CHMP assessment report

Nivestim

International Non-proprietary Name: filgrastim

Procedure No. EMEA/H/C/001142

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Ltd. submitted on 27 February 2009 an application for Marketing Authorisation to the European Medicines Agency for Nivestim, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product.

The application submitted is a complete dossier composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The applicant applied for the following indications:

- Filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

- The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

- Filgrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

- In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$ /l and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

- Filgrastim is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9 /l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

1.1.1. Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 February 2005 and 30 June 2006. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.1.2. Licensing status

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Jaana Kallio** Co-Rapporteur: **Martin Votava**

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 27 February 2009.
- The procedure started on 25 March 2009.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2009 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2009
- During the meeting on 20-23 July 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2009
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 November 2009
- During the CHMP meeting on 14 – 17 December 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 February 2010.
- During the meeting on 15-18 March 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nivestim on 18 March 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 March 2010

2. SCIENTIFIC DISCUSSION

2.1. Introduction

The current combination therapy for cancers often targets proliferating cells leading to bone marrow damage. Anemia and thrombocytopenia and, most importantly, neutropenia results in impaired host defence, which leaves patients more susceptible to bacterial infections and sepsis. This leads to delays in subsequent chemotherapy cycles. The recovery of bone marrow is stimulated by various growth factors. The most important growth factor for the recovery of neutrophils is granulocyte colony-stimulating factor, G-CSF. Filgrastim is a human G-CSF produced by recombinant DNA technology. G-CSF is a 20,000 Dalton glycoprotein hormone that stimulates the proliferation of neutropoietic progenitor cells and their differentiation to granulocytes, and functionally activates mature neutrophils. Commercial forms of recombinant human G-CSF include *Escherichia coli*-derived G-CSF, which has no sugar chain (unglycosylated G-CSF; filgrastim; Neupogen, Amgen) and Chinese hamster ovary cell-derived G-CSF (glycosylated G-CSF; lenograstim, Chugai Pharma UK Ltd).

Human G-CSF is a single polypeptide chain protein of 174 amino acids with O-glycosylation at one threonine residue. It acts by binding to a specific transmembrane receptor (G-CSF receptor), a member of the class I cytokine receptor family expressed on various hematopoietic cells such as stem cells, multipotent progenitors, myeloid-committed progenitors, neutrophils, and monocytes. This receptor forms homo-oligomeric complexes upon ligand binding. Seven membrane-bound and one soluble isoform of the G-CSF receptor have been isolated; the membrane-bound isoforms arise from alternative RNA splicing leading to differences in the cytoplasmic sequences, but the extracellular, ligand-binding domains are identical. Consequently, the effects of G-CSF (and of recombinant human G-CSF, rhG-CSF) are mediated via a single affinity class of receptors. The same mechanism of action and receptor mediated biological activity operates in mobilization of mature neutrophils into the circulating neutrophil pool and acceleration of granulopoiesis.

Nivestim (also referred to as Pliva/Mayne filgrastim) is a 175 amino acid protein – recombinant methionyl human granulocyte-colony stimulating factor (r-metHuG-CSF) that is produced in *E. coli* and has a molecular weight of 18,800 daltons. Unlike the human protein, Nivestim is unglycosylated and contain an N-terminal methionine.

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The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Filgrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$ /l and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Filgrastim is indicated for the treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$ /l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Nivestim is administered by the subcutaneous (S.C.) or intravenous (I.V.) route, normally at a dose of 5 µg/kg or 10 µg/kg body weight.

2.2. Quality aspects

2.2.1. Introduction

Filgrastim, the active substance of Nivestim, is a recombinant human granulocyte-colony stimulating factor (G-CSF) produced in *E. coli* as a non-glycosylated protein containing an N-terminal methionyl extension. It stimulates the proliferation, differentiation and activation of late progenitor cells of the granulocyte lineage, as well as enhances the activity of mature neutrophils.

Nivestim has been developed as a similar biological medicinal product according to Article 10(4) of Directive 2001/83/EC as amended. The reference medicinal product used throughout the quality, safety and efficacy development programme is Neupogen marketed in the Community by Amgen. The reference medicinal product was sourced from UK, Germany and Poland for the purpose of the comparability exercise.

Nivestim solution for injection or infusion in prefilled syringes is a clear, colourless, and sterile solution. Three strengths have been developed, 120µg/0.2ml, 300µg/0.5ml and 480µg/0.5ml. The qualitative and quantitative composition of Nivestim and Neupogen is the same, with the exception of the 120µg/0.2ml presentation, which is not marketed by Amgen. However, this presentation only differs in fill volume from the 300µg/0.5 ml presentation.

2.2.2. Active substance

2.2.2.1. Manufacture

The filgrastim Active substance, manufactured at Hospira Zagreb d.o.o., Croatia, is produced in *E. coli* bacteria transformed with an expression plasmid which contains the gene for human granulocyte-colony stimulating factor The manufacturing process consists of two major production phases; 1. biosynthesis and filgrastim inclusion bodies recovery, and 2. Filgrastim purification. The process starts

by thawing one ampoule of the *E. coli* working cell bank, which is propagated to the biosynthesis step performed in bioreactor. Following completion of fermentation, the biomass is separated from the fermentation broth by flow-through centrifuge and used for release of inclusion bodies by homogenization in high pressure homogenizer. The wet paste of filgrastim inclusion bodies is packed as portions in containers with closure and following extraction of inclusion bodies and refolding, filgrastim is purified by two chromatographic steps. Filgrastim Active substance solution is filled into containers which are stored at 2-8°C for up to 24 months.

Master and working cell banks have been established and characterised for purity, identity, and viability. The genetic stability of the cell substrate has been adequately demonstrated throughout the production time.

The manufacturing process is controlled by in-process controls (IPCs). The Applicant has identified three critical steps for the upstream as well as three for the downstream process.

The performance of the manufacturing process was validated using six consecutive batches. Along with routine in process testing, additional samples were taken and analysed for bacterial growth, reproducibility of wet weight reduction from biomass to inclusion bodies paste, appearance, SDS-PAGE/WB pattern, and dry weight of inclusion bodies, as well as for downstream removal of product related impurities. The results were considered acceptable.

The filgrastim Active substance manufacturing process has undergone optimization during development. After Phase I, but prior to Phase III clinical trials, the process for Active substance production was improved in terms of its robustness. The Applicant has conducted a thorough comparability exercise and adequately demonstrated that the current and the previous manufacturing process produced Active substance of comparable quality.

Characterisation of the Active substance has been conducted on three filgrastim batches. Physicochemical properties were studied using a variety of analytical methods (appearance, pH, IEF, SDS-PAGE, protein concentration by uv spectroscopy, SEC-HPLC, RP-HPLC, IC, peptide mapping with C- and N-terminal amino acid sequencing, CD analysis, fluorescence spectroscopy, intact molecular mass determination, determination of disulphide bridges by peptide mapping, amino acid analysis, N-terminal sequence analysis). In addition, biological activity (using in vitro assay), immunochemical properties (Western blot) and purity (by SEC-HPLC, SDS-PAGE, RP-HPLC, IC and IEF) have been determined. For product related impurity profiling, the Applicant has considered formylmethionine-filgrastim, oxidised forms, dimer and HMW species, unfolded and partially folded filgrastim, as well as other filgrastim related impurities such as deamidated and truncated forms. Removal of process-related impurities was adequately addressed. In conclusion, the characterisation studies are satisfactory and state-of-the-art analytical procedures have been used.

2.2.2.2. Specification

Before application for marketing authorisation, Active substance specification was adjusted in order to be in agreement with Ph. Eur. monograph for Filgrastim concentrated solution 01/2009:2206 (official from 1 January 2009). During the Marketing Authorisation Application procedure, the Applicant has amended the Active substance specifications according to the requirements of the CHMP, to take into account manufacturing experience and batch data.

A Major Objection was raised with regard to the performance of the potency assay and the proposed acceptance limits for the biological activity at release. In response, the Applicant provided further justifications, including additional data and a proposal to tighten the acceptance criteria. The Applicant also provided additional experimental data demonstrating the correct assignment of protein content and biological activity of the in-house reference standard, and that the filgrastim dosing in the clinical

trials was accurate. The Major Objection was thereby considered satisfactorily resolved, taking into account also a commitment to review the acceptance limits once more experience is gained, see Letter of Undertaking.

For control of host cell protein (HCP), the commercially available assay proposed by the Applicant was not considered sufficiently sensitive towards HCP originating from the producer bacteria *E. coli*. The Applicant will develop post-approval a new in-house HCP assay with sufficient sensitivity and will submit a follow-up measure accordingly. Meanwhile, the commercially available assay in combination with SDS-PAGE silver staining will be used to control the HCP content of the Active substance.

The Applicant also committed to review the acceptance limits for all quantitative parameters in the Active substance and Medicinal Product specifications once 30 commercial scale batches has been produced.

Considering the above, the specifications and acceptance limits are considered as justified and acceptable.

2.2.2.3. Stability

The Applicant has conducted real-time, real-condition stability studies, as well as studies under accelerated conditions on three filgrastim batches produced using the current manufacturing process. In addition, one batch has been analysed under stressed conditions as well as for stability under freeze-thaw cycles, high-low temperature cycles, and for photostability. The proposed shelf-life of 24 months at 5°C±3°C is considered justified.

2.2.2.4. Comparability exercise for Active substance

The Applicant has conducted a comprehensive comparability exercise in order to demonstrate biosimilarity between Nivestim and the reference medicinal product Neupogen. The analytical methods used are regarded as suitable and state-of-the-art for the intended purpose. The comparability has mainly been addressed on the level of the Medicinal Product, but in addition, one batch of Neupogen was included as reference in most of the characterisation studies performed for the Active substance. Reference is made to section 3.2.2.1 (Manufacture) for further details on the characterisation and the analytical methods used.

2.2.3. Medicinal Product

2.2.3.1. Pharmaceutical Development

Filgrastim solution for injection or infusion in prefilled syringes is a clear, colourless, and sterile solution. Three strengths have been proposed, 120µg/0.2ml, 300µg/0.5ml and 480µg/0.5ml. The excipients used in the formulation are polysorbate 80, sorbitol, acetic acid, sodium hydroxide and water for injections. The qualitative and quantitative composition of Nivestim and Neupogen reference medicinal product is the same, with the exception of the 120µg/0.2ml presentation, which is not marketed by Amgen for Neupogen. However, this presentation contains the same active substance concentration (0.6mg/ml) and the same excipients, in the same concentration as the 300µg/0.5 ml marketed for Neupogen. Only the fill volume is smaller.

There is no overage in the formulation for Filgrastim or any excipient. However, each prefilled syringe is filled with 0.52 ml to deliver 0.5 ml (for Filgrastim PFS 480 µg/0.5 ml and 300 µg/0.5 ml) or with 0.22 ml to deliver 0.2 ml (for Filgrastim PFS 120 µg/0.2 ml) of Medicinal Product.

During development the manufacturing processes for both Active substance and Medicinal Product have undergone optimization, which resulted in slight changes in clinical formulation from Phase I to Phase III study.

During product development, formulation studies were performed, even though the excipients are qualitatively and quantitatively the same as of the reference product. These studies were well described and were considered appropriate for biosimilar product.

2.2.3.2. Adventitious Agents

Apart from growth media and chromatographic resin, no other raw materials or excipients of biological origin are used in the manufacture of the Active substance and the Medicinal Product. These raw materials are considered to pose very low risk with respect to viral safety.

Both the Active substance and Medicinal Product manufacturing processes are well controlled for microbiological safety. Master and working cell banks have undergone appropriate testing.

2.2.3.3. Manufacture of the Product

The manufacturing process is conducted at the same facility as the Active substance manufacturing (Hospira Zagreb d.o.o., Croatia).

Manufacturing consists of mixing active substance with excipients, pH adjustment, filtration and filling into sterile syringes.

The Medicinal Product is presented in transparent 1 ml glass syringes with preassembled steel needle gauge 27G 1/2, stopped with a coated rubber stopper, and plunger rod inserted in the stopper.

The Medicinal Product manufacturing process has been adequately validated using three consecutive batches of each presentation. In addition, since the validation batches for the 480 µg/0.5ml presentation did not fully cover the proposed batch size range, the Applicant has committed to re-validate the manufacturing process for Filgrastim prefilled syringes 480 µg/0.5ml using three consecutive commercial scale batches.

2.2.3.4. Product Specification

The proposed Medicinal Product specifications (release and end of shelf life) are primarily based on the requirements of the Ph. Eur. monograph for the active substance. During the Marketing Authorisation Application procedure, the Applicant has amended the Medicinal Product specifications according to the requirements of the CHMP, to take into account manufacturing experience and batch data. The current specifications, including the acceptance limits, are thereby considered as justified and acceptable. The Applicant also committed to review the acceptance limits for all quantitative parameters in the Active substance and Medicinal Product specifications once 30 commercial scale batches has been produced.

2.2.3.5. Stability of the Product

The Applicant has provided real-time, real-condition stability data for three batches of each presentation as follows:

- 30 months for the 480 µg/0.5ml presentation
- 24 months for the 300 µg/0.5 ml presentation
- 12 months for the 120 µg/0.2 ml presentation

All results from the real-time stability study were within the acceptance criteria. In addition, the Applicant has conducted cyclic and freezing tests, as well as stability studies under accelerated and stressed conditions. Extrapolation of stability data from pre-filled syringes 300 µg/0.5 ml to pre-filled syringes 120 µg/0.2 ml is has been justified and is considered to be acceptable. No significant differences between results for the 120 µg/0.2 ml and 300 µg/0.5 ml presentations were observed.

The stability data provided supports a shelf life of 30 months at 2-8°C for the 480µg/0.5ml presentation and a shelf life of 24 months at 2-8°C for the 300µg/0.5ml and 120µg/0.2 ml presentations.

2.2.3.6. Comparability exercise for Medicinal Product

In accordance with the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005), the Applicant has conducted state-of-the-art comparative characterisation studies between Nivestim and the reference medicinal product Neupogen, authorised in the Community. The comparability has mainly been assessed on the level of the Medicinal Product, but one batch of Neupogen was additionally included as reference in most of the characterisation studies performed for the Active substance.

The comparability study included both release tests and assessment of additional characteristics. The identity, the physical properties, the primary and higher order structures, the biological activity, the content, as well as the purity/impurity profiles were compared and found to be highly similar between Nivestim and Neupogen.

In addition to the characterisation studies, the Applicant also conducted a comparative side-by-side stability study under stressed conditions. The stability related changes seen were similar for Nivestim and Neupogen. Also the decrease in biological activity was similar between the biosimilar and the reference medicinal product.

In conclusion, no significant differences between Nivestim and the reference medicinal product Neupogen were observed in the comparative characterisation studies and forced degradation studies. The analytical methods used are regarded as suitable and state-of-the-art for the intended purpose. The characterisation studies of the Active substance further support the conclusion that the two products are similar. Altogether, biosimilarity between Nivestim and Neupogen has been satisfactorily demonstrated on the quality level.

2.2.3.7. GMO

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the Active substance and Medicinal Product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development program with Nivestim was performed in agreement with the EMEA Scientific Advice (EMEA/CHMP/SAWP/50208/05, Procedure No.: EMEA/H/SA/562/1/2004/III) and with the Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/31329/2005). The nonclinical bioequivalence program between Nivestim versus reference medicinal product Neupogen included pharmacodynamic and toxicological studies. The *in vivo* pharmacodynamics in neutropenic rats, local tolerance in rabbits, and repeated dose toxicity studies, were performed according to Good Laboratory Practice (GLP).

2.3.2. Pharmacology

The pharmacodynamic data package contained *in vitro* cell based bioassay and receptor-binding assay, and an *in vivo* study in neutropenic rodents. In addition, efficacy was examined in healthy animals.

2.3.2.1. Primary pharmacodynamics

Biological activity was determined using a cell-based potency assay relying on the ability of G-CSF to stimulate cell proliferation.

Receptor-binding properties of Nivestim and Neupogen were determined using an assay measuring competitive binding of the test compounds to the GCSF receptor (Study report M388-06). Nivestim and Neupogen exhibited comparable receptor-binding properties *in vitro*, the IC50 values were 35.56 ng/ml and 36.35 ng/ml, respectively.

Pharmacodynamic response in terms of increase in absolute neutrophil counts (ANC) was determined in a neutropenic rat model (Study report M470-06), as well as in healthy rats in a repeat-dose toxicity study. Neutropenia was induced in male Sprague-Dawley rats with a single intraperitoneal injection of cyclophosphamide (CPA) at 50 mg/kg/day on Day 0. Nivestim or Neupogen were administered SC at dose levels 30 and 100 µg/kg once daily for 4 days, starting the day after CPA injection (Days 1 through 4). The study included an untreated control group as well as one that received CPA followed by treatment with placebo (vehicle). White blood cell (WBC) count and WBC differential count were measured 3 days prior to CPA and on days 2, 3, 4, 5, 6, 8, 9, 11 and 14 after the CPA injection. The results for ANC are shown in Table 1.

Table 1 Mean values for absolute neutrophil count (x 1000/uL)

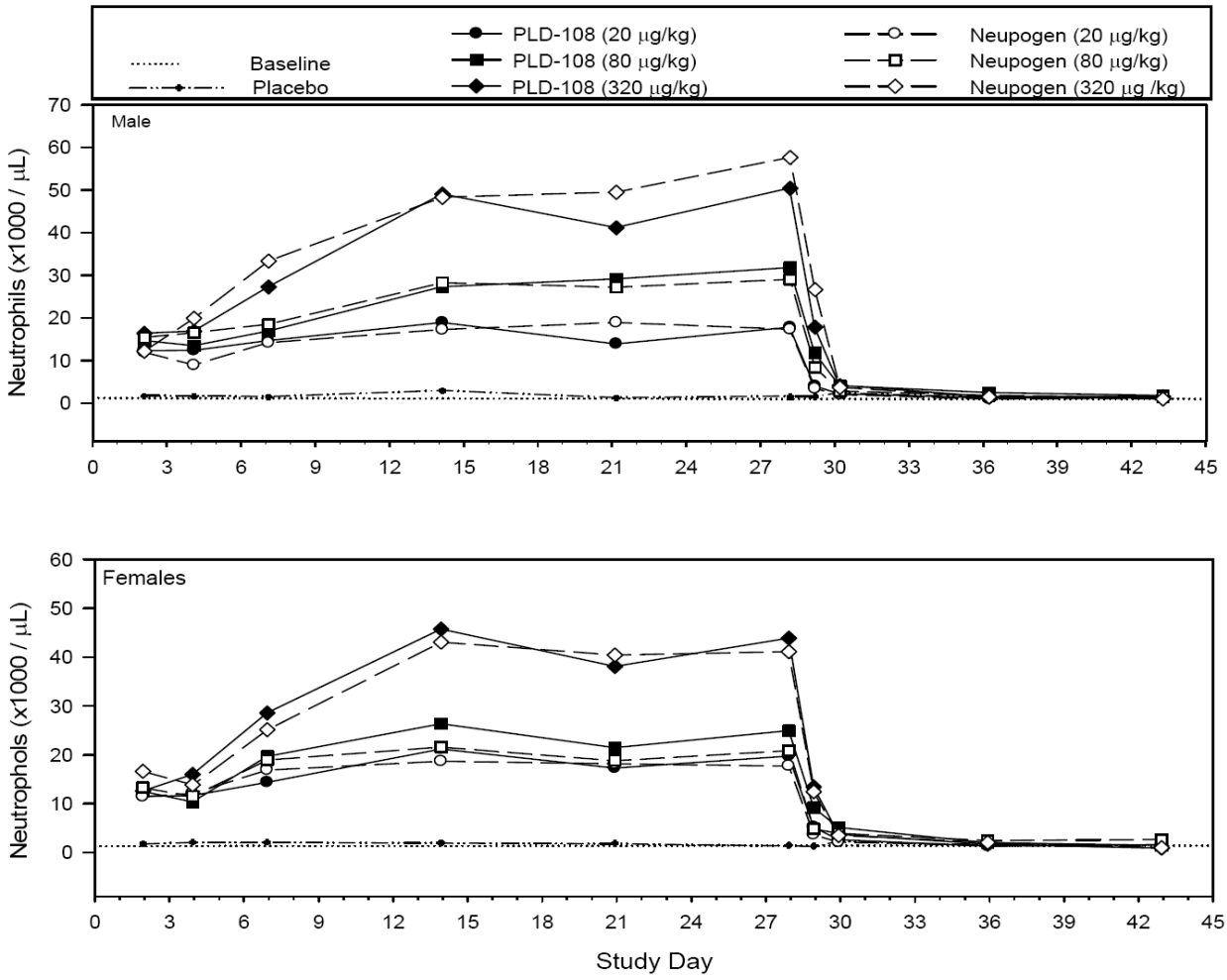
Days	Mean Absolute Neutrophils (ANS) ± SD (x1000/µL) (N = 8)[a]					
	Untreated	Placebo	PLD108 (30µg/kg/day)	PLD108 (100µg/kg/day)	Neupogen (30µg/kg/day)	Neupogen (100µg/kg/day)
2	1.82 ± 0.69	0.50 ± 0.24**	3.00 ± 0.89 *	3.53 ± 1.14**	2.07 ± 0.68	3.06 ± 0.76*
3	1.70 ± 0.66	0.65 ± 0.25	0.93 ± 0.52	2.01 ± 3.55	0.73 ± 0.37	0.76 ± 0.47
4	1.95 ± 0.57	0.24 ± 0.09*	1.49 ± 1.30	2.44 ± 1.01	1.96 ± 1.69	2.17 ± 1.68
5	2.10 ± 0.62	0.59 ± 0.13*	1.72 ± 0.78	3.40 ± 1.68	1.23 ± 0.60	2.79 ± 1.65
6	2.25 ± 1.17	0.74 ± 0.50**	1.01 ± 0.37*	1.85 ± 1.26	1.15 ± 0.82	1.49 ± 0.83
8	2.82 ± 0.84	3.58 ± 1.18	5.09 ± 3.14	3.09 ± 0.96	3.37 ± 1.28	2.99 ± 1.82
9	1.84 ± 0.98	3.62 ± 1.09	4.91 ± 1.90**	4.81 ± 1.67**	4.17 ± 1.11**	3.92 ± 1.46*
11	1.77 ± 0.75	2.49 ± 0.41	2.10 ± 0.78	2.03 ± 0.64	2.15 ± 1.01	2.56 ± 0.86
14	2.06 ± 0.74	2.22 ± 0.64	1.56 ± 0.53	1.60 ± 0.71	1.73 ± 0.87	1.84 ± 0.74

Mean ANS ± SD for prestudy was 1.48 ± 0.82 (x1000/µL) (N = 8)
a, N = 7 for Days 9 and 11
N, number of animals in each group
* Significant difference from untreated control (P < 0.05; ANOVA Followed by Dunnett's)
** Significant difference from untreated control (P < 0.01; ANOVA Followed by Dunnett's)

The neutropenic rat model included only male animals. The treatment with both Nivestim and Neupogen at two dose levels resulted in increased neutrophil counts after two days when compared to placebo treatment. Based on the statistical analysis, Nivestim and Neupogen induced a comparable pharmacodynamic response in male neutropenic rats except on Day 2 at the low dose level.

Neutrophil counts were also determined as part of the repeat-dose toxicity study in healthy male and female rats. (Figure 1). Increased ANC was observed one day after the first dose, and continued through the end of the treatment period. On cessation of treatment, neutrophil counts rapidly declined and had returned to normal levels two days after the last treatment. During the 28-day treatment period, Nivestim and Neupogen induced a comparable pharmacodynamic response. The regression analysis of dose-response curves for neutrophil counts were also comparable.

Figure 1 Neutrophil counts in male and female rats after multiple SC doses during the treatment (D2-28) and recovery period (D29-43)



2.3.2.2. Secondary pharmacodynamics

There were no secondary pharmacodynamic studies submitted.

2.3.2.3. Safety pharmacology programme

There were no safety pharmacology studies submitted.

2.3.2.4. Pharmacodynamic drug interactions

There were no secondary pharmacodynamic drug interactions studies submitted.

2.3.3. Pharmacokinetics

Pharmacokinetics studies of Nivestim and the reference product Neupogen were performed as part of the 28-day repeat-dose toxicity study.

Drug plasma levels were determined in groups of 4 animals/sex/time-point on Day 1 and Day 28. An adequately adjusted and validated commercial ELISA-based Quantikine human G-CSF immunoassay was used for quantification of plasma levels of Nivestim and Neupogen (Study report MN386-06). Statistically significant differences were observed in exposure (AUC), peak concentration (C_{max}) and half-life of the two products at certain dose levels and study days in both males and females. The

observed differences were not consistent in direction of change, dose or gender. Statistical analysis of the linear relationship between dose and AUC for Nivestim and Neupogen on Day 1 and Day 28 showed no statistically significant differences in both males and females, except for female rats on Day 28. Evaluation of the regression equation for AUC on Day 1 versus AUC on Day 28 indicated there was no statistically significant difference between Nivestim and Neupogen for either males or females. The C_{max} values were significantly lower for Nivestim in three groups and significantly higher in one group for Nivestim; thus a consistent dose related change in C_{max} was not observed. The elimination half life did not differ between the two products. Statistically significant differences in $T_{1/2}$ between Day 1 and Day 28 was noted in two treatment groups for Neupogen but were not considered biologically significant.

2.3.4. Toxicology

The toxicological data package consisted of 28-day subcutaneous repeated-dose toxicity study in rats (Study report. M386-06) followed by a 14-day recovery period with the assessment of antibody formation (binding and neutralising antibody), and a single dose local tolerance study in rabbits (Study report M387-06) after SC and IV administration.

2.3.4.1. Single dose toxicity

There were no single dose toxicity studies submitted.

2.3.4.2. Repeat dose toxicity (with toxicokinetics)

Each product was administered SC to male and female Sprague Dawley rats once a day for 28 consecutive days, at dose levels of 20, 80 or 320 µg/kg/day. Control animals received vehicle. Changes attributable to pharmacological activity, such as dose-dependent increases in white blood cell counts, absolute neutrophil counts, monocytes and basophils were observed in both sexes. Other findings included a dose-dependent decrease in red blood cell count, myeloid hyperplasia of the bone marrow, increased extramedullary hematopoiesis in spleen and liver, and dose-related increased absolute and relative spleen weights in both sexes, as well as decreased absolute and relative liver weights in males only. A dose-related articular swelling of the hind legs and hind leg dysfunction was observed in both treatment groups. Histopathological analysis revealed joint alterations, such as periostal inflammatory changes, hyperostosis, osteolysis and/or myelofibrosis. The bone changes were accompanied by a dose-dependent increase in alkaline phosphatase (ALP) activity over control values.

2.3.4.3. Genotoxicity

There were no genotoxicity studies submitted.

2.3.4.4. Carcinogenicity

There were no carcinogenicity studies submitted.

2.3.4.5. Reproduction Toxicity

There were no reproduction toxicity studies submitted.

2.3.4.6. Toxicokinetic data

The toxicokinetic data was collected in the repeat-dose toxicity study and is described under the section Pharmacokinetics.

2.3.4.7. Local tolerance

Local tolerance (Study report M387-06) was investigated in New Zealand White rabbits. One group received Nivestim IV (left ear vein) and SC (two sites on the upper dorsal torso) and the vehicle (right ear vein and two sites on the lower dorsal torso). The second group received Neupogen and vehicle in a similar manner. A single administration was given at each injection site using undiluted drug at a volume of 0.5 ml/injection (480 µg/0.5 ml). Thus each rabbit received a total dose of 1,440 µg Nivestim or Neupogen.

Evaluation of local tolerance showed that both were well tolerated when administered once by SC and IV routes. Injection sites were examined after repeated SC dosing as part of the repeat-dose toxicity study. All lesions were scored as minimal to mild.There were no differences in the injection site reactions between the two products.

2.3.4.8. Other toxicity studies - Immunogenicity

Main, recovery and satellite animal groups were tested for antibody formation, and animals from the recovery and satellite groups were tested for neutralising antibodies (NAbs). The occurrence of anti-G-CSF antibodies appeared to be low in both Nivestim and Neupogen treated groups. NAbs were detected in only a few of those animals that had developed binding antibodies. A decrease in plasma drug levels was detected in four animals in which NAbs were detected. When it was possible to compare antibody formation with toxicokinetic data, it was observed that in two animals from Nivestim (20 µg/kg/day) and two animals from Neupogen (20 µg/kg/day) treated groups, the plasma drug concentration was substantially reduced after 28 days of treatment when both binding antibodies and NAbs titer were detected simultaneously (Day 30).There was no significant difference in occurrence of NAbs between the two products.

2.3.5. Ecotoxicity/environmental risk assessment

The lack of an environmental risk assessment for Nivestim is justified by two reasons:

1. Nivestim is being developed as a biological medicinal product similar (Article 10.4 of Directive 2001/83/EC as amended) to Neupogen, medicinal product with marketing authorisation valid in the European Union. Based on the fact that filgrastim medicinal product is prescription only medicine and because it is intended to substitute other identical products on the market, the approval of the referred product should not result on an increase of the total quantity of filgrastim released in the environment. Therefore, it should not result in an increase of risk to the environment.
2. Furthermore, in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Humans Use (EMEA/CHMP/SWP/4447/00), amino acid, peptides and proteins are unlikely to result in significant risk to the environment and no environmental risk assessment is required.

The CHMP agreed with the justification proposed by the applicant.

2.3.6. Discussion on the non-clinical aspects

The pharmacodynamic data presented in the MAA dossier are considered sufficient and in accordance with the current guidance from the non-clinical aspect and with respect to the legal basis of the application. The pharmacokinetic behaviour and pharmacodynamic response in healthy rats to Nivestim and the reference product Neupogen can be considered to be comparable.

The pharmacological activity and pharmacodynamic response of Nivestim and Neupogen exhibited comparable receptor-binding properties *in vitro* in cell-based assays and comparable biological activity *in vivo* in neutropenic rats.

Neutrophil counts were also determined as part of the repeat-dose toxicity study in healthy male and female rats. During the 28-day treatment period, Nivestim and Neupogen induced a comparable pharmacodynamic response. The results showed statistically significant dose-dependent increases in neutrophil counts (ANC) over vehicle controls. On cessation of treatment, neutrophil counts rapidly declined and had returned to normal levels two days after the last treatment. Sporadic statistically significant differences between the two products were observed during the recovery period. However, the regression analysis of dose-response curves for neutrophil counts were comparable.

Drug plasma levels were determined in the groups of 4 animals/sex/time-point on Day 1 and Day 28. An adequately adjusted and validated commercial ELISA-based human G-CSF immunoassay was used for quantification of plasma levels of Nivestim and Neupogen. Differences were observed in exposure (AUC), peak concentration (C_{max}) and half-life of the two products at certain dose levels and study days in both males and females. The observed differences were not consistent in direction of change, dose or gender. Regression analysis explored difference in the slopes of the lines for Nivestim and Neupogen on Day 28. The small number of animals per group may partly explain the substantial inter-animal variation in plasma drug levels. Although differences in some of the PK parameters were observed, the pharmacodynamic response in healthy animals appeared to be comparable. Thus, the pharmacokinetic behaviour of Nivestim and the reference product Neupogen can be considered to be comparable.

Histopathologic changes in the 28-day repeat-dose toxicity study were in general qualitatively and quantitatively similar between Nivestim and Neupogen treated groups. The minor differences in degree and/or frequency of the various changes observed were not considered to be biologically meaningful. Therefore, the toxicological profile of Nivestim can be considered comparable to the reference product Neupogen.

Evaluation of local tolerance showed that both compounds were well tolerated when administered once by SC and IV routes. No difference between Nivestim and Neupogen could be seen. Injection sites were examined and there were no relevant differences between injection-related lesions at SC sites treated with placebo, Nivestim or Neupogen for either males or females. Injection site reactions were considered comparative between the two products.

The occurrence of anti-G-CSF antibodies appeared to be low in both Nivestim and Neupogen treated groups. NAbs were detected in only a few of those animals that had developed binding antibodies. A decrease in plasma drug levels was detected in four animals in which neutralising antibodies were detected. There was no significant difference in occurrence of neutralising antibodies between the two products.

During the assessment, minor concerns were raised on the demonstration of biosimilarity of Nivestim and the reference product Neupogen in terms of biological activity, the impact of retrospective validation of immunogenicity assays on the interpretation of the results and the contradiction in reporting related to statistical analysis of the pharmacodynamic response data. The applicant provided

adequate and sufficient responses to the questions. Analytical comparative data was presented for both products where characterisation data indicated very similar characteristics and biological activity for both products. The retrospectively extended method validation appeared to induce no additional changes than those indicated for the results of the ELISA screening assay and thus, interpretation and conclusions drawn from the data were considered valid. Finally, the contradiction in reporting was clarified as caused by erroneous reporting.

2.3.6.1. Conclusion on the non-clinical aspects

In conclusion, the non-clinical assessment of Nivestim did not reveal any important differences in terms of activity and toxicity between Nivestim and Neupogen.

2.4. Clinical aspects

A clinical development programme was designed to show biosimilarity of Nivestim to Neupogen. The first stage of the programme consisted of two phase I, single-centre, randomised, open-label, healthy volunteer studies designed to compare the PK, PD, and safety characteristics of Nivestim and Neupogen when given as single (study GCF061) and multiple doses (study GCF062). The second stage of the programme consisted of a phase III, randomised, multicentre, double-blind study designed to demonstrate the therapeutic equivalence of Nivestim and Neupogen in the prophylaxis of neutropenia in patients undergoing a myelosuppressive chemotherapy regimen (study GCF071).

2.4.1. Introduction

The clinical development program was performed in agreement with the Scientific Advices issued by EMA on February 18, 2005 (EMEA/CHMP/SAWP/50208/05, Procedure No.: EMEA/H/SA/562/1/2004/III) and on June 28, 2006 (EMEA/CHMP/SAWP/228511/2006, Procedure No.: EMEA/H/SA/562/1/FU/1/2006/II). The PK and PD studies were designed and developed in accordance with the Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/31329/2005), in order to show similarity between Nivestim and Neupogen. The phase III study design and endpoints were in accordance with the recommended clinical guidance for the demonstration of comparability of Nivestim to Neupogen. In agreement with the guidelines on clinical safety, data on adverse events (AEs) were collected in all studies and, as there is potential for an immune response in the form of antibodies against G-CSF, information on immunogenicity was collected in studies GCF062 and GCF071 using two validated bioanalytical assays.

Tabular overview of clinical studies

Type of Study/ Study Identifier	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**

Phase I PK, PD, safety GCF061	To compare PK and PD of PLIVA / Mayne filgrastim with Neupogen	An open-label, single centre, randomised, single dose, active comparator-controlled (Neupogen, Amgen), two-way crossover study in each of two parallel groups of subjects. Subjects were randomised to one of two parallel groups (IV and SC) and further randomised to order of treatment; 13 days washout	PLIVA/Mayne filgrastim; 10µg/kg; IV infusion or SC injection	44 evaluable	Healthy subjects	Single dose
Phase I PD, PK, safety GCF062	To compare the PD and PK of PLIVA / Mayne filgrastim with Neupogen	A single centre, randomised, double-blind, multiple-dose, active comparator-controlled (Neupogen, Amgen), two-way crossover study. Subjects were randomised to one of two parallel doses (5 or 10 µg/kg) and further randomised to order of treatment; 13 days washout	PLIVA/Mayne filgrastim; 5 or 10 µg/kg; multiple subcutaneous (SC) injections (a total of 5) of test (at least on of two doses) or active comparator (at a matching level)	48 evaluable	Healthy subjects	Multiple doses; a total of 5 SC injections over 5 consecutive days , crossing over to the alternative treatment in the second treatment period
Phase III efficacy, safety GCF071	To demonstrate the therapeutic equivalence of PLIVA/Mayne filgrastim and Neupogen. To compare the efficacy, safety and tolerability of PLIVA/Mayne filgrastim nad Neupogen. To compare the immunogencity of PLIVA/Mayne filgrastim and Neupogen.	A multicentre, randomised, double-blind therapeutic equivalence study. Subjects were randomised (2:1) to one of the two treatment arms (5 µg/kg PLIVA/Mayne filgrastim or 5 µg/kg Neupogen). Subjects were followed up 28 days after the last dose of PLIVA/Mayne filgrastim or Neupogen, and at 6 months.	PLIVA/Mayne filgrastim or Neupogen, doses of 5 µg/kg by SC up to 6 cycles post chemotherapy	250 evaluable	Patients with invasive breast cancer	Multiple doses; up to 6 cycles at 3-weekly intervals

The applied and approved indication for Nivestim was:

Filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the

duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Filgrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$ /l and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Filgrastim is indicated for the treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$ /l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

2.4.2. GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.3. Pharmacokinetics

Two phase I trials (GCF061 and GCF062) were carried out to study pharmacokinetics (PK) and demonstrate biosimilarity between Nivestim and Neupogen, the reference product.

Subjects in study GCF061 received a single dose (10 µg/kg) of Nivestim and Neupogen in random order and the primary objective was to compare the PK of Nivestim with Neupogen, administered as a single IV or SC dose. There was a washout period of at least 13 days between treatments. A secondary objective was to compare the pharmacodynamics (PD) and safety of Nivestim with Neupogen, administered as a single IV or SC dose. The primary endpoint for both the IV and SC routes of administration was $AUC_{(0\text{-tlast})}$ for the plasma concentration of G-CSF. The secondary PK endpoints were C_{max}, T_{max}, $T_{1/2}$, $AUC_{(0\text{-inf})}$, λ, and Cl for the plasma concentration of G-CSF; the secondary PD endpoints were absolute neutrophil count (ANC) $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max}, ANC_{min}.

Study GCF062 was a single-centre, randomised, double-blind, multiple-dose, comparator-controlled, two-way crossover study which compared the PD of Nivestim with Neupogen, administered as multiple SC doses. Subjects were randomised to one of two doses (10 µg/kg or 5 µg/kg) and further randomised to order of treatment. Subjects received a total of five SC injections of Nivestim (at one of two doses) or Neupogen (at a matching dose level) over five consecutive days, crossing over to the alternative treatment in the second treatment period, with a washout period of at least 13 days between the last dose of the Treatment Period 1 and the first dose of Treatment Period 2. The primary and secondary objective for study GCF062 were to compare the PD, PK and safety of Nivestim with Neupogen, administered as multiple SC doses. The primary endpoint was the absolute neutrophil count (ANC) and $AUC_{(0\text{-tlast})}$ at Day 5. The secondary PK endpoints were C_{max}, C_{min}, T_{max}, $T_{1/2}$, $AUC_{(0\text{-tlast})}$, $AUC_{(0\text{-24})}$, $AUC_{(0\text{-inf})}$, λ, and Cl for the plasma concentration of G-CSF at Day 5; the secondary PD endpoints were ANC T_{max}, ANC_{max}, ANC_{min} and CD34+ cell count at Day 5.

- Analytical methods

Plasma G-CSF levels were detected using a commercial kit method (Quantikine human G-CSF ELISA), which uses the quantitative sandwich enzyme immunoassay technique. The assay was validated for use in human plasma and an initial analysis of the study plasma G-CSF samples was performed. The PK results were found to be inaccurate and a repeat validation and re-analysis of the GCF061 and GCF062 PK data were performed. The applicant established a final detection range for G-CSF between 80 pg/ml. (LLOQ) and 2500 pg/mL (ULOQ).

- Pharmacokinetic data and Statistical analysis

The PK population consisted of all subjects who completed the studies with a sufficient number of quantifiable concentrations to warrant parameter estimation in any study treatment period. Analysis of PK parameters was based on this population. For both the IV and SC routes of administration, PK data was analysed by non-compartmental methods with WinNonlin (Standard version 1, Pharsight Corporation, Mountain View, California) and modelled for constant intravenous infusion.

For each of IV and SC routes of administration, the parameter $AUC_{(0\text{-}tlast)}$ was log transformed and analysed using a mixed effects analysis of variance (ANOVA) with terms including subject within sequence as a random effect and sequence treatment and period as fixed effects. A 90% confidence interval for the ratio of the 'test' to 'reference' treatment means, after adjustment for other factors in the model, was calculated using the least square estimates of the means and the residual variance from the model. If the 90% confidence interval was within the conventional bioequivalence limits of 0.8 and 1.25, then bioequivalence was declared reached. $AUC_{(0\text{-}inf)}$ and C_{max} were log transformed and analysed in the same manner as the primary endpoint. The PK parameter $T_{1/2}$ was not initially log-transformed; however, since log transformation improved its adherence to the assumptions for analysis of variance, this parameter was subsequently transformed and analysed in the same manner as the primary endpoint.

The Cl, λ and T_{max} parameters arising from the PK data were summarised. The approximate bioavailability of the test treatment, comparing the PK variable $AUC_{(0\text{-}tlast)}$ after IV and SC administration, were evaluated as supportive data only.

Data were analysed and reported using SAS Version 8.2

2.4.3.1. Absorption

There were no studies on absorption submitted.

2.4.3.2. Distribution

PK data from study GCF061 suggests that 10 µg/kg doses of Nivestim and Neupogen are bioequivalent in healthy volunteers when administered by either the IV or SC routes (table 2, 3, 4 and 5).

Table 2: AUC(0-tlast) for plasma concentration of G-CSF (IV Subjects) (pg.h/mL) – Study GCF 061

	PLIVA/Mayne Filgrastim	**Neupogen®**
N	20	20
Geometric mean	987787.821	973891.599
Median	981766.528	939233.341
Minimum	646397.94	685166.92
Maximum	1782898.59	1629412.73
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	1.009
	90% CI	0.931, 1.093

Table 3: AUC(0-tlast) for plasma concentration of G-CSF (SC Subjects) (pg.h/mL) – Study GCF 061

	PLIVA/Mayne Filgrastim	**Neupogen®**
N	26	26
Geometric mean	676926.897	654492.435
Median	704712.086	658028.661
Minimum	266862.04	420503.52
Maximum	932440.15	972782.81
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	1.034
	90% CI	0.941, 1.137

Table 4: Summary of Secondary Pharmacokinetics (IV Subjects) – Study GCF 061

	N=20	**$AUC_{(0\text{-}inf)}$ (pg.h/mL)**	**C_{max} (pg/mL)**	**$T_{1/2}$ (h)**	**T_{max} (h)**	**λ_z**	**CL (mL/h/kg)**
PLIVA/Mayne filgrastim	GM	991200.388	249871.929	4.084	0.680	0.1697	10.0888
	Median	985455.948	236000.000	3.481	0.750	0.1992	10.1520
	Min	649492.34	161000.00	2.80	0.50	0.089	5.599
	Max	1786032.09	446000.00	7.80	1.00	0.247	15.397
Neupogen®	GM	976821.361	240007.935	3.801	0.681	0.1823	10.2373
	Median	941729.885	222000.000	3.462	0.750	0.2002	10.6198
	Min	687265.84	135000.00	2.33	0.50	0.066	6.126
	Max	1632466.97	461000.00	10.55	1.00	0.298	14.550
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.009	1.036	1.091			
	90% CI for ratio	0.931, 1.093	0.921, 1.166	0.974, 1.223			

Table 5: Summary of Secondary Pharmacokinetics (SC Subjects) – Study GCF 061

	n=26	**$AUC_{(0\text{-}inf)}$ (pg.h/mL)**	**C_{max} (pg/mL)**	**$T_{1/2}$ (h)**	**T_{max} (h)**	**λ_z**	**CL (mL/h/kg)**
PLIVA/Mayne filgrastim	GM	679716.412	74070.635	3.910	5.065	0.1773	14.7120
	Median	707095.433	75800.000	3.548	6.000	0.1954	14.1424
	Min	268141.19	34500.00	2.09	3.00	0.087	10.698
	Max	934785.79	107000.00	7.99	10.00	0.332	37.294
Neupogen®	GM	657344.705	71012.206	3.617	5.318	0.1916	15.2127
	Median	663654.963	71400.000	2.964	6.000	0.2339	15.0692
	Min	423049.34	31400.00	1.98	3.00	0.093	10.255
	Max	975144.41	108000.00	7.44	10.00	0.349	23.638
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.034	1.043	1.081			
	90% CI for ratio	0.940, 1.137	0.941, 1.157	0.898, 1.301			

The PK data from study GCF062 is presented in Table 6 and 7 below. The results show that in the 10 µg/kg subgroup, the ratio of $AUC_{(0\text{-}tlast)}$ between Nivestim and Neupogen was 1.150 (90%CI, 1.034-1.279) and the ratio of C_{max} between Nivestim and Neupogen was 1.136 (90%CI, 1.002-1.287). The 90%CIs were slightly above the upper limit of the pre-defined equivalence range of 0.80-1.25.

The ratios of $AUC_{(0\text{-}tlast)}$ ($AUC_{(0\text{-}24)}$) in the 5 µg/kg subgroup between Nivestim and Neupogen was 1.097 (90%CI, 0.988-1.218) where the 90%CIs were within the pre-defined equivalence range of 0.80-1.25. The ratio of C_{max} between Nivestim and Neupogen was 1.129 (90%CI, 0.980-1.300). The 90%CI was above the upper limit of the pre-defined equivalence range of 0.80-1.25.

Table 6 Summary of Statistical Analysis of Plasma Concentration of G-CSF (Test vs Reference Treatment) for 10 µg/kg dose – Study GCF 062

Treatment		$AUC_{(0\text{-}tlast)}$ (pg.h/ml) (n=24)	$AUC_{(0\text{-}24)}$ (pg.h/ml) (n=24)	C_{max} (pg/ml) (n=24)	C_{min} (pg/ml) (n=24)	T_{max} (h) (n=24)
PLIVA/Mayne filgrastim	Geometric mean	257841.09	257841.09	37376.0	304.7	4.419
	Median	273139.98	273139.98	43250.0	277.5	4.000
	Minimum	110536.1	110536.1	11000	162	3.00
	Maximum	471122.8	471122.8	75600	858	6.02
Neupogen®	Geometric mean	221246.57	221246.57	32628.7	295.0	4.172
	Median	227480.81	227480.81	32300.0	241.0	4.000
	Minimum	93350.5	93350.5	9180	158	2.00
	Maximum	380409.4	380409.4	79600	1070	6.00
PLIVA/Mayne filgrastim / Neupogen®	Ratio	1.150	1.150	1.136	1.028	
	90% CI for Ratio	1.034, 1.279	1.034, 1.279	1.002, 1.287	0.914, 1.157	

Table 7 Summary of Statistical Analysis of Plasma Concentration of G-CSF (Test vs Reference Treatment) for 5 µg/kg dose – Study GCP 062

Treatment		$AUC_{(0\text{-}tlast)}$ (pg.h/ml) (n=23)	$AUC_{(0\text{-}24)}$ (pg.h/ml) (n=23)	C_{max} (pg/ml) (n=23)	C_{min} (pg/ml) (n=23)	T_{max} (h) (n=23)
PLIVA/Mayne filgrastim	Geometric mean	105223.09	105223.09	17112.0	213.9	3.799
	Median	105479.50	105479.50	18400.0	204.0	4.000
	Minimum	58462.6	58462.6	9320	165	2.00
	Maximum	216429.6	216429.6	31200	501	6.00
Neupogen	Geometric mean	95809.79	95809.79	15187.5	242.9	4.137
	Median	100527.67	100527.67	16700.0	221.0	4.000
	Minimum	40646.3	40646.3	6130	165	3.00
	Maximum	163110.5	163110.5	25900	1480	6.00
PLIVA/Mayne filgrastim / Neupogen	Ratio	1.097	1.097	1.129	0.881	
	90% CI for Ratio	0.988, 1.218	0.988, 1.218	0.980, 1.300	0.731, 1.061	

2.4.3.3. Elimination

There were no elimination studies submitted.

2.4.3.4. Dose proportionality and time dependencies

There were no dose proportionality and time dependencies studies submitted.

2.4.3.5. Special populations

There were no special populations studies submitted.

2.4.3.6. Pharmacokinetic interaction studies

There were no pharmacokinetic interaction studies submitted.

2.4.3.7. Pharmacokinetics using human biomaterials

There were no pharmacokinetics studies using biomaterials submitted.

2.4.4. Pharmacodynamics

2.4.4.1. Mechanism of action

There were no studies on the mechanism of action submitted.

Based on the SmPC of Neupogen, human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Nivestim containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within twenty-four hours, with minor increases in monocytes. In some severe chronic neutropenia patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days (SmPC section 5.1).

2.4.4.2. Primary and Secondary pharmacology

The primary PD endpoint for study GCF062 was ANC $AUC_{(0\text{-tlast})}$ at Day 5. Results for the 10 µg/kg dose group and the 5 µg/kg dose group are shown in Table 8 and 9, respectively.

Table 8 ANC AUC (0-tlast) for 10µg/kg dose (pg.h/ml) – Study GCF062

	PLIVA/Mayne Filgrastim	Neupogen®
N=23		
Geometric Mean	2170.387	2249.496
Median	2233.294	2293.648
Minimum	1091.32	1099.31
Maximum	3341.43	3970.06
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	0.969
	90% CI	0.928, 1.012

Table 9 ANC AUC (0-tlast) for 5µg/kg dose (pg.h/ml) – Study GCF062

	PLIVA/Mayne Filgrastim	Neupogen®
N=24		
Geometric Mean	1632.962	1659.826
Median	1625.485	1657.936
Minimum	918.07	695.84
Maximum	2633.27	2535.48
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	0.984
	90% CI	0.922, 1.050

The geometric mean ANC $AUC_{(0\text{-tlast})}$ values for treatment with 10 µg/kg and 5 µg/kg dose Nivestim and Neupogen were similar and the ratio was 0.969 (90%CI, 0.928-1.012) and 0.984 (90%CI, 0.922-1.050), respectively. The 90%CI was within the pre-defined equivalence range of 0.80-1.25. When outliers were excluded, the ratio for ANC $AUC_{(0\text{-tlast})}$ for 10 µg/kg and 5 µg/kg dose between Nivestim and Neupogen was 0.980 (90%CI, 0.942-1.020) and 0.995 (90%CI, 0.960-1.030), respectively.

Figure 2 and 3 shows the mean ANC in the PD population for the 10µg/kg and 5 µg/kg dose, respectively.

Figure 2 Mean ANC (10^9/L) in PD population 10µg/kg dose group – Study GCF062

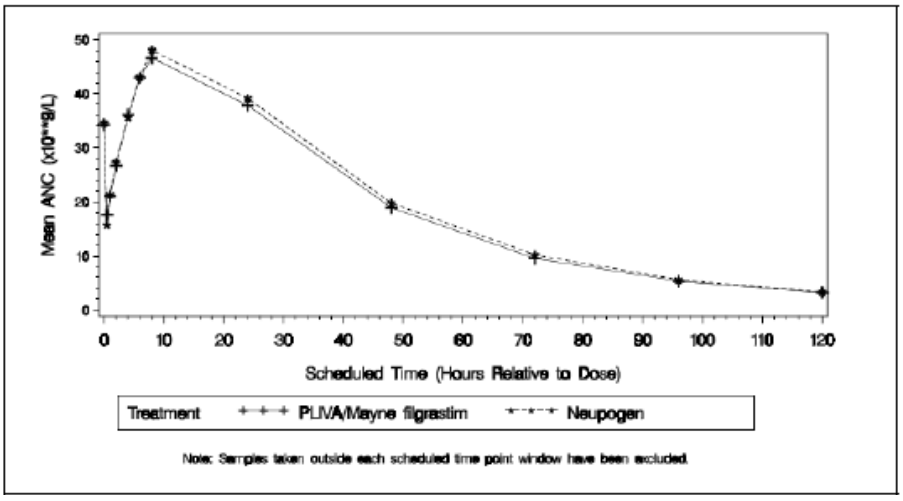
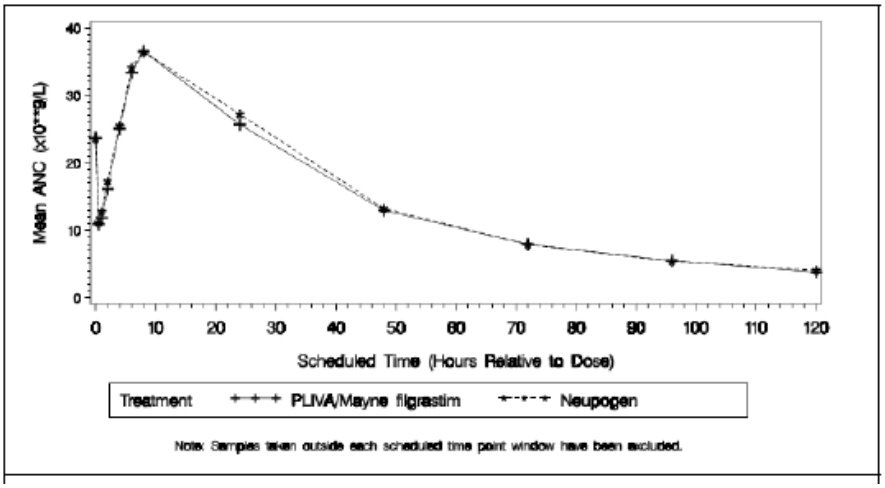


Figure 3 Mean ANC (10^9/L) in PD population 5µg/kg dose group – Study GCF062



Pharmacodynamic endpoints for subjects receiving SC treatment in PD Population 1 are presented in Table 10 and the results for subjects receiving SC treatment in PD Population 2 (excluding subjects with 2 consecutive missing values) are shown in Table 11.

Table 10 Pharmacodynamic results PD population 1 (SC) – Study GCF-061

	n=26	ANC AUC$_{(0\text{-last})}$ (10^9.h/L)	ANC T_{max} (h)	ANC_{max} (10^9/L)	ANC_{min} (10^9/L)
PLIVA/Mayne filgrastim	Geometric mean	1334.479	19.442	23.463	0.231
	Median	1327.605	24.000	23.260	0.205
	Min	954.16	8.00	16.74	0.07
	Max	2168.98	24.10	34.45	3.38
Neupogen®	Geometric mean	1299.750	21.490	22.503	0.205
	Median	1293.501	24.000	23.210	0.185
	Min	731.80	6.00	14.02	0.08
	Max	2031.20	48.12	37.43	2.72
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.027		1.043	1.128
	90% CI for ratio	0.991,1.064		0.981,1.109	0.828,1.537

Table 11 Pharmacodynamic results in PD population 2 (SC) – Study GCF-061

	n=23	ANC AUC$_{(0\text{-last})}$ (10^9.h/L)	ANC T_{max} (h)	ANC_{max} (10^9/L)	ANC_{min} (10^9/L)
PLIVA/Mayne filgrastim	Geometric mean	1334.181	19.837	23.551	0.199
	Median	1322.728	24.000	22.490	0.200
	Min	954.16	8.00	16.74	0.07
	Max	2168.98	24.07	34.45	0.51
Neupogen®	Geometric mean	1285.850	21.823	22.747	0.197
	Median	1288.843	24.000	23.530	0.180
	Min	731.80	8.00	14.02	0.08
	Max	2031.20	24.15	37.43	2.72
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.036		1.036	1.005
	90% CI for ratio	1.001, 1.071		0.967, 1.110	0.747, 1.350

The geometric mean ANC $AUC_{(0\text{-tlast})}$ values for the SC Nivestim and Neupogen treatment groups were similar and the ratio of means was 1.027 (90%CI, 0.991-1.064) for population 1. When outliers were excluded, the ratio of $AUC_{(0\text{-tlast})}$ between Nivestim and Neupogen was 1.048 (90%CI, 1.020-1.077).

Average values for ANC T_{max} were generally comparable for subjects receiving IV and those receiving SC, but were slightly later in the latter group. The geometric mean ANC_{max} values for the SC Nivestim and Neupogen treatment groups were also similar; the ratio of means was 1.043 (90%CI, 0.981-1.109) for PD population 1. When outliers were excluded, the ratio of ANC_{max} between Nivestim and Neupogen was 1.058 (90%CI, 0.998-1.122). The geometric mean ANC_{min} values for the SC Nivestim and Neupogen treatment groups were comparable; the ratio of means was 1.128 (90%CI, 0.828-1.537), meaning the CI was outside the pre-defined equivalence range of 0.80-1.25. The same occurred for the ratio of ANC_{min} between Nivestim and Neupogen which was 1.148 (90%CI, 0.938-1.405), when outliers were excluded.

In general, the results for the Population 2 were similar to Population 1 for SC and IV administration.

When the 95%CI for the ratio of the mean ANC AUC(0-tlast) value measured at Day 5 in the PD population 1, it was also well within the pre-defined equivalence range in both IV treatment group (95%CI, 0.986-1.085) as well as SC treatment group (95%CI, 0.984-1.072). Also in PD population 2, the 95%CI for the ratio was within the range 0.974 - 1.082 and 0.994 - 1.079 in IV and SC groups, respectively. The equivalence was not shown for the ANC_{min} value which was out of 95%CI equivalence range in both upper and lower boundary (0.777, 1.639 and 0.703, 1.436) in SC subjects (PD Population 1 and 2) and below lower limit (0.654, 1.060 and 0.728, 1055) in IV subjects.

Secondary pharmacology was studied only in trial GCF062. Pharmacodynamic endpoints (mean ANCmax, ANCmin, ANC Tmax and CD34+) for subjects in the 10 µg/kg dose group and 5 µg/kg dose group are presented in Table 12 and 13. Results show the mean ANCmax, ANCmin and CD34+ were equivalent for subjects receiving both Nivestim and Neupogen and ANC Tmax occurred slightly earlier following treatment with Nivestim (7.845 h) compared to treatment with Neupogen (9.448 h). Similar results were obtained with 5 µg/kg dose group.

Table 12 Pharmacodynamic results 10 µg/kg dose subjects – Study GCF062

Treatment	N=23	ANC_{max} (x10**9.h/L)	ANC_{min} (x10**9.h/L)	$CD34^+$ (cells. µl)	ANC T_{max} (h)
PLIVA/Mayne filgrastim	Geometric mean	46.103	3.014	81.9	7.845
	Median	48.720	2.630	77.0	8.000
	Minimum	30.53	1.86	19	4.000
	Maximum	69.65	6.11	184	24.00
Neupogen®	Geometric mean	47.202	3.241	77.5	9.448
	Median	48.390	3.170	77.0	8.000
	Minimum	25.09	1.69	28	6.000
	Maximum	66.44	4.90	232	24.07
PLIVA/Mayne filgrastim / Neupogen®	Ratio	0.980	0.928	1.059	
	90% CI for Ratio	0.950, 1.010	0.831, 1.037	0.902, 1.243	

Table 13 Pharmacodynamic results 5 µg/kg dose subjects – Study GCF062

Treatment	N=24	ANC_{max} (x10**9.h/L)	ANC_{min} (x10**9.h/L)	$CD34^+$ (cells.ml)	ANC T_{max} (h)
PLIVA/Mayne filgrastim	Geometric mean	36.092	3.385	47.2	7.810
	Median	38.635	3.440	50.0	8.000
	Minimum	24.12	1.01	14.0	6.000
	Maximum	52.19	8.32	158.0	8.000
Neupogen®	Geometric mean	35.658	3.821	46.0	7.798
	Median	36.825	3.835	50.0	8.000
	Minimum	18.14	1.71	12.0	6.000
	Maximum	58.17	7.83	187.0	24.000
PLIVA/Mayne filgrastim / Neupogen®	Ratio	1.012	0.886	1.027	
	90% CI for Ratio	0.955, 1.073	0.804, 0.976	0.854, 1.235	

2.4.4.3. Discussion on clinical pharmacology

The healthy volunteer study GCF061 demonstrated that bioequivalence between Nivestim and Neupogen could be established and the results from study GCF062 support this conclusion.

Study GCF062 was performed according to the EMEA/CHMP Guidance on Similar Medicinal Products containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005). It is not a requirement to study PD parameters in both SC and IV administration, however it may be useful to have the information. The applicant studied PD in two different dose levels (5 and 10 µg/kg). The 5 µg/kg dose curve showed linearity in the ascending part of the dose-response curve. There is consistency in the results of both doses, demonstrating the equivalence between Nivestim and Neupogen in the SC route. The CHMP noted that a shorter wash-out period was used in comparison to the reference products BE study referred (EMEA/502481/2008) but this had no impact on the clinical relevance.

The CHMP noted that the results of the primary endpoints in pharmacology confirmed the bioequivalence between Nivestim and Neupogen. The primary endpoint ANC AUC was equivalent with both IV and SC administration and within the pre-defined 90%CI equivalence range of 0.80-1.25. Tmax seems to appear slightly earlier with Nivestim but this was considered to have no clinical relevance. The only value outside the pre-defined 90%CI equivalence rate was ANC_{min} in Study GCF061 for both SC and IV administration. It is of note that when given IV, Nivestim had lower values than Neupogen, while with SC administration the situation was reversed.

As per the guideline, the CD34+ cell count was reported as a secondary endpoint. The level of CD34+ cells exceeded the upper limit of the allowed equivalence range in Nivestim PD population in both 10 µg/kg dose group (95%CI, 0.872-1.285), and in 5 µg/kg dose group (95%CI, 0.821-1.283). However, the geometric mean CD34+ values were similar for both Nivestim and Neupogen hence establishing equivalence between the two products.

As part of a major objection at D120, the CHMP requested a discussion on the choice of 90% CI instead of 95% CI for the pharmacodynamic endpoint in study GCF062 and to demonstrate assay sensitivity for the primary PD parameters. At the request of the CHMP, the applicant reanalyzed the data for the PD endpoint according to the 95% confidence interval. The ratio of the mean ANC $AUC_{(0-tlast)}$ value, in both 10 µg/kg and 5 µg/kg single dose groups was within the 95%CI range of 0.80 - 1.25, fulfilling the equivalence criteria. Pharmacodynamic endpoints for subjects in PD Population 1 and for subjects in PD Population 2 demonstrated that IV and SC Nivestim and Neupogen are considered equivalent. Except for ANC_{min}, generally the 95%CIs were within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for these endpoints. The ANC value curves for both treatments were also considered comparable.

The CHMP had some concern about the reliability of G-CSF plasma concentration analysis. The applicant addressed the concern by providing data from an assay that was designed to measure G-CSF levels in plasma and data from an ELISA assay validated for measuring G-CSF in human plasma The stability assay in different temperatures and G-CSF concentrations showed no loss of G-CSF activity even after 3 freeze-thaw cycles. The applicant provided further comments on the specificity of the assay for the intact G-CSF protein and the specificity of the antibodies used for the detection of all forms of G-CSF.

2.4.4.4. Conclusions on clinical pharmacology

In conclusion, the clinical pharmacology assessment of Nivestim did not reveal any important differences in terms of bioequivalence between Nivestim and Neupogen.

2.4.5. Clinical efficacy

The clinical programme for demonstrating biosimilarity between Nivestim and Neupogen included one phase III study, which was conducted in patients with breast cancer who received G-CSF prophylaxis in addition to a normal chemotherapy (Study GCF071).

2.4.5.1. Dose response study(ies)

As this application relates to a biosimilar product, there is no requirement for dose-response studies and no dose response studies were submitted. The dose for Nivestim is the same as for the reference products Neupogen. The recommended dose of Neupogen is 5–12 µg/kg/day, depending on the indication. The dose of 5 µg/kg/day Nivestim or Neupogen was chosen as this is the dose licensed for breast cancer.

2.4.5.2. Main study(ies)

GCF071: A Phase III randomised, multicentre, double-blind, therapeutic equivalence study of biosimilar G-CSF (PLIVA/Mayne filgrastim) versus Neupogen (filgrastim - Amgen) in subjects receiving doxorubicin and docetaxel as combination therapy for breast cancer

2.4.5.2.1. Methods

2.4.5.2.1.1. Study Participants

The main inclusion criteria were:

1. Females ≥ 18 and ≤ 70 years of age;

2. Subjects with invasive breast cancer appropriate for treatment with doxorubicin and docetaxel combination therapy in the neoadjuvant, adjuvant or first line metastatic treatment setting, who have not previously received treatment with anthracyclines or taxanes;

3. ECOG Performance Status 0 or 1 as determined on Day 1 of Cycle 1 prior to administration of chemotherapy;

4. Adequate bone marrow function, as determined within 1 day prior to administration of chemotherapy on Day 1 of Cycle 1 and as indicated by:

- . Hb ≥ 10 g/dL (transfusion permitted)
- . ANC ≥ 1.5 x 10^9/L
- . Platelets ≥ 100 x 10^9/L;

5. Adequate renal and hepatic function, as determined within 1 day prior to administration of chemotherapy on Day 1 of Cycle 1 and as indicated by:

- . Creatinine < 1.5 x ULN
- . Total bilirubin within normal reference range (unless elevation is known to be due to Gilbert's disease)
- . Subjects must also meet one of the following criteria:

  a) Alkaline phosphatase within normal reference range and both AST (aspartate aminotransferase) and ALT (alanine aminotransferase) < 2.5 x ULN

  b) Alkaline phosphatase < 2.5 x ULN and both AST and ALT < 1.5 x ULN

  c) Alkaline phosphatase < 5 x ULN and both AST and ALT within normal reference range;

6. Female subjects with reproductive potential must use a medically-acceptable method of contraception throughout the treatment period and for 3 months after discontinuation of treatment.

7. Estimated life-expectancy > 6 months.

The main exclusion criteria were:

1. Chemotherapy within the 4 weeks prior to the first dose of Chemotherapy (Day 1 of Cycle 1) (or a longer period depending on the defined characteristics of the agents used,e.g., 6 weeks for mitomycin);

2. Radiotherapy within the 6 weeks prior to the first dose of chemotherapy, except for localised spot radiotherapy for bone metastases (Day 1 of Cycle 1);

3. Any prior radiotherapy to the mediastinal/pericardial region;

4. Any concurrent anti-cancer therapy, including endocrine therapy (with the exception of corticosteroids), immunotherapy and monoclonal antibody therapy. Concurrent treatment with

bisphosphonates was also excluded unless the subject has been on a stable dose for four weeks prior to the first dose of chemotherapy (Day 1 of Cycle 1);

5. Prior bone marrow or stem cell transplant;

6. Any known myeloid abnormality (to include a pre-malignant myeloid condition or malignant condition);

7. Co-existing active infection, or received systemic anti-infectives for the treatment of infection within 72 hours prior to the first dose of chemotherapy (Day 1 of Cycle 1);

8. Significant cardiovascular disease

9. Clinically symptomatic brain metastases (baseline computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the brain required only if there is clinical suspicion of central nervous system metastases);

10. Previously received any G-CSF;

11. Pregnant or breast-feeding women;

12. Concurrent treatment with erythropoietin or prior treatment within 4 weeks prior to the first dose of chemotherapy (Day 1 of Cycle 1).

2.4.5.2.1.2. Treatments

Prior to receiving chemotherapy, all subjects were to receive pre-medication in the form of dexamethasone 8 mg b.i.d. for 3 days starting on Day -1, the day before chemotherapy is given.

Eligible subjects received chemotherapy comprising doxorubicin 60 mg/m^2 (bolus injection) and docetaxel 75 mg/m^2 on day 1 of cycles 1 to 6.

Treatment with Nivestim or Neupogen at 5 µg/kg by SC injection was initiated on Day 2 of each cycle at least 24 hours after of administration of chemotherapy. It was administered once daily for 14 days, on Days 2 to 15 of each cycle, or until the documented nadir had passed and the ANC was >3 x 10^9/L, whichever occurs first. During cycle 1, the decision to dose the subject was based on the ANC result from the previous day. Since haematology was assessed less frequently from cycle 2 onwards, the decision to dose the subjects in the following cycles was based on the most recent ANC result.

The required volume of IMP for administration during each cycle was based on the subject's actual bodyweight on Day 1 of the cycle.

2.4.5.2.1.3. Objectives

The primary objective of this trial was to demonstrate the therapeutic equivalence of Nivestim and Neupogen.

The secondary objectives were to compare the efficacy, safety and tolerability of Nivestim and Neupogen and to compare the immunogenicity of Nivestim and Neupogen.

2.4.5.2.1.4. Outcomes/endpoints

The primary endpoint of this study was the duration of severe neutropenia (DSN) in days (ANC <0.5 x 10^9/L) in cycle 1.

<u>Secondary efficacy endpoints were:</u>

• DSN (ANC <0.5 x 10^9/L) in cycles 2 to 3;

• Time to ANC recovery (ANC >3 x 10^9/L) in cycles 1 to 3;

• Incidence of febrile neutropenia (ANC <0.5 x 10^9/L and body temperature of 38.5 ºC) in cycles 1 to 3;

• Incidence of documented infection in cycles 1 to 3;

• Cumulative dose of Nivestim or Neupogen

Secondary safety endpoints were:

• Incidence and duration of hospitalisation of subjects with febrile neutropenia;

• Incidence of adverse events;

• Changes in laboratory safety parameters;

• G-CSF antibody formation

2.4.5.2.1.5. Sample size

For a 2:1 randomisation of filgrastim Nivestim versus Neupogen, the sample size required would be 144 and 72 evaluable subjects respectively (total of 216 subjects). This sample size is based on using a primary endpoint of DSN in cycle 1 (measured in days) with an equivalence range of (±1 day), an expected true difference in mean DSN of <0.25 days, a common standard deviation of 1.6 days and a power of 90%. Assuming at least a 20% drop-out rate (where these subjects will not be eligible for the Per Protocol analysis) a total of 279 subjects (186 and 93 subjects for Nivestim and Neupogen, respectively) would be required to be randomised into the study.

2.4.5.2.1.6. Randomisation

Subjects were randomly allocated (2:1) to one of two treatment arms: Nivestim (5 µg/kg) or Neupogen (5 µg/kg). Subjects were stratified according to country and treatment setting: neoadjuvant/adjuvant versus metastatic. Randomisation was performed using IVRS.

2.4.5.2.1.7. Blinding (masking)

The treatment was double-blind that is, neither the subject nor study site staff knew which treatment (Nivestim or Neupogen) was being taken.

2.4.5.2.1.8. Statistical methods

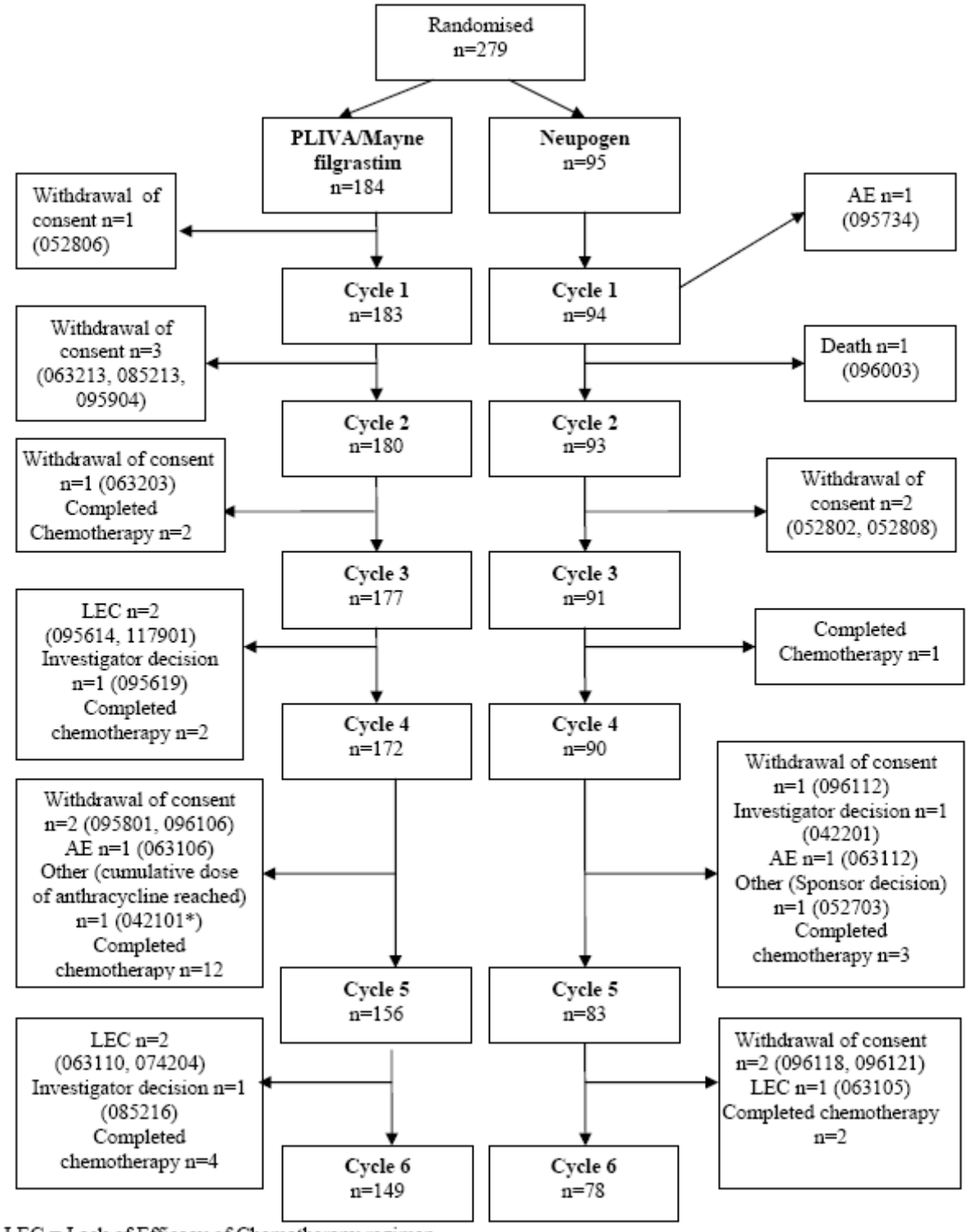
No interim analysis was planned.

Continuous data was summarised by treatment group using summary statistics (n, mean, standard deviation (SD), coefficient of variation (as a percentage CV%= SD/mean*100) median, minimum and maximum).

Categorical data was summarised by treatment group using frequency counts and percentages. Percentages in summary tables were calculated out of the population denominator (the number of subjects in the relevant population or subgroup of a population) or out of the number of subjects with relevant recorded values, as indicated on each table template. Unless otherwise specified in the SAP missing data was not imputed, and analyses/summary presentations was based on available data at assessment time points.

Results

Participant flow



LEC = Lack of Efficacy of Chemotherapy regimen.

2.4.5.2.1.9. Recruitment

A total of 279 subjects were randomised; 184 to Nivestim and 95 to Neupogen.

2.4.5.2.1.10. Conduct of the study

Subjects were to receive up to 6 cycles of chemotherapy supported by IP; they did not have to complete all 6 cycles of chemotherapy in order to complete the study. Of the 184 subjects randomised to Nivestim, 8.2% (15/184) did not complete the study compared with 11.6% (11/95) of subjects randomised to Neupogen.

There were 4 amendments to the final protocol dated 19 April 2007.

Common deviations included those relating to incorrect visit windows, timing of IP/chemotherapy administration and timing of/missing laboratory assessments. The statistical analysis plan included prospective definitions of the Major Protocol Violations which would exclude subjects from the PP population.

Following a review of the subject listings and the major protocol deviations by the applicant at the blinded data review meeting it was decided that 28 of the 278 subjects in the ITT and safety populations should be excluded from the PP population in Cycle 1 due to major protocol deviations, 41 subjects in Cycle 2, and 46 subjects in Cycle 3. Eight subjects in the Nivestim group and 5 subjects in the Neupogen group had protocol deviations related to entry criteria, the majority of which were regarding hepatic function (alkaline phosphatase, bilirubin, ALT and/or AST concentrations). Four subjects in the Nivestim group and 3 subjects in the Neupogen group were excluded from the PP population in all cycles due to hepatic function entry violation. One subject in the Nivestim group had a missing ANC result at study entry, which also excluded the subject from the PP population. Due to a misunderstanding of the dosing regimen in the protocol, study treatment was incorrectly stopped before ANC nadir which resulted in exclusion of a number of subjects from the PP population due to missed IP doses and ANC measurements (8), 14 subjects for Cycle 2, 11 subjects for Cycle 3, and 3 subjects for Cycle 4. The subjects remained in the study and were included in the Safety population.

2.4.5.2.1.11. Baseline data

In line with the study entry criteria, all subjects had breast cancer. The most common tumour stage was Stage IIB in the Nivestim group (24.6%) and Stage IIIA in the Neupogen group (24.2%).

In both treatment groups, the most common treatment setting was adjuvant; 49.7% in the Nivestim group compared with 42.1% in the Neupogen group. Treatment was in the adjuvant/neoadjuvant setting for 84.7% of subjects in the Nivestim group and 81.1% in the Neupogen group.

Treatment was in the metastatic setting for only 15.3% of subjects in the Nivestim group and 18.9% in the Neupogen group. The most common site of metastases in both treatment groups was the lymph node, recorded in 9.8% of subjects in the Nivestim group and 7.4% in the Neupogen group.

The majority of subjects in both treatments groups had had past surgical treatment for their malignant disease (60.7% in the Nivestim group and 55.8% in the Neupogen group).

2.4.5.2.1.12. Numbers analysed

The ITT population are those subjects in the safety population who had at least one post-dose ANC recorded. This population was used for supportive analysis of all primary and secondary efficacy

endpoints. The PP population include those subjects in the ITT population with no clinically significant protocol violations. This population was used as the primary analysis population for the primary analysis of DSN, and also used for all secondary efficacy endpoints. A total of 250, 237 and 232 subjects were included in the PP population for Cycles 1, 2 and 3, respectively.

Table 14 Summary of the analysis population

	Overall subject number	PLIVA/Mayne treatment group	Neupogen® treatment group
Randomised	279	184	95
PP population – Cycle 1 [Primary analysis population]	250	165	85
ITT Population	278	183	95

2.4.5.2.1.13. Outcomes and estimation

Primary Efficacy Results

Duration of Severe Neutropenia (DSN) in Cycle 1 (PP Population)

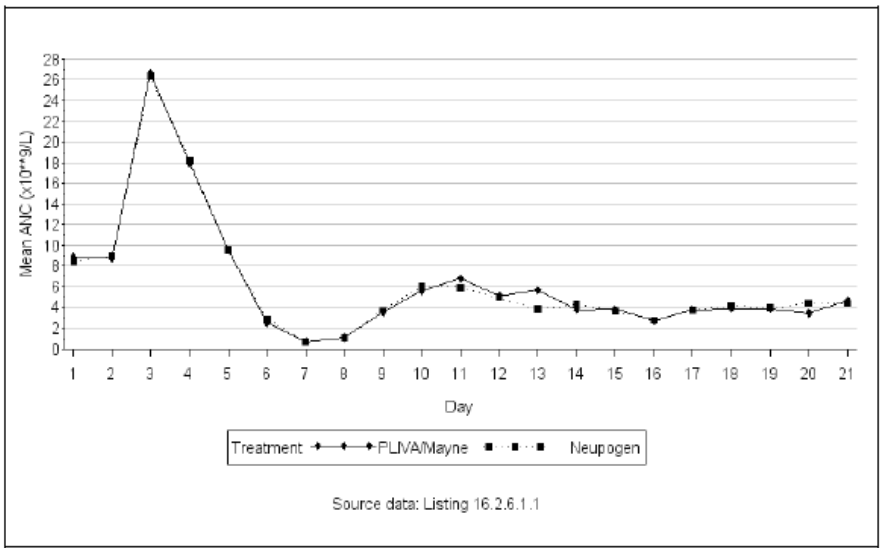
The primary endpoint, DSN in Cycle 1, is presented in Table 15 and Figure 4 for the PP population.

Table 15 Summary of duration of severe neutropenia in cycle 1 in the PP population – Study GCF071

	PLIVA/Mayne filgrastim	Neupogen®
PP Population	165	85
Number of subjects starting the cycle	165	85
Number (%) of subjects with severe neutropenia	128 (77.6)	58 (68.2)
DSN (days)		
0	37 (22.4)	27 (31.8)
1	36 (21.8)	23 (27.1)
2	55 (33.3)	21 (24.7)
3	26 (15.8)	14 (16.5)
4	10 (6.1)	0 (0.0)
5	1 (0.6)	0 (0.0)
>5	0 (0.0)	0 (0.0)
DSN (days)		
n	165	85
Mean	1.6	1.3
SD	1.20	1.08
CV%	73.65	85.94
Median	2.0	1.0
Min	0	0
Max	5	3

Severe neutropenia defined as ANC $< 0.5 \times 10^9$/L. Percentages based on the number of subjects starting the cycle within that population.

Figure 4 Mean neutrophil count over time in cycle 1 in the PP population – Study GCF071



The mean DSN was 1.6 days (SD 1.20) in the Nivestim group compared with 1.3 days (SD 1.08) in the Neupogen group. The 90%CI for the difference of the treatment means lies within the pre-defined range -1 to +1 day. A higher proportion of Nivestim subjects experienced severe neutropenia in Cycle 1 compared with Neupogen subjects: 128/165 (77.6%) on Nivestim compared with 58/85 (68.2%) on Neupogen. Analysis of DSN in Cycle 1 gave adjusted means (adjusted for treatment setting, i.e. ANOVA least square means) of 1.85 and 1.47 days for Nivestim and Neupogen, respectively, with a difference between the two treatment groups means of 0.38 (95%CI, 0.08-0.68) (Table 16).

Table 16 Analysis of duration of severe neutropenia in cycle 1 in the PP population – Study GCF 071

	PLIVA/Mayne filgrastim (N=165)	Neupogen® (N=85)
N	165	85
Adjusted mean DSN in Cycle 1 (days)	1.85	1.47
95% confidence interval	(1.63, 2.08)	(1.19, 1.75)
Comparison of PLIVA/Mayne filgrastim with Neupogen®		
Difference of the means PLIVA/Mayne filgrastim – Neupogen®		0.38
95% confidence interval		(0.08, 0.68)

Equivalence of the treatment groups will be assumed if the two-sided 95% confidence interval for the difference of the means lies entirely within the range -1 to +1 day.

A comparable result was achieved with the ITT population where the difference in DSN means between the treatments was 0.43 days (95%CI, 0.13-0.73).

In subjects with severe neutropenia, the majority (93.3%) of subjects in the Nivestim group and all (100%) subjects in the Neupogen group had a DSN of less than 3 days. Eleven subjects (6.7%) in the Nivestim group had a DSN of 4 or 5 days: 10 (6.1%) had a DSN of 4 days and 1 (0.8%) had a DSN of 5 days. Of the 10 subjects in the Nivestim group with a DSN of 4 days, two had febrile neutropenia (ANC < 0.5 x 10^9/L and body temperature ≥ 38.5°C) in the same cycle. The one subject with a DSN of 5 days also had febrile neutropenia in the same cycle.

Secondary Efficacy Endpoints

The DSN in cycle 2 for the PP population is presented in Table 17. In subjects with severe neutropenia in Cycle 2, the DSN was 1-3 days for 98.7% (74/75) of subjects in the Nivestim group and 93.1% (27/29) in the Neupogen group. One (1.3% (1/75)) and two (6.9% (2/29)) cases of severe neutropenia in the Nivestim group and the Neupogen group, respectively, lasted 4 days. No subjects experienced DSN beyond 4 days. A higher proportion of Nivestim subjects experienced severe neutropenia in Cycle 2 compared with that of Neupogen subjects: 75/154 (48.7%) subjects on Nivestim compared with 29/83 (34.9%) on Neupogen.

Table 17 Analysis of duration of severe neutropenia in cycle 2 in the PP population – Study GCF 071

	PLIVA/Mayne filgrastim (N=154)	Neupogen® (N=83)
N Adjusted mean DSN in Cycle 2 (days) 95% confidence interval	154 0.89 (0.69, 1.08)	83 0.75 (0.52, 0.98)
Comparison of PLIVA/Mayne filgrastim with Neupogen® Difference of the means PLIVA/Mayne filgrastim – Neupogen® 95% confidence interval		 0.14 (-0.12, 0.39)

The DSN in cycle 3 for the PP population is presented in Table 18. A lower proportion of Nivestim subjects experienced severe neutropenia in Cycle 3 compared with that of Neupogen subjects: 60/154 (39.0%) for Nivestim compared with 33/78 (42.3%) for Neupogen. In subjects with severe neutropenia in cycle 3, the DSN was 1-3 days in 96.7% (58/60) and 100% (33/33) of subjects for Nivestim and Neupogen, respectively. Two (3.3% (2/60)) cases of severe neutropenia in the Nivestim group lasted 4 days. No subjects experienced DSN beyond 4 days.

Table 18 Analysis of duration of severe neutropenia in cycle 3 in the PP population – Study GCF071

	PLIVA/Mayne filgrastim (N=154)	Neupogen® (N=78)
N Adjusted mean DSN in Cycle 3 (days) 95% confidence interval	154 0.93 (0.74, 1.12)	78 0.90 (0.67, 1.14)
Comparison of PLIVA/Mayne filgrastim with Neupogen® Difference of the means PLIVA/Mayne filgrastim – Neupogen® 95% confidence interval		 0.02 (-0.23, 0.28)

Time to ANC-recovery in Cycles 1-3

Time to ANC recovery is presented in Table 19 (in days). ANC recovery was defined as the number of days from the first dose of study medication to an ANC of > 3 x 10^9/L (post-documented nadir).

Table 19 Summary of time to ANC recovery in the PP population – Study GCF071

Time to ANC recovery (days)	PLIVA/Mayne filgrastim (N=165)	Neupogen® (N=85)
Cycle 1		
PP Population	165	85
n	165	85
Mean	7.8	7.8
SD	1.12	1.44
CV%	14.46	18.50
Median	8.0	8.0
Min - Max	5 - 13	6 - 17
Cycle 2		
PP Population	154	83
n	154	83
Mean	7.4	7.6
SD	1.28	2.20
CV%	17.23	28.95
Median	7.0	7.0
Min - Max	6 - 17	6 - 20
Cycle 3		
PP Population	154	78
n	154	78
Mean	7.5	7.6
SD	2.11	1.93
CV%	27.90	25.43
Median	7.0	7.0
Min - Max	4 - 19	6 - 19

Time from first dose of study medication (within respective cycle) to ANC > 3 x 10^9/L

The incidence of febrile neutropenia is presented in Table 20.

Table 20 Incidence of febrile neutropenia in cycle 1-3 in the PP population – Study GCF071

Febrile neutropenia (ANC < 0.5 x 10^9/L and body temperature of ≥ 38.5°C)	PLIVA/Mayne filgrastim		Neupogen®	
	n	%	n	%
Cycle 1				
PP Population	165		85	
n	165		85	
Yes	3	1.8	2	2.4
No	162	98.2	83	97.6
Cycle 2				
PP Population	154		83	
n	154		83	
Yes	1	0.6	0	0.0
No	153	99.4	83	100.0
Cycle 3				
PP Population	154		78	
n	154		78	
Yes	0	0.0	0	0.0
No	154	100.0	78	100.0
Cycles 1-3				
PP Population	165		85	
n	165		85	
Yes	4	2.4	2	2.4
No	161	97.6	83	97.6

Percentages based on the number of subjects starting the cycle (n) within that population. For the Cycles 1-3 summary, the Cycle 1 PP population was used.

2.4.5.2.1.14. Ancillary analyses

To determine whether there were differences seen in the clinical variables between Nivestim and Neupogen which could bias the conclusion observed between the two arms in mean DSN Cycles 1-3, incidence of infection, use of prophylactic antibiotic and cumulative dose in the study treatment was reported.

The incidence of documented infection was low and was similar between the two treatment groups. The proportion of subjects experiencing one or more infections in Cycles 1-3 was 3.0% in the Nivestim compared with 3.5% in the Neupogen group.

Prophylactic antibiotics were administered to 15 (8.2%) and 8 (8.4%) subjects in Cycle 1 for Nivestim and Neupogen, respectively; 11 (6.0%) and 4 (4.2%) subjects, respectively, in Cycle 2; and 11 (6.0%) and 4 (4.2%) subjects, respectively, in Cycle 3. Taking Cycles 1-3 combined, this affected 17 (9.3%) and 8 (8.4%) subjects for Nivestim and Neupogen respectively.

The mean number of injections given to subjects in Cycles 1-3 and Cycles 4-6 were similar between the two treatment groups (Table 21).

Table 21 Cumulative dose in the study treatment for the PP population – Study GCF071

Number of injections	PLIVA/Mayne (N=165)	Neupogen® (N=85)	Total (N=250)
Cycles 1 to 3			
n	165	85	250
Mean	22.5	22.4	22.4
SD	3.54	3.26	3.44
CV%	15.76	14.52	15.32
Median	22.0	22.0	22.0
Min - Max	8 - 31	12 - 30	8 - 31
Cycles 4 to 6			
n	155	83	238
Mean	21.2	21.1	21.2
SD	5.70	5.30	5.56
CV%	26.87	25.16	26.24
Median	22.0	22.0	22.0
Min - Max	4 - 33	4 - 34	4 - 34
Total			
n	165	85	250
Mean	42.4	43.0	42.6
SD	9.91	8.44	9.42
CV%	23.36	19.62	22.11
Median	43.0	43.0	43.0
Min - Max	8 - 64	12 - 63	8 - 64

2.4.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

There were no analyses performed across trials submitted.

2.4.5.4. Clinical studies in special populations

There were no clinical studies in special populations submitted.

2.4.5.5. Supportive study(ies)

There were no supportive studies submitted.

2.4.5.6. Discussion on clinical efficacy

As this application relates to a biosimilar product, there is no requirement for dose-response studies. The chosen dose referenced to the reference product Neupogen was acceptable. This view was supported by CHMP/SAWP based on the fact that Nivestim and Neupogen are structurally identical and as long as the bioequivalence with Neupogen in phase I studies showing similar ANC profiles and comparable pharmacokinetics could be demonstrated.

The statistical data provided demonstrated the similarity between the test and reference products in both pharmacodynamic and pharmacokinetic effects. There were concerns over the statistical design of the ANOVA analysis and the recording of the subjects included. The CHMP noted that the clarification of the model design used in two-way, two-period, crossover trial was adequate and the p values provided for the sequence effect indicated a low probability for carryover effect.

Overall, the two treatment groups in the pivotal phase III study GCF071 had similar baseline characteristics, including tumour staging, sites of metastasis, and past treatment for malignant disease. There were no major differences between the two treatment groups in any demographic variable or baseline disease characteristic (including tumour staging, sites of metastases, and past treatment for malignant disease).

The CHMP noted that the study GCF071 was conducted according to the guideline EMEA/CHMP/BMWP/42832/2005 and supported the use of the chosen reference product as a comparator. The assay sensitivity of the study, as required in the guideline, was part of the major objection as it had not been demonstrated. The applicant responded by providing literature references that the combination chemotherapy induced severe neutropenia and also gave historical evidence of sensitivity of the drug effect in the form of a comparison with the results of a similar conducted trial XM02 study (Ratiograstim EPAR) to the GCF071 trial (same study population, concomitant therapy and endpoints). The CHMP noted that the applicant justified adequately the issues concerning the study sensitivity to detect equivalence and the validation of the measurement.

The CHMP had concerns over the results obtained for the PP and ITT population with regards to its clinical relevance. The applicant justified the use of PP population for the calculation of the primary endpoint accordingly and the results from the bioequivalence study show that the non-inferiority was proven for both populations, i.e. PP and ITT. The exclusion of subjects in the clinical trial was conducted according to the predefined criteria. The applicant was asked to explain the discrepancy in the number of withdrawn subjects reported. The applicant provided an explanation which was considered acceptable by the CHMP.

The mean time to ANC recovery in Cycles 1, 2 and 3 in the PP population were similar in both treatment groups. The proportion of subjects with ANC > 3 x 10^9/L in Cycles 1, 2 and 3 was lowest within the expected period of severe neutropenia, Days 4-10 of the cycle, which is as expected for this class of treatment.

The Nivestim study group showed a greater proportion of patients with severe neutropenia than Neupogen study group in Cycle 1 (77,6 % vs 68,2%) and cycle 2. Also DSN lasted longer in the Nivestim study group. The clinical significance of the difference was part of a major objection. It was concluded that the incidence of febrile neutropenia, the number of infections as well as the number of needed injections were similar in both groups. The difference in the proportion of the severe neutropenia does not seem to affect the other variables measuring the severity of clinical condition of the subjects. These findings were not statistically significant. The number of drop outs in the study population was the main concern with regards to the significance of the slightly inferior response to the treatment in Nivestim group. According to the data provided, the duration of the severe neutropenia in subjects withdrawn was proportionally similar in both treatment arms thus having no significant effect on the result.

2.4.5.7. Conclusion on clinical efficacy

In summary, the data submitted were sufficient to allow to conclude therapeutic equivalence between the two products in terms of efficacy. Both the primary efficacy results (DSN in Cycle 1) and the

secondary efficacy results (DSN in Cycles 2 and 3 among the others) showed no significant difference between Nivestim and Neupogen.

2.4.6. Clinical safety

2.4.6.1. Patient exposure

Of the 279 randomised subjects in the GCF071 study, 278 were included in the Safety population. There were 183 Patients which received Nivestim and 95 patients received Neupogen. The extent of exposure by the number of injection received is summarised in the Table 22.

Table 22 Extent of exposure of breast cancer patients to Nivestim and Neupogen – Study GCF071

Number of 5 µg/kg injections in each cycle	PLIVA/Mayne filgrastim (N = 183)	Neupogen® (N = 95)	Total (N = 278)
Cycle 1, n	183	95	278
Mean (SD)	7.8 (1.25)	7.7 (1.19)	7.8 (1.23)
Cycle 2, n	180	93	273
Mean (SD)	7.3 (1.32)	7.4 (1.38)	7.3 (1.34)
Cycle 3, n	177	91	268
Mean (SD)	7.4 (1.28)	7.3 (1.35)	7.3 (1.30)
Cycle 4, n	172	90	262
Mean (SD)	7.5 (1.41)	7.5 (1.34)	7.5 (1.38)
Cycle 5, n	156	83	239
Mean (SD)	7.6 (1.27)	7.5 (1.34)	7.6 (1.30)
Cycle 6, n	149	78	227
Mean (SD)	7.7 (1.15)	7.7 (1.42)	7.7 (1.24)
Cycles 1–6, n	183	95	278
Mean (SD)	42.0 (9.74)	41.9 (10.49)	42.0 (9.98)

Source: GCF071 clinical study report, Section 14.1, Table 14.1.9
Abbreviations: SD, standard deviation

Mean doses of Nivestim over cycles 1–6 received during the study was 42.0 (SD 9.74) compared with 41.9 (SD 10.49) doses of Neupogen.

2.4.6.2. Adverse events

In study GCF061, in the 10µg/kg group IV, the most common adverse events in each treatment group was nervous system disorders [considered treatment related for headache in 5 (25.0%) subjects receiving Nivestim and 8 (36.4%) subjects receiving Neupogen], musculoskeletal and connective tissue disorders [considered treatment related in 7 (35.0%) subjects receiving Nivestim and 5 (22.7%) subjects receiving Neupogen]. In the 10µg/kg SC group, the most common treatment-related adverse events were back pain [nine (34.6%) and nine (34.6%), respectively, after Nivestim and Neupogen] and headache [seven (26.9%) and eight (30.8%) respectively].

In the multiple-dose study GCF062, most subjects (> 75%) experienced AEs during the study. The most common treatment-related AEs were back pain and headache in both the 10 µg/kg and 5 µg/kg dose groups. In the 10 µg/kg dose group, back pain was reported by 16 (61.5%) and 14 (56.0%) subjects and headache was reported by 14 (53.8%) and 11 (44.0%) subjects following Nivestim and Neupogen treatment, respectively. In the 5 µg/kg dose group, treatment-related back pain was

reported by 11 (45.8%) and nine (37.5%) subjects and headache was reported by 11 (45.8%) and 13 (54.2%) subjects following Nivestim and Neupogen treatment respectively.

In the study GCF071, a similar proportion of patients in the two treatment groups experienced AEs (86.9% and 84.2% in the Nivestim and Neupogen groups, respectively) and treatment-related AEs (24.6% and 23.2% in the Nivestim and Neupogen groups, respectively). The Table 23 is a summary of the adverse events and adverse reactions.

Table 23 Summary of the treatment-emergent and treatment-related AEs – Study GCF071

	Nivestim Filgrastim Adverse Events N=183 n(%)	Neupogen Adverse Events N=95 n(%)	Nivestim Filgrastim Adverse Reactions N=183 n(%)	Neupogen Adverse Reactions N=95 n(%)
Any event	159 (86.9)	80 (84.2)	45(24.6)	22(23.2)
Gastrointestinal Disorders	105(57.4)	52(54.7)	7(3.8)	2(2.1)
Nausea	94 (51.4)	47 (49.5)	4(2.2)	1(1.1)
Diarrhoea	28 (15.3)	15 (15.8)	1(0.5)	1(1.1)
Vomiting	22 (12.0)	13 (13.7)	1(0.5)	1(1.1)
Stomatitis	19 (10.4)	12 (12.6)	0	1(1.1)
Abdominal pain upper and pain	3(1.6) 5 (2.7)	5(5.3) 2 (2.1)	2(1.1)	0
General Disorders and Administration Site Conditions	98(53.6)	39(41.1)	14(7.7)	6(6.3)
Fatigue	75 (41.0)	34 (35.8)	9(4.9)	2(2.1)
Asthenia	18 (9.8)	5 (5.3)	0	1(1.1)
Pyrexia	10 (5.5)	5 (5.3)	3(1.6)	3(3.2)
Oedema peripheral	9(4.9)	1(1.1)	1(0.5)	0
Chills	0	3(3.2)	0	1(1.1)
Skin and subcutaneous tissue disorders	88 (48.1)	45 (47.4)	2(1.1)	0
Alopecia	86 (47.0)	43 (45.3)	1(0.5)	0
Musculoskeletal and Connective Tissue Disorders	69 (37.7)	28 (29.5)	35(19.1)	18(18.9)
Bone Pain	48 (26.2)	16 (16.8)	26(14.2)	9(9.5)
Myalgia	26 (14.2)	9 (9.5)	2(1.1)	1(1.1)
Arthralgia	12 (6.6)	6 (6.3)	4(2.2)	2(2.1)
Back Pain	7(3.8)	3(3.2)	2(1.1)	2(2.1)
Musculoskeletal pain	3(1.6)	3(3.2)	2(1.1)	3(3.2)
Vascular disordes	34 (18.6)	13 (13.7)	3(1.6)	1(1.1)
Hyperanemia	13 (7.1)	7 (7.4)		
Hypotension	14 (7.7)	3 (3.2)	3(1.6)	1(1.1)
Infections & Infestations	22 (12.0)	13 (13.7)		
Nervous System disorders	17 (9.3)	13 (13.7)	1(0.5)	1(1.1)
Headache	4(2.2)	4(4.2)	1(0.5)	1(1.1)
Paraesthesia	5(2.7)	3(3.2)		
Respiratory, Thoracic and Mediastinal Disorders	15 (8.29	10 (10.5)	1(0.5)	1(1.1)
Dyspnoea	5 (2.7)	5 (5.3)		
Blood & lymphatic system disorders	16 (8.7)	8 (8.4)	1(0.5)	0
Thrombocythaemia			1(0.5)	0
Febrile neutropenia	6(3.3)	3(3.2)		
Neutropenia	4(2.2)	4(4.2)		
Anaemia	3(1.6)	3(3.2)		

Metabolism and nutrition disorders	19 (10.4)	6 (6.3)	2(1.1)	0
Anorexia	12 (6.6)	5 (5.3)	1(0.5)	0
Ear and labyrinth disorders	12 (6.6)	6 (6.3)	2(1.1)	0
Vertigo	12 (6.6)	5 (5.3)	2(1.1)	0
Cardiac disorders	10 (5.5)	2 (2.1)		
Reproductive system & breast disorders	4 (2.2)	4 (4.2)		
Psychiatric disorders	7 (3.8)	3 (3.2)		
Eye disorders	6 (3.3)	3 (3.2)		
Injury, poisoning & procedural complications	1 (0.5)	3 (3.2)		

The total number of subjects experiencing one or more treatment-emergent AEs during Cycle 1 were 125 (68.3%) on Nivestim and 56 (58.9%) on Neupogen. In general, AEs were most frequently reported in the system organ class of gastrointestinal disorders (the most common individual event was nausea); whereas, adverse reactions were most frequently reported in the system organ class of musculoskeletal and connective tissue disorders in both treatment groups (Nivestim: n=35, 19.1%; Neupogen: n=18, 18.9%). The most common individual adverse reaction was bone pain; there was a higher incidence of bone pain in the Nivestim group (Nivestim: n=26, 14.2%; Neupogen: n=9, 9.5%). All of these events were mild or moderate in nature except one subject on Neupogen who had severe pain in the extremity. The vast majority of the cases with bone pain responded to non-narcotic drugs.

During clinical studies 183 cancer patients and 96 healthy volunteers were exposed to filgrastim. The safety profile of filgrastim observed in these clinical studies was consistent with that reported with the reference product used in these studies (SmPC section 4.8).

The occurrence of Sweet's syndrome (acute febrile dermatosis) has been reported occasionally. However, since a significant percentage of these patients were suffering from leukaemia, a condition known to be associated with Sweet's syndrome, a causal relationship with filgrastim has not been established (SmPC section 4.8).

2.4.6.3. Serious adverse event/deaths/other significant events

In Study GCF062 there were no serious adverse events (SAEs) reported. There were two severe AEs (NCI CTCAE grade 4) reported in the healthy volunteer multiple dose Study (GCF062). One subject in the 10 µg/kg dose group suffered from headache, which was reported as severe and classed as possibly related to Neupogen treatment. One subject in the 5 µg/kg dose group suffered muscle spasms, which were classed as severe and probably related to Nivestim treatment.

In the GCF071 study, with regard to serious adverse events, there were 12 (6.6%) subjects in the Nivestim group and 4 (4.2%) of subjects in the Neupogen group who experienced serious adverse events. Severe AEs (NCI CTCAE grade 4) were reported by 15 (8.2%) patients in the Nivestim group and 10 (10.5%) patients in the Neupogen group. Eight (4.4%) patients in the Nivestim group and 2 (2.1%) patients in the Neupogen group reported life-threatening/disabling AEs. None of the SAEs was considered related to study treatment.

The organ system with the most severe or life-threatening/disabling AEs was blood and lymphatic system disorders. Febrile neutropenia was the most common individual severe AE reported and neutropenia was the most common life-threatening/disabling AE. The frequency of protocol-defined febrile neutropenia (ANC<0.5 x 109/L and body temperature ≥ 38.5°C) was similar in the two treatment arms. A total of six subjects [four (2.4%) in the Nivestim arm and two (2.4%) in the Neupogen arm] had febrile neutropenia over the Cycles 1 - 3 of the study.

There were no deaths reported during the studies GCF061 and GCF062. There was one death during study GCF071, a 49-year-old female subject with previous medical history of obesity, diabetes mellitus and essential hypertension. The cause of death was unknown. The investigator concluded that the patient's death was unlikely to be related to the treatment but that an infection could not been ruled out.

2.4.6.4. Laboratory findings

In severe chronic neutropenia patients, anemia is a very common undesirable effect of filgrastim. In addition, elevated gamma-glutamyl-transpeptidase GGT, alkaline phosphatase, LDH and uric acid values are also common undesirable effects of filgrastim which are documented in the SmPC of Neupogen. Based on the laboratory findings in study GCF071, no differences in these parameters were observed between the Nivestim group and the Neupogen reference group.

Immunological events

Blood samples for the assessment of anti-G-CSF antibodies were taken in patients in the study GCF062 and study GCF071. Two assays were developed and validated to measure the presence of G-CSF antibodies: a screening antibody assay and a cell-based neutralising antibody assay. The neutralising assay was used to further analyse any positive samples. Subjects were either positive or negative for the presence of G-CSF antibodies and neutralising activity of antibodies.

In the GCF062 study, two subjects gave a positive antibody response following treatment. The incidence of detectable G-CSF antibodies was low. Three patients in the Nivestim treatment group (1.6%) had one or more post-treatment samples with a borderline positive result. NAbs were not found in three samples having borderline positive responses in the anti-G-CSF antibody screening. There was no evidence of a clinical effect on efficacy (neutrophil counts) or safety in the patients with borderline positive results. No patient in the Neupogen treatment group tested positive for G-CSF antibodies.

2.4.6.5. Safety in special populations

There were no studies submitted in special populations.

2.4.6.6. Safety related to drug-drug interactions and other interactions

There were no studies submitted for drug-drug interactions and other interactions.

2.4.6.7. Discontinuation due to adverse events

In study GCF061, one subject (5.0%) withdrew from the study owing to AEs where the subject experienced agitation, dyspnoea, dizziness, headache, a respiratory disorder, arthralgia, nausea, and pharynx dysaesthesia after receiving a single IV dose of 10 µg/kg Neupogen. All AEs were moderate in intensity and considered probably related to study treatment.

In study GCF062, one subject (3.8%) was withdrawn from the study owing to AEs where the subject experienced moderate musculoskeletal chest pain and mild back pain following administration of three doses of 10 µg/kg Nivestim treatment. Both AEs were considered related to study treatment and both AEs subsequently resolved.

There were six subjects (3.2%) in the study GCF071 who experienced AEs which led to withdrawal from the study (four [2.2%] patients in the Nivestim group and two [2.1%] patients in the Neupogen group). Two patients in the Nivestim group experienced three SAEs (lymphopenia, asthma, and deep vein thrombosis) and one patient in the Neupogen group experienced one SAE (appendicitis) leading to

withdrawal. One subject (0.5%) in the Nivestim group (117802) discontinued due to an AE reported as "febrile neutropenia".

2.4.6.8. Post marketing experience

There were no post-marketing studies submitted.

2.4.6.9. Discussion on clinical safety

The CHMP considered that the study design with regards to evaluating the safety of Nivestim was acceptable. The applicant clarified the duration of the drug exposure adequately. A higher incidence of bone pain was observed with Nivestim, the pain being mild or moderate in intensity, and manageable by NSAID or paracetamol. Due to the higher incidence of bone pain and myalgia, these adverse events are addressed in the RMP and in section 4.8 of the SmPC.

The CHMP considered that that the development of antibody assays were poorly described and did not follow the guideline EMEA/CHMP/BMWP/14327/2006. The applicant was asked to present the antibody testing strategy and define the cut-off points. The applicant responded by describing the analytical methods and the screening method. The bioanalytical test strategy used for evaluating serum samples for anti-G-CSF antibody included simultaneously screening for and confirmation of anti-G-CSF antibodies.

The CHMP asked the applicant to submit a follow-up measure to present 6 month follow-up results for the NAbs assay results and follow up results. The applicant presented results which were consistent with the data provided from Neupogen. The CHMP considered that according to the data presented, there were no immune-mediated adverse effects or loss of efficacy. Due to the low number of patients that tested positive for anti-G-CSF antibodies, it could be possible that immunogenicity could go undetected. A potential higher risk of immunogenicity in individuals treated with Nivestim compared to Neupogen cannot be excluded. Therefore, the CHMP recommended that follow-up measures with regards to immunogenicity should be implemented in the event of a possibility of low-level immunogenicity not detected by the analytical method used. This issue is addressed in the RMP.

The report and the conclusion of the one death case in the GCF071 study was found to be sufficient. The applicant was also asked to explain the higher number of febrile neutropenia cases reported in the Nivestim group in relation to the Neupogen group. The applicant clarified that the incidence of febrile neutropenia in both treatments were identical.

2.4.6.10. Conclusion on clinical safety

The CHMP considers that the overall safety profile of the product is acceptable.

2.5. Pharmacovigilance

2.5.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the regulatory requirements.

2.5.2. Risk management plan

The MAA submitted a risk management plan.

Summary table of the risk management plan

IDENTIFIED RISKS (with Neupogen)		
Risk	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Splenomegaly and splenic rupture (PT - splenomegaly, splenic rupture)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Malignant cell growth (haematological malignancy and myelodysplastic syndrome) in patients with severe chronic neutropenia (PT - haematological malignancy, myelodysplastic syndrome)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Section 4.4 of the Nivestim SPC includes wording highlighting this effect.
Cutaneous vasculitis (PT- cutaneous vasculitis)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Osteoporosis (PT - osteoporosis)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Exacerbation of rheumatoid arthritis (PT- rheumatoid arthritis)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Allergic type reactions (PT - hypersensitivity)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Sweet's syndrome (PT - acute febrile neutrophilic dermatosis)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Acute respiratory distress syndrome (ARDS) (PT - acute respiratory distress syndrome)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Pulmonary adverse events included within section 4.8 of Nivestim SPC.
Alveolar haemorrhage manifesting as pulmonary infiltrates and hemoptysis (PT - lung infiltrates, hemoptysis)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Pulmonary adverse events included within section 4.8 of Nivestim SPC.
Severe sickle cell crises (PT - sickle cell anaemia with crisis)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Included within section 4.8 of Nivestim SPC.
Increased risk of GvHD (PT - graft versus host disease, chronic graft versus host disease, acute graft versus host disease)	* Routine Pharmacovigilance * Targeted questionnaire	* Included within sections 4.8 and 5.1 of Nivestim SPC.

Transformation to leukaemia or myelodysplastic syndrome in chronic severe leukaemia patients (PT - chronic myeloid leukaemia transformation, myelodysplastic syndrome)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCN registry	* Section 4.4 of the Nivestim SPC includes a warning to this effect.
Interaction with Myelosuppressive cytotoxic chemotherapy (Decreased effectiveness of filgrastim) (PT - Drug interaction)	* Routine Pharmacovigilance * Targeted questionnaire	* Interaction warning given in section 4.5 of Nivestim SPC.
Interaction with Lithium (PT - Drug interaction)	* Routine Pharmacovigilance* Targeted questionnaire	* Interaction warning given in section 4.5 of Nivestim SPC.
Bone pain (PT - Bone pain)	* Included within section 4.8 of Nivestim SPC.	* Included within section 4.8 of Nivestim SPC.
Myalgia (PT – Myalgia)	* Included within section 4.8 of Nivestim SPC.	* Included within section 4.8 of Nivestim SPC.
POTENTIAL RISKS		
Risk	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Immunogenicity which may manifest as lack of effect	* Routine Pharmacovigilance * Targeted questionnaire	No additional risk minimisation steps are currently considered necessary.
Off label use (PT - Off label use)	* Routine Pharmacovigilance * Targeted questionnaire	No additional risk minimisation steps are currently considered necessary.
Malignant cell growth (haematological malignancy and myelodysplastic syndrome) associated with GCSF use in normal donors. (PT - haematological malignancy, myelodysplastic syndrome)	* Routine Pharmacovigilance * Targeted questionnaire * Co-operative program with hematological transplant centres	* Section 4.4 of the Nivestim SPC includes wording highlighting this effect.
Long term use	* Routine Pharmacovigilance * Specialised follow up for long term data	No additional risk minimisation steps are currently considered necessary.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall conclusions, risk/benefit assessment and recommendation

2.6.1. Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The Applicant has successfully demonstrated biosimilarity between Nivestim and the reference medicinal product Neupogen (Amgen).

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The Applicant gave a Letter of Undertaking and committed to resolve these as follow-up measures after the opinion.

2.6.2. Non-clinical pharmacology and toxicology

The non-clinical evaluation of Nivestim is considered sufficient. Pharmacodynamic, pharmacokinetic and toxicology data from published literature and from original studies did not reveal any differences in serious or common adverse effect in animals tested. There were no differences in the pharmacological activity of the test compound as demonstrated and compared to the activity of the reference product.

2.6.3. Efficacy

The pharmacokinetic and pharmacodynamic data in healthy volunteers (ANC and CD34+ counts) with both IV and SC administration was presented to establish comparability between Nivestim and Neupogen. A randomised, open-label, single-dose, comparator-controlled, two-way crossover study in 46 healthy volunteers showed that the pharmacokinetic profile of Nivestim was comparable in terms of $AUC_{(0\text{-tlast})}$ for the plasma concentration of G-CSF to that of the reference product after subcutaneous and intravenous administration. The secondary endpoints (C_{max}, T_{max}, $T_{1/2}$, $AUC_{(0\text{-inf})}$, λ_z, and Cl for the plasma concentration of G-CSF and absolute neutrophil count (ANC) $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max}, ANC_{min} for the PD endpoints) were supportive of the primary endpoint. Another randomised, double-blind, multiple-dose, comparator-controlled, two-way crossover study in 50 healthy volunteers showed that the pharmacokinetic profile of Nivestim was comparable to that of the reference product after subcutaneous administration.

The efficacy and safety of Nivestim has been assessed in randomised, controlled phase III study in breast cancer. There were no relevant differences between Nivestim and the reference product with regard to duration of severe neutropenia in cycle 1. This was supported by the secondary endpoints such as time to ANC recovery and the incidence of febrile neutropenia.

2.6.4. Safety

A comparison in the safety profile between Nivestim and Neupogen was based on the studies in healthy volunteers. The overall safety profile of Nivestim was similar to the reference product Neupogen where the AEs, SAEs and common undesirable effects of Nivestim are consistent with those documented with Neupogen. A higher incidence of bone pain was met with Nivestim, the pain being mild or moderate in intensity, but manageable with NSAID or paracetamol. Due to the higher incidence of bone pain and myalgia in the Nivestim group, follow-up of these adverse events is recommended in the RMP. The incidence of febrile neutropenia in both treatments were similar.

The occurrence of antibodies and NAbs in patients treated with Nivestim remains unclear. According to the data available, there were no immune-mediated adverse effects or loss of efficacy in patients having borderline positive responses in the anti-G-CSF antibody screening. Nevertheless, follow-up measures for determining the possible development of immunogenicity should be implemented as there is not enough data to demonstrate sensitivity and detection of anti-G-CSF antibodies. Additional long term safety and immunogenicity data will be collected in the post-marketing phase, as described in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. There are no new important adverse reactions observed with Nivestim which are different than what has been described with Neupogen.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

2.6.4.1. User consultation

The applicant performed standard readability testing. No major issues regarding the content were found. The test showed that the PL was well structured and organised, easy to understand, written in a comprehensible manner and readable to patients/users which were able to act upon the information. The layout of the package leaflet was considered acceptable. Thus, the PL meets the legal requirements for user testing under Art. 59(3) and 61(1) of Directive 2001/83/EC, as amended by directive 2004/27/EC.

2.6.5. Risk-benefit assessment

This application for Nivestim, a recombinant human G-CSF (rhG-CSF), is based on the claim of biosimilarity to the approved reference product Neupogen. The phase I studies GCF061, GCF062 and phase III pivotal study GCF071 were conducted in accordance with the EMEA/CHMP guidelines on bio-technology derived proteins and rh-G-CSF and CHMP scientific advice. The primary purpose of this assessment is not the characterisation of the benefit/risk of the product but the qualitative and quantitative evaluation of the similarity between Nivestim and Neupogen. The quality, non-clinical and clinical data presented supported the conclusion of similarity between Nivestim and Neupogen. PD and PK parameters for IV or SC administration allowed to conclude on the bioequivalence of the test product with the reference product, where the majority of PK and PD endpoints fell within the predefined 90%CI for both 5 and 10µg/kg. The primary and secondary efficacy endpoints of the Phase III trial were met and results showed therapeutic equivalence between Nivestim and Neupogen. The safety profile of Nivestim was consistent with the reference product. However, the CHMP had concerns over the determination of antibody formation and the presence of NAbs in patients treated with Nivestim. This issue will be addressed as a follow up measure. The CHMP also asked the applicant to agree to certain post-authorisation commitments to obtain more safety data related to patients with severe chronic neutropenia, to assess long term effects of G-CSF in healthy donors and to follow up on events of special interest through targeted questionnaires.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

2.6.6. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Nivestim in the following indications

> Filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.
>
> The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.
>
> Filgrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).
>
> In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$ /l and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.
>
> Filgrastim is indicated for the treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$ /l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

was favourable and therefore recommended the granting of the marketing authorisation.