Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Filgrastim (rbe)

Proprietary Product Name: Zarzio

Sponsor: Sandoz Pty Ltd

**Date of CER: 23 April 2012**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | Adverse event |
| AG | Aktiengesellschaft |
| ALT/SGPT | Alanine aminotransferase |
| AMG | German Drug Act |
| ANC | Absolute Neutrophil Count |
| ANOVA | Analysis of variance |
| ANOVA-CV | lntraindividual coefficient of variation |
| AST/SGOT | Aspartate aminotransferase |
| AUC | Area under the serum concentration-time curve |
| $AUC_{0\text{-}t,\ sd}$ | Area under the serum concentration-time curve from 0 h to 24 h after a single dose |
| $AUEC_{144\text{-}168\ h,\ ss}$ | Area under the serum concentration-time curve at steady-state from 144 h to 168 h after first dose |
| $AUEC_{144\text{-}168\ h,\ ss}$ | Area under the effect (ANC and $CD34^+$ cells)-time curve at steady-state |
| $AUEC_{0\text{-}24\ h,\ sd}$ | Area under the effect (ANC and $CD34^+$ cells)-time curve from 0 h to 24 h after a single dose |
| $AUEC_{144\text{-}168\ h,\ ss}$ | Area under the effect (ANC and $CD34^+$ cells)- time curve at steady-state from 144 to 216 h after first dose |
| BGBI. | Bundesgesetzblatt |
| BMI | Body Mass Index |
| BQL | Below Quantification Limit |
| CBC | Complete Blood Count |
| CI | Confidence Interval |
| cm | Centimeter |
| $C_{max,\ sd}$ | Maximal serum concentration after a single dose |
| $C_{max,ss}$ | Maximal serum concentration at steady-state |

| Abbreviation | Meaning |
|---|---|
| Co | Compagnon |
| CRO | Clinical Research Organisation |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case Report Form |
| CV | Coefficient of variation |
| DNA | Deoxyribonucleic acid |
| E | Effect |
| $E_{max, sd}$ | Maximal effect on ANC and CD34+ cells after a single dose |
| $E_{max, ss}$ | Maximal effect on ANC and CD34+ cells at steady-state |
| ECG | Electrocardiogram |
| EDTA | Ethytendiaminetetraacetic acid |
| ELISA | Enzyme linked immunosorbent assay |
| ESR | Erythrocyte sedimentation rate· |
| EU | European Union |
| EWP | Efficacy Working Party |
| FDA | Food and Drug Administration |
| fMLP | N-formyl-methionyl-leucyl-phenylalanine |
| g | Gram |
| γ-GT | Gamma glutamyltransferase |
| G-CSF, GCSF | Granulocyte-colony stimulating factor |
| GCP | Good Clinical Practice |
| GmbH | Gesellschaft mit beschrankter Haftung |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GTF mbH | Gesellschaft tor Therapeutische Forschung mbH |
| HIV | Human immunodeficiency virus |

| Abbreviation | Meaning |
|---|---|
| ICH | International Conference on Harmonisation |
| IMP | Investigational medicinal product |
| i.p. | Intraperitoneal |
| ISR | Injection Site Reaction |
| ITECRA | Institute for tailored early clinical research and advice |
| IV | lntravenous(ly) |
| $k_{el, sd}$ | Elimination rate constant after a single dose |
| $k_{el, ss}$ | Elimination rate constant at steady-state |
| kg | Kilogram |
| KG | Kommanditgesellschaft |
| LDH | Lactate dehydrogenase |
| LOD | Limit of detection |
| log | Logarithm |
| MCH | Mean corpuscular hemoglobin |
| MCV | Mean corpuscular volume |
| min | Minute |
| mL | Milliliter |
| MRT | Mean residence time |
| µg | Microgram |
| ng | Nanogram |
| No., N, n | Number |
| PBPC | Peripheral Blood Progenitor Cell |
| PD | Pharmacodynamics |
| p | p-value |
| pH | Negative logarithm to the base 10 of the hydrogen-ion activity |
| PK | Pharmacokinetics |

| Abbreviation | Meaning |
|---|---|
| QC | Quality control sample |
| QWP | Quality Working Party |
| RIP | Radioimmunoprecipitation assay |
| r-metHuG-CSF | Recombinant methionyl granulocyte-colony stimulating factor |
| rpm | Rounds per minute |
| SAE | Serious adverse event |
| SAS | Statistical Analysis System |
| SC | Subcutaneous |
| SD/sd | Standard Deviation/ single dose |
| SOP | Standard operating procedure |
| sac | Spiked quality control standard |
| ss | Steady-state |
| STAT | Statistic |

# 1. Clinical rationale

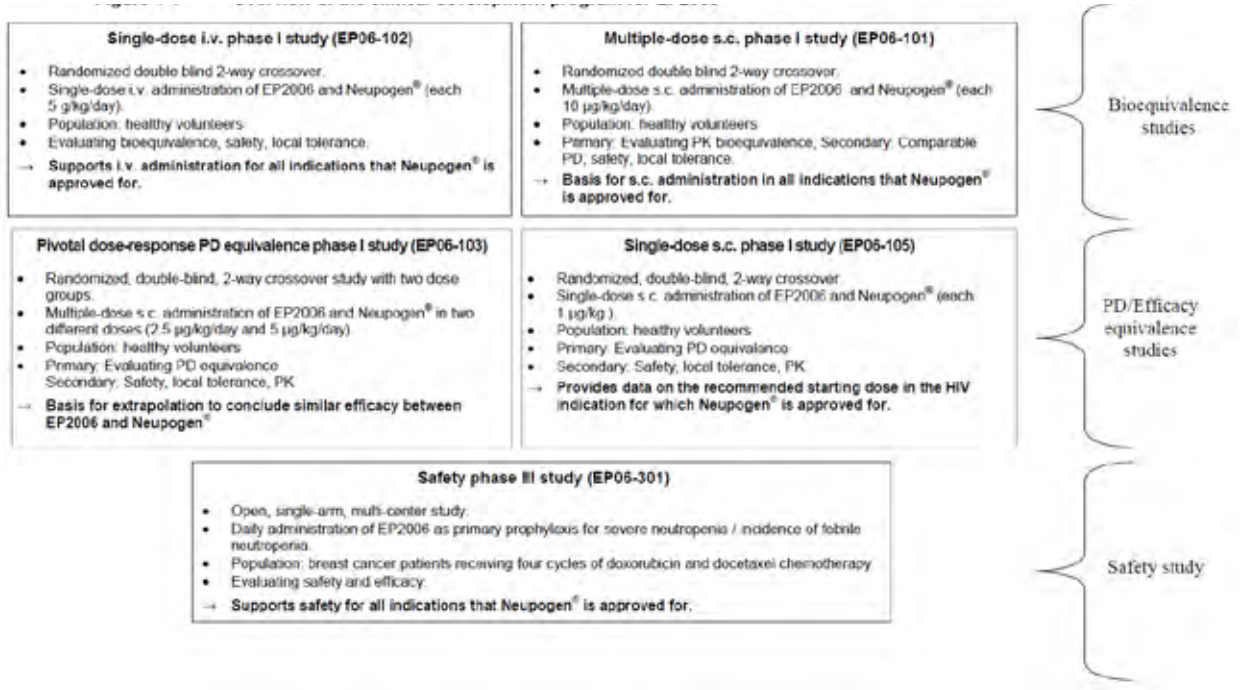
This is a Category 1 submission to register a Similar Biological Medicinal Product.

The proposed drug is rhG-CSF (EP2006) and is claimed by the sponsor to be similar to the reference product Neupogen in terms of quality, safety and efficacy.

The sponsor states that the development of EP2006 was in keeping with the regulatory requirements for similar biological medicinal products as laid down in the EMEA guidelines (EMEA/CHMP/42832/05, EMEA/CHMP/BWMP/31329/05). The objective of the clinical development program was to demonstrate pharmacokinetic and pharmacodynamic equivalence of EP2006 and Neupogen, safety of EP2006 and absence of anti-G-CSF antibodies.

The submission consisted of 4 Phase 1 studies (Study EP06-101, EP06-102, EP06-103, and EP06-105) and one Phase 3 study (EP06-301). See Figure 1.

**Figure 1. Overview of the clinical development program for EP2006**




# 2. Contents of the clinical dossier

## 2.1. Scope of the clinical dossier

Filgrastim Sandoz (Zarzio), the subject of this dossier, was referred to in the clinical trials as EP2006. This terminology will be used in this evaluation report. The reference product will be referred to as Neupogen.

The submission contained the following clinical information:

Module 5

- clinical pharmacology studies, including Studies EP06-101 and EP06-102 that provided pharmacokinetic data and EP06-103 and EP06-105 that provided pharmacodynamic data.
- Study EP06-301 provided efficacy/safety data.

Module 1

- Application letter, application form, draft Australian PI and CMI, FDA-approved product label [for the reference product Neupogen], European Summary of Product Characteristics,

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and Literature references.

### 2.2. Good clinical practice

The studies were conducted according to the principles enunciated in the Declaration of Helsinki, Good Clinical Practices (ICH).

# 3. Pharmacokinetics

The EMEA guidelines specify that PK properties of similar biological medicinal products and the reference medicinal product should be compared in single dose cross-over studies using subcutaneous and intravenous administration. The primary PK parameter is AUC and the secondary PK parameters are $C_{max}$ and $T_{1/2}$.

### 3.1. Studies providing pharmacokinetic data

The objective of the pharmacokinetics data provided in this submission was to demonstrate bioequivalence between the test product (EP2006) and the reference product (Neupogen). This was the primary objective of the bioequivalence studies, Studies EP06-101 (10 µg/kg SC) and EP06-102 (5µg/kg IV). It was a secondary objective for the PD/Efficacy studies EP06-103 (5 µg/kg and 2.5 µg/kg SC) and EP06-105 (1 µg/kg SC).

A cross-over design was chosen as the within-subject variability was expected to be smaller than the between-subject variability.

### 3.2. Summary of pharmacokinetics

The primary objective in studies EP06-101 and EP06-102 and the secondary objective in studies EP06-103 and EP06-105 was to evaluate pharmacokinetic bioequivalence of Filgrastim Sandoz and Neupogen.

The design of the studies was similar so as to provide a large pool of comparable data. They were all Phase I, single-centre, double-blind, randomised, two-way cross-over studies.

The selection criteria were very similar in all four studies. The subjects were all healthy Caucasians, aged 18 to 55 years, with a small preponderance of males over females. All the subjects were non-smokers.

The filgrastim doses used ranged from 10 µg/kg body weight (EP06-101: 10 µg/kg SC) to 1 µg/kg body weight (Study EP06-105 1 µg/kg SC). The dose used in Study EP06-102 was 5 µg/kg body weight. In study EP06-103, two dose levels (2.5 µg/kg body weight and 5 µg/kg body weight) were administered to two groups (Group I: 2.5 µg/kg body weight; Group II: 5 µg/kg body weight). The frequency of dosing was daily SC injections for seven days in studies EP06-101 and EP06-103. In the other two studies a single dose was administered (EP06102: IV; EP06-105: SC). **[Information redacted]** the washout period was at least 28 days for studies where the drug was administered subcutaneously. In study EP06-102, **[Information redacted]**, the washout period was 14-21 days.

The PK sampling (blood) was done at regular intervals. The sampling times were similar in all the Phase I studies. A validated ELISA method **[Information redacted]** was used in the assays.

The PK parameters were AUC, $C_{max}$ and $t_{max}$. For equivalence testing, the 90% confidence interval of the least-squares means of AUC of filgrastim to the reference treatment was to be within 80% to 125%.

In studies employing a multi-dose approach, the $C_{max}$ was 2-5 times lower than after a single dose. This is because clearance of filgrastim is via neutrophils and is enhanced by the neutrophilia that develop in response to filgrastim. Filgrastim also displays a dose-dependent non-linearity in terms of both total and maximum exposure (AUC and $C_{max}$). Because of the non-linear, receptor mediated clearance of filgrastim, the 90% confidence interval of the least-squares means of $C_{max}$ of filgrastim to the reference treatment was to be within 75% to 133%. In studies employing a single intravenous dose approach, the sponsor argues that because of inter- subject variability and intra-subject variability, the 90% confidence interval of the least-squares means of $C_{max}$ of filgrastim to the reference treatment was widened to be within 70% to 143%.

**[Information redacted]**

**Table 1. [Information redacted]**

**[Information redacted]**

**[Information redacted]**

The study summaries are listed below.

**Table 2. Pharmacokinetics Study Summaries**

| Study | EP06-101 | EP06-102 | EP06-103 | EP06-105 |
|---|---|---|---|---|
| Type of study | Randomized, double-blind, 2-way crossover | Randomised, double-blind, 2-way cross-over | Randomised, double-blind, 2-way cross-over with 2 dose groups | Randomized, double-blind, 2-way cross-over. |
| Study population | Healthy volunteers | Healthy volunteers | Healthy volunteers | Healthy volunteers |
| No. Of subjects | 40 | 26 | 56 | 24 |
| Age range of volunteers | Age range: 25-45 years | Age range: 23-39 years. | Age range: 21-54 years. | Age range: 21-53 years. |
| Sex/Race distribution | Race: 100% Caucasian<br>Sex distribution: 52.5% male and 47.5% female | Race: 100% Caucasian<br>Sex distribution: 54% males and 46% female | Race: 100% Caucasian<br>Sex distribution: 59% male and 41% female. | Race: 100% Caucasian.<br>Sex distribution: 54% male and 46% female |
| Dose | 10 µg/kg | 5 µg/kg | 2.5 or 5 µg/kg | 1 µg/kg |
| Frequency of dosing | Daily SC injections for seven days | Single IV injection | Daily SC injections for 7 days. | Single SC injection |
| Objectives | Primary: Evaluate PK bioequivalence<br>Secondary: Compare PD, safety, local tolerance. | Primary: Evaluate PK bioequivalence<br>Secondary: Compare PD and Safety | Primary: Evaluate PD equivalence.<br>Secondary: Safety, local tolerance, PK | Primary: Evaluate PD equivalence.<br>Secondary: Safety, local tolerance, PK. |
| Main PK results | Confirmatory analysis demonstrate that at 10µg/kg/day, EP2006 and Neupogen are bioequivalent within the predefined accepted criteria of 80-125% | Confirmatory analyses demonstrate that EP2006 is bioequivalent to Neupogen for both AUC and $C_{max}$. The 90% confidence intervals were within the pre- | Descriptive analyses demonstrate that the 90% confidence intervals for all single-dose and multiple-dose AUCs were fully included within the conventional 80-125% criterion, as | Descriptive analyses demonstrate that EP2006 is bioequivalent to Neupogen for both AUC and $C_{max}$. The 90% confidence intervals were within the pre-defined acceptance |

| Study | EP06-101 | EP06-102 | EP06-103 | EP06-105 |
|---|---|---|---|---|
| | for the 90% confidence intervals of AUC and 75-133% confidence intervals of $C_{max}$, both after the first dose and at steady state. | defined accepted range of 80-125% for AUC and 70-143% for $C_{max}$. | was the 90% CI for $C_{max}$ after a single dose of 5 µg/kg. The CI for $C_{max}$ after a single dose of 2.5 µg/kg was within the boundaries of 75-133%. At 2.5 µg/kg and at 5 µg/kg (multiple dose) the CIs for $C_{max}$ were contained within the extended boundaries 70-143%. | range of 80-125%. |

### 3.2.1. Results

The PK exploration of filgrastim at single dose and multiple dose formats was performed in 146 healthy volunteers. The results showed that EP2006 and Neupogen are pharmacokinetically bioequivalent in terms of AUC after the first and last administrations for each dose tested in all the studies.

In relation to $C_{max}$, bioequivalence was established between 80-125% after first administration and at steady state of the 10 µg/kg dose and after first administration of the 5 µg/kg dose. The confidence interval after first administration of the 2.5µg/kg dose and at steady state after the 2.5 µg/kg and the 5 µg/kg doses lay within the extended boundaries of 75-133%, confirming bioequivalence.

## 3.3. Evaluator's overall conclusions on pharmacokinetics

Pharmacokinetic equivalence was demonstrated between EP2006 and Neupogen by the Phase I studies.

# 4. Pharmacodynamics

The objective of the studies was to compare the PD of EP2006 with Neupogen with respect to ANC and $CD34^+$ cells. The pharmacodynamic response to EP2006, with respect to ANC and $CD34^+$ cells, was provided by the Phase I pivotal comparative study EP06-103, and the Phase I studies EP06-101, EP06-102, and EP06-105.

The results for ANC and $CD34^+$ cells were summarized and tabulated. **[Information redacted]**

A high level of concordance was demonstrated in the PD responses between EP2006 and Neupogen in all the Phase I studies. The 95% confidence intervals of the effect on AUEC of ANC in the pivotal study and the other Phase I studies were within the pre-defined equivalence boundaries. The results of the 95% confidence interval for the secondary parameters also showed that EP2006 is biosimilar to Neupogen.

## 4.1. Evaluator's overall conclusions on pharmacodynamics

The results confirmed that the ANC response to EP2006 at all doses between 1 µg/kg/day and 10 µg/kg/day, after subcutaneous and intravenous administration, was equivalent to the response with Neupogen treatment.

# 5. Clinical efficacy

The pharmacodynamic response evaluation in healthy subjects is considered sufficient, according to the EMEA guidelines, for establishing efficacy of biosimilar rhG-CSF (EMEA/CHMP/BMWP/42832/2005 and EMEA/CHMP/BWMP/31329/2005). According to the guidelines, at least one PD biomarker should be considered as a surrogate marker for efficacy and the relationship between dose/exposure to the product and this surrogate marker should be well known. Also, therapy induced changes in the surrogate marker should explain changes in clinical outcome to a large extent. The absolute neutrophil count (ANC) satisfies the requirements of a surrogate marker for efficacy. $CD34^+$ was used as a secondary efficacy endpoint in some studies.

The studies that were considered pertinent for efficacy included the Phase I studies (studies EP06-103, EP06-101, EP06-102, and EP06-105) and a Phase III study, Study EP06-301, and are summarised in Table 3.

**Table 3. Studies pertinent to efficacy**

| Study | EP06-101 | EP06-102 | EP06-103 | EP06-105 | EP06-301 |
|---|---|---|---|---|---|
| **Type of study** | Randomized, double-blind, 2-way crossover | Randomized, double-blind, 2-way crossover | Randomized, double-blind, 2-way crossover, with two dose groups | Randomized, double-blind, 2-way crossover | Open, single-arm, multi-center study |
| **Study population** | Healthy volunteers | Healthy volunteers | Healthy volunteers | Healthy volunteers | Breast cancer patients |
| **Number of subjects** | 40 | 26 | 56 | 24 | 170 |
| **Age range of volunteers** | Age range: 25-45 years | Age range: 23-39 years | Age range: 21-54 years | Age range: 21-53 years | Age range: >18 years |
| **Sex/race distribution** | Race: 100% Caucasian | Race: 100% Caucasian | Race: 100% Caucasian | Race: 100% Caucasian | Race: 100% Caucasian |
| | Sex distribution: 52.5% male and 47.5% female | Sex distribution: 54% male and 46% female | Sex distribution: 59% male and 41% female | Sex distribution: 54% male and 46% female | Sex distribution: 100% female |
| **Dose** | 10 µg/kg | 5 µg/kg | 2.5 or 5 µg/kg | 1 µg/kg | < 60 kg: 300 µg<br>≥ 60 kg: 480 µg |
| **Frequency of dosing** | Daily s.c. injections for seven days | Single i.v. injection | Daily s.c. injections for seven days | Single s.c. injection | Multiple s.c. injections |
| **Objectives** | Primary: Evaluate PK bioequivalence<br>Secondary: PD, safety, local tolerance | Primary: Evaluate PK bioequivalence<br>Secondary: PD and safety | Primary: Evaluate PD equivalence<br>Secondary: Safety, local tolerance, PK | Primary: Evaluate PD equivalence<br>Secondary: Safety, local tolerance, PK | Primary: Safety (including immunogenicity)<br>Secondary: Efficacy |
| **Main efficacy results** | Descriptive analysis demonstrates that the effect on AUEC0→216h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to standard bioequivalence criteria. | Descriptive analysis demonstrates that the effect on AUEC0→120h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to standard bioequivalence criteria. | Confirmatory analysis demonstrates that the effect on AUEC0→216h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to predefined criteria. | Confirmatory analysis demonstrates that the effect on AUEC0→120h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to standard bioequivalence criteria. | Descriptive analysis of the incidence of febrile and severe neutropenia in cycle 1 showed results comparable to historical data. |

### 5.1.1. Results

In the Phase I studies, in keeping with the EMEA guidelines, similarity of efficacy between EP2006 and Neupogen was demonstrated by the 95% confidence intervals of AUEC of ANC being within the pre-defined equivalence boundaries set. The results for the $CD34^+$ cells confirm the results for ANC.

In the Phase III study, Study EP06-301, the objective was to evaluate the safety, tolerability and efficacy of Filgrastim Sandoz.

Study EP06-301 is an open label, single-arm, multi-centre, Phase III study in patients with breast cancer who were being treated with doxorubicin and docetaxel chemotherapy and EP2006 as primary prophylaxis of severe neutropenia. All the patients were Caucasian women, aged over 18 years. The breast cancer was high-risk stage II, locally advanced metastatic breast cancer.

Chemotherapy for breast cancer consisted of doxorubicin 60 $mg/m^2$ as an intravenous bolus infusion on Day 1, followed about an hour later by a 1-hour intravenous infusion of docetaxel (75 $mg/m^2$). Treatment with EP2006 commenced on Day 2 of each chemotherapy cycle for up to 14 days (or until ANC reached $10x10^9/L$ post nadir) and was administered as a bolus injection. The treatment was repeated for 4 cycles.

The efficacy assessments included the duration of severe neutropenia in cycles 1-4 (number of days where ANC $\leq 0.5x10^9/L$ until ANC $\geq 1x10^9/L$), incidence of febrile neutropenia (oral temp $\geq 38.2°C$ and ANC $\leq 0.5x10^9/L$), time to neutrophil recovery (ANC $\geq 2.0x10^9/L$). The other efficacy assessments included duration of hospitalisation, time in intensive care unit, incidence of antibiotic use, incidence of documented infections and number of transfusions required.

Safety assessments included incidence, occurrence and severity of adverse events, anti G-CSF antibody formation and mortality.

The sample size was determined to be 150 patients, based on historical data for filgrastim.

Of the 170 patients enrolled, 153 (90%) completed the study. All the patients were Caucasian women, aged over 18 years (range: 24y to 78y). The patients' mean age was 52 years.

The breast cancer was high-risk stage II (3%), locally advanced metastatic breast cancer (66%) and metastatic breast cancer (30%). They had had previous surgery (55%), radiotherapy (18%) or hormonal/immunotherapy (5%).

Severe neutropenia was observed in 47% of patients in cycle one. The incidence of severe neutropenia declined in subsequent cycles (Cycles 2 (15.4%), 3 (20.8%) and 4 (17.5%). In all, 26% of all patients across all cycles reported severe neutropenia.

The duration of severe neutropenia was very similar in all 4 cycles of treatment. The duration of severe neutropenia ≥3 days was reported in ten patients (6%) in cycle 1 and declined to 2 patients (1%) in cycle 3 and 1 patient (<1%) in cycle 4. There were no patients (0%) in cycle 2.

Febrile neutropenia (oral temp. ≥ 38.2°C; ANC $<0.5x10^9/L$, measured on same day), was reported in 10 patients (6%) in the first treatment cycle, and none thereafter. When the definition was expanded to include patients for whom febrile neutropenia was reported as a serious adverse event, febrile neutropenia was reported in 13 (7.6%) patients in the first cycle and by 1 (0.6%) patient in the third cycle.

The protocol defined mean time to recovery (number of days from ANC nadir to the ANC $\geq 2.0x10^9/L$) was 2 days.

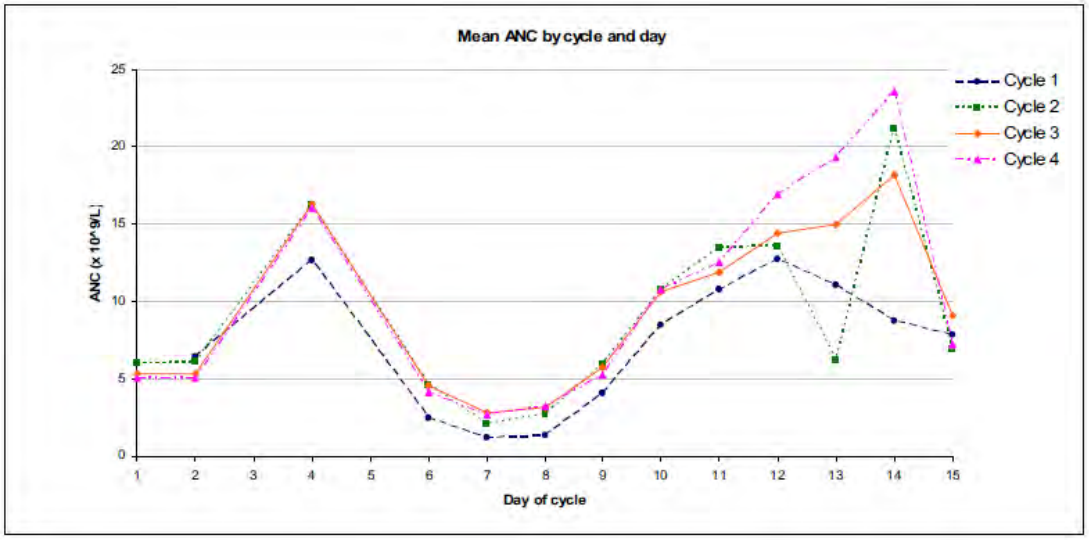
In all 124 (73%) patients were hospitalised for 297 events. The majority of hospitalisation events were for chemotherapy (90 patients, 53%, 262 events). Hospitalisation for febrile neutropenia (6 patients, 4%, 6 events) and other events (28 patients, 16%, 29 events) were the

rest. None of the 7 patients admitted to the Intensive Care Unit were for febrile neutropenia (1 patient for chemotherapy, 6 patients for other reasons).

Intravenous antibiotics were required for 9 (5%) patients with febrile neutropenia and 1 (<1%) patient required a blood transfusion.

The mean ANC curve was congruent for all cycles from Day 1 to Day 11. The depth of the nadir was greatest in Cycle 1 (Figure 2).

**Figure 2. Mean ANC curve for each cycle (ITT population)**




The study demonstrated efficacy of EP2006 as primary prophylaxis of severe neutropenia in patients with breast cancer treated with chemotherapy.

### 5.2. Evaluator's overall conclusions on efficacy

The Phase I studies demonstrated similarity in efficacy of EP2006 with Neupogen. Efficacy in the Phase III study in breast cancer patients, in terms of reduction of the incidence of severe neutropenia and reduction in the duration of severe neutropenia, was comparable with the efficacy of Neupogen when used in combination with chemotherapy.

## 6. Clinical safety

### 6.1. Studies providing evaluable safety data

These are summarised in Table 4, below.

**Table 4. Studies providing evaluable safety data**

| Study | EP06-101 | EP06-102 | EP06-103 | EP06-105 | EP06-301 |
|---|---|---|---|---|---|
| Type of study | Randomized, double blind, 2-way crossover | Randomized, double blind, 2-way crossover | Randomized, double-blind, 2-way crossover, with two dose groups | Randomized, double blind, 2-way crossover | Open, single-arm, multi-center study |
| Number of subjects/ patients | 40 | 26 | 56 | 24 | 170 |
| Study population | Healthy volunteers | Healthy volunteers | Healthy volunteers | Healthy volunteers | Breast cancer patients |
| Age range<br>Race<br>Sex distribution | 25-45 years<br>100% Caucasian<br>52.5% male and 47.5% female | 23-39 years<br>100% Caucasian<br>54% male and 46% female | 21-54 years<br>100% Caucasian<br>59% male and 41% female | 21-53 years<br>100% Caucasian<br>54% male and 46% female | >18 years<br>100% Caucasian<br>100% female |
| Duration of exposure | 2 weeks (7 days per substance) | 2 days (1 day per substance) | 2 weeks (7 days per substance) | 2 days (1 day per substance) | mean: 31 days (approximately 10 days per cycle) |
| Dose | 10 µg/kg | 5 µg/kg | 2.5 or 5 µg/kg | 1 µg/kg | < 60 kg: 300 µg<br>≥ 60 kg: 480 µg |
| Frequency of dosing | Multiple s.c. injections | Single i.v. injection | Multiple s.c. injections | Single s.c. injection | Multiple s.c. injections |
| Drug products | EP2006<br>Neupogen® | EP2006<br>Neupogen® | EP2006<br>Neupogen® | EP2006<br>Neupogen® | EP2006 |
| Number of patient-years (EP2006) | 0.69 | 0.07 | 2.5 µg/kg/day: 0.54<br>5.0 µg/kg/day: 0.53 | 0.07 | 14.418 |
| Number of patient-years (Neupogen®) | 0.69 | 0.07 | 2.5 µg/kg/day: 0.54<br>5.0 µg/kg/day: 0.54 | 0.07 | n.a. |
| Objectives | Primary: Evaluate PK bioequivalence<br>Secondary: Compare PD, safety, local tol. | Primary: Evaluate PK bioequivalence<br>Secondary: Compare PD, safety | Primary: Evaluate PD equivalence<br>Secondary: Safety, local tolerance, PK | Primary: Evaluate PD equivalence<br>Secondary: Safety, local tolerance, PK | Primary: Safety (including immunogenicity)<br>Secondary: Efficacy |
| Main safety results | Both products were well tolerated, with no relevant differences in safety profiles. Majority of AEs were graded as mild. No SAEs were observed. | Safety profiles of the two products were similar. Most drug-related AEs were of mild or moderate severity. No SAEs were observed. | Both products were well tolerated, with no relevant differences in safety profiles. Majority of AEs were graded as mild. No SAEs were reported. | Both products were well tolerated, with no relevant differences in safety profiles. Majority of AEs were graded as mild. No SAEs were reported. | Most frequent AEs were musculo-skeletal pain, back pain, bone pain, or myalgia. None of the reported SAEs were attributed to EP2006. |

## 6.2. Adverse drug reactions

The safety population consisted of 146 healthy subjects in the Phase I studies and 170 patients in the Phase III study. The exposure in the Phase I studies with multiple dosing, where the dose ranged from 2.5 to 10 µg/kg body weight, was up to 14 days. In the Phase III study EP06-301 where the dose ranged from 3.69 µg/kg body weight to 8.42 µg/kg body weight, the mean number of days of exposure to EP2006 was 31 days (range: 6–48 days).

In the Phase I studies almost all the subjects reported at least one adverse event. The adverse events in both treatment groups were mainly mild in severity and were similar in frequency and relationship to the treatment (see Table 5).

**Table 5. General summary of treatment-emergent adverse events observed in healthy volunteers**

| | STUDY EP06-101 | | STUDY EP06-102 | | STUDY EP06-103 | | | | STUDY EP06-105 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | EP2006 10 µg/kg s.c. | Neupogen® 10 µg/kg s.c. | EP2006 5 µg/kg i.v. | Neupogen® 5 µg/kg i.v. | EP2006 5 µg/kg s.c. | Neupogen® 5 µg/kg s.c. | EP2006 2.5 µg/kg s.c. | Neupogen® 2.5 µg/kg s.c. | EP2006 1 µg/kg s.c. | Neupogen® 1 µg/kg s.c. |
| No. of subjects dosed | 36 | 36 | 24 | 26 | 28 | 28 | 28 | 28 | 24 | 24 |
| No. of subjects with AEs (%) | 30 (83.3%) | 33 (91.7%) | 15 (62.5%) | 16 (61.5%) | 28 (100.0%) | 28 (100.0%) | 28 (100.0%) | 28 (100.0%) | 13 (54.2%) | 11 (45.8%) |
| No. of AEs | 114 | 119 | 35 | 38 | 177 | 167 | 145 | 154 | 34 | 24 |
| Severity | | | | | | | | | | |
| Mild | 97 (85.1%) | 99 (83.2%) | 35 (100.0%) | 35 (92.1%) | 80 (45.2%) | 61 (36.5%) | 62 (42.8%) | 65 (42.2%) | 31 (91.2%) | 21 (87.5%) |
| Moderate | 17 (14.9%) | 20 (16.8%) | 0 (0.0%) | 3 (7.9%) | 97 (54.8%) | 101 (60.5%) | 81 (55.9%) | 88 (57.1%) | 3 (8.8%) | 3 (12.5%) |
| Severe | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 5 (3.0%) | 2 (1.4%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) |
| Relationship to study drug | | | | | | | | | | |
| None | 3 (2.6%) | 2 (1.7%) | 4 (11.4%) | 3 (7.9%) | 3 (1.7%) | 1 (0.6%) | 4 (2.8%) | 1 (0.6%) | 26 (76.5%)* | 16 (66.7%)* |
| Unlikely | 11 (9.6%) | 23 (19.3%) | 5 (14.3%) | 5 (13.2%) | 8 (4.5%) | 7 (4.2%) | 10 (6.9%) | 6 (3.9%) | | |
| Possible | 11 (9.6%) | 6 (5.0%) | 19 (54.3%) | 23 (60.5%) | 59 (33.3%) | 53 (31.7%) | 45 (31.0%) | 55 (35.7%) | 8 (23.5%)* | 8 (33.3%)* |
| Probable | 89 (78.1%) | 88 (73.9%) | 7 (20.0%) | 7 (18.4%) | 107 (60.5%) | 106 (63.5%) | 86 (59.3%) | 92 (59.7%) | | |

The incidence of musculoskeletal disorders showed a relationship to dose for both EP2006 and Neupogen treatments. The commonest adverse events were myalgia, back pain, bone pain, and headache. There were no neutralizing anti-rhG-CSF antibodies detected in any of the 146 subjects.

In Study EP06-301, all 170 patients received at least one treatment course of chemotherapy and Filgrastim Sandoz. The majority of adverse events (85%) were suspected of being related to chemotherapy. In all, 39 patients experienced 89 events which were identified as being commonly reported during treatment with G-CSF. Of the 89 adverse events, 44 (49%) were considered related to EP2006 treatment.

The five adverse events that are commonly reported during treatment with G-CSF are musculoskeletal pain, and elevations of lactate dehydrogenase, alkaline phosphatise, serum uric acid and aspartate aminotransferase (AST). These five adverse events were reported by 39 (22.9%) patients as 89 events. Relationship to Filgrastim Sandoz was suspected for 19 (11.2%) patients (44 events). All of the events were considered to be mild in 34 (20%) subjects (79 events) and moderate in 7 (4.1%) subjects (10 events). The adverse events of moderate intensity were myalgia (5 events), arthralgia (4 events), and AST increased (1 event).

None of the serious adverse events and deaths was attributed to treatment with EP2006.

Assessment of antibody formation was conducted in the 643 samples collected during the study. Of these, 14 samples showed total binding values > 2.27%. These were reanalysed with a confirmatory RIP assay using Filgrastim Sandoz as unlabelled substance. There was no evidence of anti-rhG-CSF antibodies in any of the 14 samples. However, it appears that sampling data from Cycle 3 have not been provided.

### 6.3. Evaluator's overall conclusions on safety

The methods used to capture safety information were appropriate. The Phase I studies and the Phase III study have shown that the safety profile of EP2006 in healthy subjects and in patients with breast cancer treated with chemotherapy, was in keeping with the known safety profile of Neupogen.

# 7. Post-marketing experience

### 7.1. PSUR for Filgrastim

In all, 4 PSURs, covering the period from 06/02/2009 to 31/01/11, were submitted. In this period, the patient exposure **[Information redacted]**. The safety concerns that were first identified before first approval of Filgrastim on 6 February 2009 are listed below.

- Severe splenomegaly / splenic rupture
- Serious pulmonary adverse events: Interstitial pneumonia, ARDS
- Osteoporosis in SCN patients
- Transformation to MDS or leukaemia in SCN patients
- Cutaneous vasculitis
- Exacerbation of rheumatoid arthritis and arthritic symptoms
- Allergic reactions
- Graft versus Host Disease in cancer patients
- Graft versus Host Disease in recipients of allogeneic PBPC cells mobilised with
- filgrastim
- Immunogenicity (Incidence and clinical implications of anti-GCSF antibodies)
- Haematological malignancy in normal donors

A report was received on 15/06/10 of refractory cytopenia with multilineage dysplasia. The subject was in Study EP06-103 in Dose group 2 (5 µg/kg). The patient had not received any medication since the trial ended in Nov 2006. She developed Trolards vein thrombosis and was treated with heparin, levetiracetam and phenprocoumon. The differential diagnosis included myelodysplastic syndrome (MDS), aplastic anaemia, toxic/reactive alterations of bone marrow, increased consumption of neutrophils and autoimmune neutropenia. The expert haematologist and the company have ruled that the two trial medications (EP06-103 and Neupogen) are possibly related to MDS in this subject. This is the first case in all published literature of the two trial medications having a possible association with MDS.

The sponsor states that the safety data received to date is in compliance with the safety information provided in the Company Core Data Sheet.

# 8. Overall conclusions and recommendations

The application to register EP2006 (Filgrastim Sandoz), a Similar Biological Medicinal Product, is recommended for approval.

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