Bioequivalence of Two Recombinant Granulocyte Colony-Stimulating Factor Formulations in Healthy Male Volunteers


a Center for Biological Research, Clinical Trials Division, Havana, Cuba
b National Center for Toxicology, ‘Carlos J. Finlay’ University Hospital, Havana, Cuba
c Center for Medical-Surgical Research, Havana, Cuba
d University of Havana, Institute of Pharmacy and Food, Havana, Cuba

ABSTRACT: To evaluate the equivalence of the pharmacokinetic, pharmacodynamic and safety properties of two recombinant G-CSF formulations in healthy male volunteers, a standard 2-way randomized crossover double-blind study, with a 3 week washout period, was conducted. A single 300 μg G-CSF dose was administered subcutaneously. Hebrvital® (Heber Biotec, Havana, formulation A) and Neupogen® (Hoffmann-La Roche S.A, formulation B) were compared. Twenty-four healthy male volunteers were included. The serum G-CSF level was measured by enzyme immunoassay (EIA) during the first 36 h after administration. Absolute neutrophils (ANC), white blood cells (WBC) and CD34+ cells counts were the pharmacodynamic variables measured up to 120 h. Other clinical and laboratory determinations were used as safety criteria. The pharmacokinetic parameters for formulation A and B were very close to each other (i.e. AUC, 235.9 vs 270.0 ng·h/ml; Cmax, 29.2 vs 33.4 ng/ml; Tmax, 4.2 vs 4.7 h; half-life, 3.2 vs 2.8 h; CL, 260.9 vs 277.2 ml/h; Vd, 1.2 vs 1.1 l; and MRT, 7.58 vs 7.38 h). The confidence intervals for the means ratio of all these parameters were within or very close to the 0.8–1.25 acceptance range. The pharmacodynamics showed high similarity since ANC and WBC had the same profiles for both products and no differences were detected for the estimated parameters. The CD34+ cells count increments were evident for both formulations in a similar way as well. The treatments were well tolerated. Registered adverse events were similar; back/spine pain was the most frequent. According to the overall results these formulations could be considered as clinically comparable. Copyright © 2005 John Wiley & Sons, Ltd.

Key words: G-CSF; bioequivalence; pharmacokinetics; pharmacodynamics; safety

Introduction

Granulocyte colony-stimulating factor (G-CSF) is a 18 800 Dalton glycoprotein produced by monocytes, fibroblasts and endothelial cells. It induces proliferation, differentiation and activation of the neutrophil-granulocyte lineage and also enhances some mature neutrophil functions [1]. Recombinant human G-CSF is mainly applied to reduce febrile neutropenia in patients with non-myeloid malignancies that receive myelosuppressor drugs [2,3]. It is also recommended for treating congenital, cyclic or idiopathic neutropenia [4], to accelerate neutrophils recovery in bone marrow transplantation [5], to minimize other neutropenia [6–9] and for the
mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis [10]. Whether multiorigin recombinant proteins can be clinically interchangeable despite coming from different strains and manufacturing processes is a controversial matter nowadays [11,12]. If this principle is accepted, then a bioequivalence study that shows pharmacological similarity between two products would be enough to indicate its therapeutic interchangeability, given that they are chemically and pharmaceutically equivalent as well.

A new recombinant G-CSF preparation was recently obtained in bacteria (Escherichia coli) at the Center for Genetic Engineering and Biotechnology, Havana (CIGB in Spanish). To demonstrate its bioequivalence with another similar, commercially available product, their pharmacokinetic, pharmacodynamic and safety profiles were compared. The absolute neutrophils (ANC), white blood cells (WBC) and CD34+ cells counts were used as pharmacodynamic markers.

Material and Methods

Subjects

Twenty-four apparently healthy, male volunteers, who gave their written, informed consent to participate, were included. Individuals were considered healthy if they had no history of chronic diseases, had not suffered any acute illness in the past 30 days, had no symptoms or signs at the physical examination and laboratory tests, and were negative to HIV and hepatitis B and C virus infection markers in serum. The subjects were not included if they had received treatment with G-CSF or any drug that could alter hematological functions in the previous 15 days, had been operated on in the previous 6 months or had donated blood in the previous 3 months. They were withdrawn from the trial if they abandoned voluntarily, had severe adverse reactions, or if any exclusion criteria arose. The trial complied with the Helsinki Declaration. The protocol was approved by the Ethics Committee of the 'Carlos J. Finlay' University Hospital, Havana, and by the Cuban Regulatory Authority.

G-CSF formulations

Formulation A contained 300 μg G-CSF (Hebervital®, produced in E. coli at CIGB, Havana), 50 mg sorbitol, 0.04 mg polysorbate 80, 1.64 mg sodium acetate, enough acetic acid to adjust pH to 4.0, and water for injection to complete 1 ml. Formulation B consisted in a commercially available preparation (Neupogen®, F. Hoffmann-La Roche SA; under license from Amgen Inc.). Each single-use vial contained 300 μg/ml G-CSF, formulated in a 10 mM sodium acetate buffer pH 4.0, with 5% sorbitol, 0.004% polysorbate 80, and water for injection to complete 1 ml.

Study design

After an overnight fasting, 24 subjects received randomly, on the upper right arm, a single 300 μg (30 x 10^6 UI; one vial) dose of either recombinant G-CSF preparation A or B by subcutaneous administration, following a double-blind, 2-way crossover design, with a 3 week washout period between treatments. Subjects were randomized according to a computer-generated simple random number list, to receive one of two treatment sequences (i.e. AB or BA). Vials looked the same and were labeled only with the subject’s inclusion number. At each period, individuals were hospitalized during 48 h after the injection under strict medical supervision. Analgesic medication was given orally 30 min before the G-CSF injection and afterwards if needed, in order to mitigate the G-CSF-dependent back/spine pain that was expected.

Clinical and laboratory evaluations

Blood samples for serum G-CSF concentration determinations were collected by venipuncture before and 0.5, 1, 1.5, 2, 4, 5, 6, 8, 10, 12, 16, 24 and 36 h after injection. Pharmacodynamics was assessed by the evaluation of ANC, WBC and CD34+ cells every 24 h for 5 days. Vital signs, hemoglobin, hematocrit, other hematological counts (monocytes, lymphocytes, eosinophils and platelets), alanine aminotransferase (ALT) and creatinine were used as safety variables. The subjects were regularly checked for symptoms at the same times as blood sampling. Clinical
laboratory measurements were made at 0, 24, 48, 72, 96 and 120 h.

Recombinant G-CSF was quantified in serum with a commercial enzyme immunoassay (EIA) kit (Quantikine™, IVD®, R&D System, Inc, Minneapolis). Hematological determinations and blood chemistry were done according to usual clinical laboratory procedures, using automated analysers. Peripheral blood CD34+ cells were measured by flow cytometry (Stem-Kit CD34+ HPC Enumeration Kit, Beckman Coulter). All laboratory analyses were done blindly.

**Data analysis**

The systemic disposition data analysis was performed for each individual by a non-compartmental method following a combined linear/log -linear trapezoidal rule approach. The linear trapezoidal rule was used up to peak level and the logarithmic trapezoidal rule thereafter. Time-to-peak values (T\text{max}) were determined directly from the experimental data as the time of the maximum observed level (C\text{max}) considering the entire curve. The area under the serum concentration-time curve from 0 to 36 h (AUC\text{36}) was calculated using the linear/log linear trapezoidal rule. The mean residence time (MRT) was also calculated using the moments of the drug disposition curve. The parameters that were extrapolated to infinity, such as AUC (area under disposition curve) and AUMC (area under first moment of the disposition curve), were computed based on the last predicted value from the linear regression of the included terminal data points. In addition, other pharmacokinetic parameters were also calculated, such as the elimination half-life (t\text{1/2}), apparent absolute bioavailability (F), systemic clearance (CL), volume of distribution (V\text{d}), and the peak to area ratio value (CAV = C\text{max}/AUC). The apparent absolute bioavailability, F, was estimated using data from a previously reported study after intravenous dosing of recombinant G-CSF as the subcutaneous to intravenous AUC ratio [13]. Similarly, the effect parameters derived from the corresponding profiles for the biomarker variables ANC and WBC, such as the area under the increase in absolute neutrophil count-time curve from 0 to 120 h (AUEC\text{120}), were also calculated for each subject and administration period in order to characterize the kinetic pattern of the G-CSF-induced proliferative response. The WinNonlin professional software (Version 2.1, Pharsight Inc., 1997, NC, USA) was used for all these purposes.

Statistical analyses were done using SPSS for Windows version 10.0. Groups were tested for normal distribution by the Shapiro-Wilk’s test and for variance homogeneity by the Levene’s test. The 90% confidence intervals for the difference between the logarithmically transformed pharmacokinetic parameters from each formulation were then calculated according to Westlake [14]. Wilcoxon’s method, proposed by Steinijans [14], was used for the parameters that did not fulfill the normality assumption. The 90% confidence intervals were estimated by the non-parametric method proposed by the same authors [15]. The pharmacodynamic variables ANC and WBC were treated similarly. Vital signs and other laboratory variables, including CD34+ cells, were treated using paired analysis (Wilcoxon’s test), taking into account Bonferroni’s adjustment for multiple comparisons. Adverse reactions were evaluated by the McNemar’s test.

**Results**

Twenty-four healthy male volunteers were recruited. Their age ranged from 19 to 35 years (26.3 ± 4.6 years); weighed 55 to 110 kg (71.1 ± 11.7 kg) and were 161 to 196 cm (173 ± 8 cm) tall; 54% were white. Treatment groups were homogeneous according to demographic and baseline data (data not shown). All the subjects received both formulations and fulfilled the whole blood sampling.

**Pharmacokinetic analysis**

Baseline levels of recombinant G-CSF were not detected in any of the individuals. Some individual G-CSF concentrations in serum reached 40 ng/ml by EIA determinations. No carryover effect from the first treatment period onto the second period G-CSF concentration values was found. The AUC\text{36} obtained covered, in all subjects, more than 95% of the AUC extrapolated...
to infinity. The average concentration profiles obtained for both formulations were similar (Figure 1).

Table 1 shows the results of the pharmacokinetic comparisons. None of the differences between the means of any of the pharmacokinetic parameters exceeded the clinically significant level of 20%. The calculated ratios between both formulations were within or very close to the 0.8–1.25 limits.

Pharmacodynamic analysis

Increments in peripheral blood ANC and WBC were very similar for both G-CSF formulations, with the same profiles (Figure 2). The 24 h values were the highest for all individuals, and then slowly returned to baseline at 120 h. Increases were 1.7–5.6 fold (average 3.3) for WBC and 2.0–9.5 fold (average 4.9) for ANC. The calculated confidence intervals for every parameter of

Table 1. Pharmacokinetic parameters in 24 healthy male volunteers who received 300 μg of G-CSF from both formulations. Data are reported as mean ± standard deviations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation A (n = 24)</th>
<th>Formulation B (n = 24)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng.h/ml)</td>
<td>236 ± 67.3</td>
<td>270 ± 53.0</td>
<td>(0.78–0.97)</td>
</tr>
<tr>
<td>AUC36 (ng.h/ml)</td>
<td>233 ± 66.9</td>
<td>268 ± 52.8</td>
<td>(0.78–0.97)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>29.2 ± 8.3</td>
<td>33.4 ± 7.5</td>
<td>(0.77–0.99)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>4.2 ± 0.9</td>
<td>4.7 ± 0.7</td>
<td>(0.78–0.92)</td>
</tr>
<tr>
<td>F</td>
<td>0.44 ± 0.13</td>
<td>0.50 ± 0.09</td>
<td>(0.78–0.97)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>3.24 ± 0.71</td>
<td>2.82 ± 0.90</td>
<td>(1.05–1.25)</td>
</tr>
<tr>
<td>CAV</td>
<td>0.124 ± 0.018</td>
<td>0.124 ± 0.016</td>
<td>(0.96–1.05)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>7.58 ± 1.04</td>
<td>7.38 ± 1.01</td>
<td>(0.99–1.07)</td>
</tr>
<tr>
<td>CL (ml/h)</td>
<td>260.9 ± 23.5</td>
<td>277.2 ± 24.9</td>
<td>(0.94–0.94)</td>
</tr>
<tr>
<td>Vd (l)</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>(0.99–1.19)</td>
</tr>
</tbody>
</table>

CI mean confidence intervals of the mean test/reference ratio.
interest lay within the acceptance bounds (see Table 2). In addition, there was no evidence of any carryover effect for these pharmacodynamic variables. Other blood cells lineages counts did not change after G-CSF treatments (result not shown).

CD34+ cells counts showed an important individual variability and parameters could not be rigorously calculated from the experimental data. Nevertheless, an increment was observed in all but one subject in the second period (formulation A). The values increased 1.3–8.0 fold (average 2.7) for formulation A and 1.2–6.7 fold (average 2.7) for formulation B. The median time to maximal value was 72 h for both products. There was no significant difference between formulations for the increments in a paired statistical analysis (Wilcoxon’s test).

Safety analysis

Both products had a similar tolerability. Few adverse events were recorded during the 48 h that the subjects were in-patients. These were mostly mild, none of them severe, and most of them resolved without medication. The most frequent event was musculo-skeletal back/spine pain (Table 3). Four subjects that received formulation A, but none from formulation B, presented pain at the injection site. Statistical analysis could not be applied for some events due to their low frequency. Except for cough and odynophagia, reactions were associated with G-CSF administration. Back/spine pain was more frequent in the first period and pain at the injection site in the second. Vital signs and the other laboratory determinations were not affected by exogenous G-CSF.

### Table 2. Descriptive analysis of ANC and WBC kinetics in the peripheral blood of the 24 healthy male volunteers who received 300 μg of G-CSF from both formulations. Parameters analogous to those in pharmacokinetic analysis, but describing effect, were calculated. Data are reported as mean ± standard deviations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation A (n = 24)</th>
<th>Formulation B (n = 24)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUEC (×10⁹ cells · h⁻¹)</td>
<td>1523 ± 222</td>
<td>1526 ± 292</td>
<td>(0.99–1.07)</td>
</tr>
<tr>
<td>AUEC₁₂₀ (×10⁹ cells · h⁻¹)</td>
<td>1135 ± 199</td>
<td>1097 ± 205</td>
<td>(1.04–1.12)</td>
</tr>
<tr>
<td>Rₘₕₙ (×10⁹ cells/l)</td>
<td>19.0 ± 3.6</td>
<td>18.2 ± 3.6</td>
<td>(0.97–1.06)</td>
</tr>
<tr>
<td>RAV</td>
<td>0.012 ± 0.002</td>
<td>0.012 ± 0.002</td>
<td>(0.94–1.04)</td>
</tr>
<tr>
<td>MET (h)</td>
<td>89.8 ± 24.0</td>
<td>92.4 ± 19.6</td>
<td>(0.83–1.01)</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUEC (×10⁹ cells · h⁻¹)</td>
<td>2497 ± 494</td>
<td>2494 ± 571</td>
<td>(0.91–1.10)</td>
</tr>
<tr>
<td>AUEC₁₂₀ (×10⁹ cells · h⁻¹)</td>
<td>1605 ± 242</td>
<td>1516 ± 229</td>
<td>(1.02–1.09)</td>
</tr>
<tr>
<td>Rₘₙₕ (×10⁹ cells/l)</td>
<td>22.6 ± 3.7</td>
<td>22.7 ± 3.7</td>
<td>(0.96–1.04)</td>
</tr>
<tr>
<td>RAV</td>
<td>0.009 ± 0.002</td>
<td>0.009 ± 0.002</td>
<td>(0.92–1.07)</td>
</tr>
<tr>
<td>MET (h)</td>
<td>116.0 ± 42.2</td>
<td>126.3 ± 59.9</td>
<td>(0.80–1.08)</td>
</tr>
</tbody>
</table>

* AUEC (area under the effect curve); AUEC₁₂₀ (area under the effect curve up to the last sampling time); Rₘₙₕ (maximum response); RAV (maximum response to area ratio); MET (mean effect time). CI mean confidence intervals of the mean test/reference ratio.

### Table 3. Adverse reactions frequency observed in the 24 healthy male volunteers who received 300 μg of G-CSF from both formulations. Data are presented as number of individuals that presented each adverse reaction (%) (McNemar’s test)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Formulation A (n = 24)</th>
<th>Formulation B (n = 24)</th>
<th>Both formulations</th>
<th>p (McNemar’s test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back/spine pain</td>
<td>8 (33.3%)</td>
<td>6 (25.0%)</td>
<td>4 (16.7%)</td>
<td>0.687</td>
</tr>
<tr>
<td>Pain at the injection site</td>
<td>4 (16.7%)</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4.2%)</td>
<td>3 (20.8%)</td>
<td>0</td>
<td>0.625</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1 (4.2%)</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Statistics could not be carried out for some events.
Discussion

The trial design (namely, sample size, randomization, double-blind, crossover, 3 week washout period) guaranteed compliance with international guidelines for bioequivalence studies [16,17]. The fact that more than 95% of the AUC could be covered by the observed AUC$_{36}$ and that there was no residual effect on the second period G-CSF concentrations indicate that internal validity of the data was high.

The selected dose, similar to others in healthy volunteer studies [18–20], was adequate, since G-CSF titers in serum were easily detected and the treatment was quite well tolerated. The crossover design provides more statistical power to detect differences, so it is usually used in this kind of study. The 3 week washing period between both treatments seemed to be long enough regarding the G-CSF concentration in blood and their biological actions. The sample size was within the range recommended for this kind of study.

The pharmacokinetic analysis showed a high similarity between the two formulations. The differences between them for each of the calculated parameters were less than 20%. Some of the 90% confidence intervals of the mean ratios were outside the 0.8–1.25 range that is conventionally considered for decision-making in bioequivalence, although very close and just below the lower tail. The parameters that were slightly outside this acceptance range were: AUC, AUC$_{36}$, $C_{\text{max}}$, $T_{\text{max}}$ and obviously $F$.

In an earlier bioequivalence study between two recombinant G-CSF formulations, the apparent $F$ after subcutaneous administration was evaluated to be around 60% [13], which is a value similar to those in several reports [20,21] and also very close to this study. Interestingly, in this crossover study the 90% confidence interval for AUC$_{72}$ (i.e. 1.11–1.28) also lay outside the acceptance range, and the authors argued that the true difference in $F$ was amplified 2.5 times because of nonlinearity [13]. Although the reference data were taken from a study with a glycosylated CHO-derived G-CSF it has been reported that the bioavailabilities of different G-CSF molecular forms are similar [22].

In the case of AUC and AUC$_{36}$, which measure the extent of systemic exposure after absorption, the small deviation can be considered as a result of the reported nonlinear pharmacokinetics for recombinant G-CSF [13,20]. This consideration is also valid for apparent $F$ values. Consequently, the absolute bioavailability of subcutaneous administration will be an underestimate and will not express the true amount absorbed after subcutaneous administration. Therefore, any difference between the two formulations in terms of the amount absorbed should be amplified when the pharmacokinetics are nonlinear [13]. This nonlinear behavior could probably be associated with the so-called receptor-mediated endocytosis, a saturable metabolic clearance process. Actually, this saturable process should have a close relation to the amount consumed through the G-CSF receptors located mainly in the bone marrow [13]. Hence the differences would be in relation to the unbound molecules while the therapeutically active ones are those receptor-bound. This could explain why almost identical neutrophil increases were obtained despite the slight differences in bioavailabilities. Moreover, a lack of positive correlation between the AUC and the ANC increase has been observed [23], so the relationship between unbound G-CSF concentrations and its biological effects does not seem to be direct, which was confirmed in this work.

Recombinant G-CSF clearance is known to be saturable in humans [20,21]. This suggests that apparent bioavailabilities ($F$) might become closer if the bioequivalence study is carried out at a higher dose [13]. In fact, Hayashi et al. [13] stated that the difference amplification occurs maximally at a dose range of 1–5 μg/kg. Likewise, if a subject has suppressed bone marrow function, the intrinsic clearance capability ($V_{\text{max}}$) should be lower than in healthy volunteers, and the change in total clearance with increase in serum G-CSF concentration should be less. Therefore, $F$ might also become closer when the subject is such a patient.

On the other hand, $T_{\text{max}}$ depends on the experimental design (i.e. sampling) and thus it cannot be interpreted as a continuous variable. In this trial, the absolute difference between the $T_{\text{max}}$ values did not exceed 30 min. In fact, the European Guidelines recommend that this variable should be analysed by non-parametric
procedures [17]. Both products had $T_{\text{max}}$ values within the reported range for subcutaneous G-CSF, 4–5 h [1, 24, 25].

$C_{\text{max}}$, although continuous, is highly dependent on the times at which samples were taken. Therefore, several authors proposed that the bioequivalence range be expanded up to 30% [26–28], and in some cases this wider 90% CI can be accepted by international regulatory agencies [17]. $C_{\text{max}}$ is usually considered a parameter for characterizing either the extent or the rate of absorption, even though this parameter does not seem accurately to describe either of them. Other parameters such as $MRT$ and $CAV$, which satisfied the accepted range, describe these phenomena better [26, 29].

The other calculated parameters (e.g. $V_d$ and $CL$) fulfilled the 0.8–1.25 range criteria. The mean $t_{1/2}$ did not differ by more than 30 min either. The values ranged between 2.1 and 4.5 h for formulation A and between 1.5 and 4.8 for formulation B. A wider variability around approximately 3.5 h has been reported for this parameter, so the values obtained in this work are comparable with them [1, 24, 25].

Pharmacodynamics was assessed following the two clinically relevant efficacy endpoints after G-CSF treatment (i.e. ANC and WBC), which showed very similar profiles for both formulations. All the calculated effect parameters lay within the intervals considered for bioequivalence (see Table 2). Increments in circulating leukocytes were exclusively due to ANC since other lineages did not have variations. The circulating CD34+ cell count increment has been suggested to be an adequate variable that measures stem cell mobilization [30–33]. The compared formulations did not differ significantly with respect to this variable either.

The formulations were well tolerated, with similar adverse reactions, compatible with what has been described for recombinant G-CSF preparations. Light or moderate musculo-skeletal (predominantly back/spine) pain is the most frequent adverse reaction to recombinant G-CSF. Local reactions at the injection site (erythema, inflammation or pruritus) can persist for at least 2 days after administration. Hematological, gastrointestinal and biochemical reactions are less recorded [2–4, 24, 25, 34].

The integration of pharmacokinetic and pharmacodynamic characterizations into drug development provides a scientific framework for its rational and efficient application [35, 36], which was already done for G-CSF in healthy male volunteers [18, 37]. According to the results obtained, both preparations could be considered therapeutically equivalent despite their pharmacokinetic non-comparability. This statement should be verified in further studies in neutropenic patients where the product is tested in the pathologic condition for which it is indicated.

The introduction of ‘biogenerics’ to the market is a controversial matter nowadays. The use of comparability data to support therapeutic equivalence is not currently accepted by default by many regulatory agencies for follow-on biologic products. However, guidelines have been issued that consider this possibility on a case-to-case basis. In fact, the US FDA has guidance documents on that subject as for 1996 [38]; the International Conference on Harmonization released a guideline [39], which has been adopted by the European Agency and the FDA. Therefore, the regulatory agencies accept the possibility of interchangeability of biologically derived products, mostly when they are highly purified and characterized molecules. In that sense, some examples exist already in the market such as different insulins, somatotrophins and CHO cells-derived interferon beta from different manufacturing sites [11, 12].

Two recombinant G-CSF molecules could be similar from the physicochemical viewpoint, but there is always the possibility that differences in producing strains and/or manufacturing processes turn out into small differences in composition (i.e. glycosylation pattern, host contaminants, etc.) that could have a clinical impact on either safety or efficacy. The reference formulation used in this trial has been used in the clinics for several years and substantial information concerning its safety and efficacy in neutropenic patients has been gathered. The possibility that a ‘biogeneric’ G-CSF reaches the market is an attractive alternative in order to expand its use, given the high prices that the proprietary drugs have. These results suggest that both formulations can be considered as clinically comparable, according to their pharmacokinetic, pharmaco-
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