmacareforms.

Drug Plan	Criteria for Restricted Benefit
NL	**Special Authorization** **Filgrastim (Neupogen 300 mcg, 480 mcg)** Coverage is considered for patients receiving moderate to severely myelosuppressive chemotherapy. Primary prophylaxis: • When given as an integral part of an aggressive chemotherapy regimen with curative intent in order to maintain dose intensity in compressed interval or dose-dense treatment, as specified in a chemotherapy protocol (the chemotherapy protocol must be supplied with the request) • For use in patients ≥ 65 years old who are receiving CHOP. Secondary prophylaxis: • For use in patients receiving myelosuppressive chemotherapy who experienced an episode of febrile neutropenia, neutropenic sepsis, or profound neutropenia in a previous cycle of chemotherapy OR • For use in patients who have experienced a dose reduction or treatment delay longer than one week due to neutropenia. Dosing for chemotherapy support: • Manufacturer recommends an initial dose of 5 mcg/kg/day • Patients ≤ 70 kg: use 1 mL vial (300 mcg) • Patients > 70 kg: use 1.6 mL vial (480 mcg).
YK	Telephone conversation with formulary YK staff — on recommendation of hematologist or specialist; specialist's consult to be provided. For cancer: Restricted to curative treatment protocols recommended by Cancer Agency
NT	Full benefit
NIHB	Full benefit
DND	Full benefit
VAC	Telephone conversation with VAC staff — SA criteria information not available to public

AB = Alberta; ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; BC = British Columbia; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; DIN = drug identification number; DND = Department of National Defence; EAP = Employee Assistance Program; EX = exception item for which coverage is determined on a case-by-case basis; FB = full benefit; FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; R-CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab; SA = Special Assistance; SCA = Saskatchewan Cancer Agency; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

TABLE 68: RESTRICTED BENEFIT CRITERIA FOR NEUPOGEN FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA

Drug Plan	Criteria for Restricted Benefit

BC	• For rescue of prolonged febrile neutropenia following chemotherapy
	• To prevent neutropenia, which interferes with delivery of standard doses of adjuvant chemotherapy in potentially curative chemotherapy regimens meeting the following criteria:
	  • ≥ Second cycle of adjuvant chemotherapy
	  • Potentially curative regimen

AB	• Following induction and consolidation treatment for acute myeloid leukemia, for the reduction in the duration of neutropenia, fever, antibiotic use, and hospitalization
SK	Filgrastim (G-CSF) is approved to prevent or mitigate neutropenic complications resulting from cancer treatment according to the following indication: • Acute myelogenous leukemia: following induction therapy in patients aged 55 years or older to reduce the duration of antibiotic administration and hospital admission; after completion of consolidation therapy in patients of any age with AML in remission to reduce the duration of

Drug Plan	Criteria for Restricted Benefit
	neutropenia
MB	Case-by-case via CancerCare Manitoba
ON	Note: For all the listed indications in this section, the dosage approved will be based on prescriber request. Indications reviewed through the EAP submission process include: • For the treatment of patients with an intermediate or high-grade lymphoma who have relapsed after initial chemotherapy and are to receive an autologous bone marrow transplant during the 2 to 4 months of their pre-transplant chemotherapy • For the treatment of patients with an intermediate or high-grade lymphoma, leukemia, or myeloma who have relapsed after initial chemotherapy and are to receive a peripheral stem cell transplant or stem cell mobilization
NB	Not available
NS	Acute myeloid leukemia: Primary G-CSF administration after induction therapy for AML in patients aged ≥ 55 years to reduce hospitalization after antibiotic use; primary G-CSF administration after completion of consolidation therapy in patients with AML remission to reduce the duration of neutropenia
PE	Not available
NL	Case-by-case
YK	Telephone conversation with formulary YK staff — on recommendation of hematologist or specialist; specialist's consult to be provided. For cancer: Restricted to curative treatment protocols recommended by Cancer Agency
NT	Full benefit
NIHB	Full benefit
DND	Full benefit
VAC	Telephone conversation with VAC staff — SA criteria information not available to public

AB = Alberta; AML = acute myelogenous/myeloid leukemia; BC = British Columbia; DND = Department of National Defence; EAP = Employee Assistance Program; G-CSF = granulocyte-colony stimulating factor; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SA = Special Assistance; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

TABLE 69: RESTRICTED BENEFIT CRITERIA FOR NEUPOGEN FOR CANCER PATIENTS RECEIVING MYELOABLATIVE CHEMOTHERAPY FOLLOWED BY BONE MARROW TRANSPLANTATION

Drug Plan	Criteria for Restricted Benefit
BC	• Post-BMT to stimulate bone marrow engraftment (start greater than or equal to d + 1) • Post-BMT for rescue of failure to engraft (start greater than or equal to d + 14) • Pre-BMT after high dose cyclophosphamide for multiple myeloma
AB	Not available
SK	Filgrastim (G-CSF) is approved to prevent or mitigate neutropenic complications resulting from cancer treatment according to the following indication: • As required by protocol in pediatric patients and within the Blood and Marrow Transplant Program (from Formulary Exception Drug Status) • Non-cancer patients who have undergone bone marrow transplantation
MB	Case-by-case via CancerCare Manitoba
ON	Note: For all the listed indications in this section, the dosage approved will be based on prescriber request. Indications reviewed through the EAP submission process include: • For the treatment of patients with an intermediate or high-grade lymphoma who have relapsed after initial chemotherapy and are to receive an autologous bone marrow during the 2 to 4 months of their pre-transplant chemotherapy • For the treatment of patients with an intermediate or high-grade lymphoma, leukemia, or myeloma who have relapsed after initial chemotherapy and are to receive a peripheral stem cell

Drug Plan	Criteria for Restricted Benefit
	transplant or stem cell mobilization
NB	**Use in Stem-Cell Transplantation** Reconstitution or engraftment: Post-BMT or PBSC transplantation to speed hematopoietic reconstitution. The recommended dosage is 5 mcg/kg/day
NS	Not available
PE	Not available
NL	Case-by-case
YK	Telephone conversation with formulary YK staff — on recommendation of hematologist or specialist. Specialist's consult to be provided. For cancer: Restricted to curative treatment protocols recommended by Cancer Agency
NT	Full benefit
NIHB	Full benefit
DND	Full benefit
VAC	Telephone conversation with VAC staff — SA criteria information not available to public

AB = Alberta; BC = British Columbia; BMT = bone marrow transplantation; d = day; EAP = Employee Assistance Program; G-CSF = granulocyte-colony stimulating factor; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PBSC = peripheral blood stem cell; PE = Prince Edward Island; SA = Special Assistance; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

TABLE 70: RESTRICTED BENEFIT CRITERIA FOR NEUPOGEN FOR CANCER PATIENTS UNDERGOING PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY

Drug Plan	Criteria for Restricted Benefit
BC	Pre-BMT to augment or prime stem cell and progenerative cell collection before peripheral blood harvest
AB	For the treatment of patients undergoing PBPC collection and therapy when prescribed by a designated prescriber
SK	Not available
MB	Case-by-case via CancerCare Manitoba
ON	**Pre-Stem Cell Transplant Mobilization** • For PBPC collection for peripheral stem cell transplant as treatment for malignant disease Note: For all the listed indications in this section, the dosage approved will be based on prescriber request. Indications reviewed through the EAP submission process include: • For the treatment of patients with an intermediate or high-grade lymphoma, leukemia, or myeloma who have relapsed after initial chemotherapy and are to receive a peripheral stem cell transplant or stem cell mobilization.
NB	**Use in Stem-Cell Transplantation** a) Mobilization: As an adjunct to progenitor cell transplantation, for mobilization of PBSC; the recommended dosage is 10 mcg/kg/day b) Reconstitution or engraftment: Post-BMT or PBSC transplantation to speed hematopoietic reconstitution; the recommended dosage is 5 mcg/kg/day
NS	PBPC transplant (autologous and allogenic): To mobilize PBPC to facilitate cell collection; to shorten the period of neutropenia after cytoreduction and PBPC transplantation (for autologous only)
PE	**High-Dose Chemotherapy With Stem Cell Support** For use in mobilizing stem cells in preparation for stem cell collection
NL	Case-by-case

Drug Plan	Criteria for Restricted Benefit
YK	Telephone conversation with formulary YK staff — on recommendation of hematologist or specialist; specialist's consult to be provided. For cancer: Restricted to curative treatment protocols recommended by Cancer Agency
NT	Full benefit
NIHB	Full benefit
DND	Full benefit
VAC	Telephone conversation with VAC staff — SA criteria information not available to public

AB = Alberta; BC = British Columbia; BMT = bone marrow transplantation; d = day; EAP = Exceptional Access Program; G-CSF = granulocyte-colony stimulating factor; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PBPC = peripheral blood progenitor cell; PBSC = peripheral blood stem cells; PE = Prince Edward Island; SA = Special Assistance; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

TABLE 71: RESTRICTED BENEFIT CRITERIA FOR NEUPOGEN FOR PATIENTS WITH SEVERE CHRONIC NEUTROPENIA

Drug Plan	Criteria for Restricted Benefit
BC	Patients with benign disorders • Chronic benign cyclical neutropenia
AB	In patients with a diagnosis of congenital, cyclic, or idiopathic neutropenia to increase neutrophil counts and reduce the incidence and duration of infection.
SK	Congenital, cyclic, or idiopathic neutropenia in patients with ANCs of ≤ 500.
MB	Case-by-case via CancerCare Manitoba (if seen by a hematologist)
ON	For patients with non-malignant severe chronic neutropenia (i.e., congenital, cyclic, idiopathic); approvals are assessed on a case-by-case basis. Chronic neutropenia is considered as: • CBC showing neutrophil counts < 0.5×10^9 cells/L for 3 months prior to filgrastim therapy AND • A documented history of recurrent infections AND • A recent bone marrow examination report with cytogenetics testing. Renewals for congenital neutropenia will be considered on a case-by-case basis. Submissions must include the following information: a) updated monitoring plan b) blood work (i.e., WBC count and ANC) with corresponding filgrastim (Neupogen) doses c) recent bone marrow report with cytogenetics testing d) history of infections (if applicable).
NB	Treatment of congenital neutropenia, idiopathic neutropenia, or cyclic neutropenia in patients with recurrent clinical infections. Refer to product monograph for dosing recommendations.
NS	Case-by-case via Cancer Care Nova Scotia
PE	Case-by-case
NL	Case-by-case
YK	Telephone conversation with formulary YK staff — On recommendation of hematologist or specialist; specialist's consult to be provided. For cancer: Restricted to curative treatment protocols recommended by Cancer Agency
NT	Full benefit
NIHB	Full benefit
DND	Full benefit
VAC	Telephone conversation with VAC staff — SA criteria information not available to public

AB = Alberta; ANC = absolute neutrophil count; BC = British Columbia; CBC = complete blood count; DND = Department of National Defence; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SA = Special Assistance; SK = Saskatchewan; VAC = Veterans Affairs Canada; WBC = white blood cell; YK = Yukon.

TABLE 72: RESTRICTED BENEFIT CRITERIA FOR NEUPOGEN FOR PATIENTS WITH HIV INFECTION

Drug Plan	Criteria for Restricted Benefit
BC	Criteria not available from BC Centre for Excellence in HIV/AIDS
AB	Not available
SK	AIDS patients with ANCs < 500
MB	For use in patients with HIV infection for the prevention and treatment of neutropenia to maintain a normal ANC
ON	For the treatment of patients with HIV/AIDS and who have: a) a persistent (> 3 months) ANC < 0.5×10^9 cells/L, OR b) an ANC between 0.5 to 1.0×10^9 cells/L with a prior history of three or more opportunistic infections and a persistently low CD4 count ≤ 20×10^6 cells/L Note: Dosage approved will be based on prescriber request
NB	Drug-induced neutropenia (e.g., anti-viral therapy in patients with HIV); refer to product monograph for dosing recommendations
NS	Case-by-case via Cancer Care Nova Scotia
PE	Case-by-case
NL	Case-by-case
YK	Telephone conversation with formulary YK staff — on recommendation of hematologist or specialist; specialist's consult to be provided. For cancer: Restricted to curative treatment protocols recommended by Cancer Agency
NT	Full benefit
NIHB	Full benefit
DND	Full benefit
VAC	Telephone conversation with VAC staff — SA criteria information not available to public

AB = Alberta; ANC = absolute neutrophil count; BC = British Columbia; CBC = complete blood count; DND = Department of National Defence; MB = Manitoba; NIHB = Non-insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SA = Special Assistance; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

APPENDIX 3: SUMMARY OF PATIENT INPUT

This section was summarized by CADTH Common Drug Review (CDR) staff based on input provided by patient groups.

1. Information About the Grastofil Patient Input Summary
Grastofil has been approved by Heath Canada for the following indications:

- Cancer patients receiving myelosuppressive chemotherapy
- Patients with acute myeloid leukemia
- Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation
- Cancer patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy
- Patients with severe chronic neutropenia
- Patients with HIV infection.

2. Brief Description of Patient Groups Supplying Input
One patient group provided input regarding Grastofil.

The Consumer Advocare Network (Advocare) is a registered not-for-profit organization that aims to provide education and support to patient groups. Advocare created Patient Experts in Health Technology in 2012 to promote informed patient engagement at all levels of health policy and decision-making. In the past 12 years, it has received unrestricted educational grants to develop materials and workshops on health technology assessment from Canada's Research-Based Pharmaceutical Companies (Rx&D), Merck Canada, Pfizer Canada, Sanofi, Janssen-Ortho, Amgen Canada, Lilly Canada, Hoffmann-La Roche, Novartis Canada, and Wyatt Health Management, as well as in-kind support from the University of Alberta to develop and conduct training.

Advocare declared no conflict of interest in the preparation of this submission.

3. Condition and Current Therapy-Related Information
Advocare obtained information for its submission through a survey, which was developed through interviews with four key patient informants and two clinicians who had conducted clinical trials using Grastofil, one in Canada and the other in Italy. The survey participants were patients and patient groups recruited by email requests or through social media such as Twitter and Facebook. Advocare warned about three potential limitations in the survey results:

- Most of the survey participants might have had other conditions, and some of the symptoms from these conditions might be similar to those resulting from neutropenia
- Many patients recalled neutropenia symptoms from the past; therefore, recall bias was possible
- It was unclear how many of the patients with the indicated conditions actually experienced neutropenia, or how many of the survey responses were reflective of the entire patient population.

Among the 60 participants who completed the survey between September 14 and September 28, 2015, about 25% were cancer patients receiving myelosuppressive chemotherapy; 20% had congenital, cyclic or idiopathic neutropenia; 13% had acute myeloid leukemia; 13% received bone marrow transplantation; 5% were undergoing PBPC collection; and one or two patients had lymphoma, bone marrow failure, aplastic anemia, amyloidosis, myelodysplastic syndromes, or vasculitis. Approximately one in eight patients said they had no symptoms of neutropenia.

Symptoms Impact for Patients With Neutropenia

The patients completing the survey reported multiple symptoms with neutropenia, and the symptoms were, in general, severe and frequent. Fatigue (in one-third of patients) and high fever (in one-third of patients) were the most frequently experienced symptoms. Approximately 25% of the patients complained about infections in the mouth or on the skin. Laryngeal symptoms, including sore throats, coughing, sinus infections, or shortness of breath, were reported in about 10% of the patients. Other severe or frequent symptoms included diarrhea, painful urination, nausea, vomiting and, in one case, sepsis from gall bladder infection. Among the patients suffering symptoms of neutropenia, all reported that their quality of life and daily living were negatively impacted. One patient noted that she "had beaten cancer" with chemotherapy but almost died from the infections due to a suppressed immune system. Prolonged hospitalization resulting from severe drug-resistant infections and resulting multi-organ failure were also reported.

4. Caregiver Experiences With Patients With Neutropenia Resulting From the Indicated Conditions

Caregivers, especially spouses and parents, expressed greater distress regarding the impact of neutropenia on the patient than on themselves. They felt frustrated about the extra burden of neutropenia on the patient, in addition to the cancer or other conditions, and chemotherapy. They also indicated that with filgrastim treatment, "a normal family doing normal things with normal worries" would be possible for them.

5. Treatment Experiences for Neutropenia

The treatments received for neutropenia by respondents included antibiotics (about 75%), immunosuppressive medications (such as cyclosporine, monoclonal antibodies, and/or corticosteroids; about 40%), and filgrastim or other forms of granulocyte-colony stimulating factor (about 40%). Some patients had received more than one treatment. Most respondents relied on their physician to decide treatment for neutropenia (including prophylaxis or not).

According to the participants, antibiotics were "much" or "very much" effective in resolving the symptoms of neutropenia in 75% of the patients who received them, while they had no satisfactory treatment effect in 25% of these patients. About 80% of the patients who received immunosuppressive drugs said they were effective or very effective, although about 25% said they did not know how well the medications worked to reduce neutropenia. All patients who received filgrastim said the drug worked "well" or "very well."

In terms of the adverse effects related to treatments for neutropenia, nearly two-thirds of patients who received antibiotics experienced no or mild side effects, while one-fourth reported moderate side effects, and one-eighth reported severe side effects. About two-thirds of patients treated with immunosuppressive medications reported "much" or "severe" side effects and the remainder reported the side effects as "some" or "moderate." The side effects of filgrastim were considered mild or nonexistent.

As this submission is for a subsequent entry biologic (SEB), experiences with the reference product, Neupogen, are informative. Prior to the survey, about one-third of the participants said they were familiar with the term "filgrastim" while two-thirds were unaware of this drug. More participants (about two-thirds) were aware of the reference product (Neupogen).

6. Related Information About Grastofil

None of the survey participants had heard of the term "SEB" or "biosimilar," which Advocare found surprising, based on feedback from other patient populations. None of the participants had heard of Grastofil by name prior to the survey (although a few were unsure). A brief introduction to biosimilars and the fact that Grastofil is biosimilar to Neupogen was explained to the participants in the introduction to the survey.

Based on the introduction, patients provided opinions as to their feeling about Grastofil compared with Neupogen in managing the symptoms related to neutropenia (stimulating white blood cells, reducing or preventing infection, reducing or preventing fever, increasing tolerance of primary therapy and reducing fatigue). Patients' opinions on Grastofil included the following:

- Four out of five participants had no knowledge as to whether Grastofil would be "better," "not different," or "worse" than Neupogen in symptom control; the remainder thought they had the same the treatment effect; none thought Grastofil would be less effective than Neupogen.
- Four out of five participants had no knowledge as to the safety profile of Grastofil compared with Neupogen; the remainder expected that Grastofil had the same side effects as Neupogen; none felt Grastofil would have more or worse side effects than Neupogen.
- Ten per cent of the participants felt that Grastofil had the same cost as Neupogen, while the vast majority of them had no knowledge as to the drug cost.
- Half of the participants said the SEB should be available as an option through the hospital or public drug plans, with physician approval, while the remainder had no knowledge as to the accessibility of the SEB.

None of the respondents said they would support Grastofil use without physician approval — regardless of their previous experience with Neupogen. Moreover, almost half said that the SEB and Neupogen should not be substituted for one another without physician consent.

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