A Randomized Phase II Study of the Efficacy, Safety and Cost-Effectiveness of Pegfilgrastim and Filgrastim After Autologous Stem Cell Transplant for Lymphoma and Myeloma (PALM Study)

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Abstract

Purpose

This multicenter randomized study evaluated the effect on duration of febrile neutropenia (FN), the safety and cost-effectiveness of a single subcutaneous pegfilgrastim injection compared with daily injections of filgrastim after peripheral blood stem cell transplantation in patients receiving high dose chemotherapy for myeloma and lymphoma.

Patients and methods

Patients were randomly assigned to a single dose of pegfilgrastim at day 5 (D5) or daily filgrastim from D5 to the recovery of absolute neutrophil count (ANC) to 0.5G/L. Duration of FN, of neutrophil and platelet recovery, length of hospitalization, incidence of infectious events, transfusion and antibiotic requirements were the endpoints of the study. Costs were calculated from D0 until transplant unit discharge. The incremental cost-effectiveness ratio (ICER) of pegfilgrastim was expressed as the cost per day of FN prevented. Probabilistic sensitivity analysis was performed by nonparametric bootstrap methods.

Results

Between October 2008 and September 2009, ten centers enrolled 151 patients: 80 with lymphoma and 71 with myeloma. Pegfilgrastim and filgrastim were similar for all efficacy and safety endpoints. The mean duration of FN was 3.07 days (SD 1.96) in the pegfilgrastin arm and 3.29 (SD 2.54) in the filgrastim one. Mean total costs were 23,256 euros and 25,448 euros for pegfilgrastim and filgrastim patients respectively.

There was a 62% probability that pegfilgrastim was both more effective and less expensive overall than filgrastim.

Conclusions

Pegfilgrastim after PBSC transplantation in myeloma and lymphoma is safe, effective and cost-effective when compared with filgrastim and could represent a cost-effective alternative in this setting.

Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (HDC-SCT) is an established treatment that improves outcome in certain patients with lymphoma and multiple myeloma[1-4]. Post-transplant Granulocyte Colony-Stimulating Factor (G-CSF) such as filgrastim accelerates neutrophil engraftment and reduces duration of hospitalization and medical costs. It has been approved in Europe as well as in the ASCO guidelines[5] 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.

Pegylation of filgrastim decreases plasma clearance and increases its half-life without loss of clinical activity[6;7]. A single dose of pegfilgrastim seems as effective as many daily doses of filgrastim in cancer patients treated by conventional dose chemotherapy[8-11]. A single dose of pegfilgrastim significantly improves neutrophil recovery following autologous bone marrow transplantation in Rhesus macaques[12].

The efficacy and tolerance of pegfilgrastim after HDC-SCT have been evaluated in non comparative studies[13-17]. All of them reported the feasibility of using pegfilgrastim in this setting and find that hematological reconstitution is similar when retrospectively compared with filgrastim. A decrease of the duration of febrile neutropenia (FN) was observed in one small randomized study in myeloma[18]. However, there have been no convincing prospective studies comparing pegfilgrastim and filgrastim in HDC followed by PBSC and the economic issues have not been adequately addressed. We therefore undertook a phase II, randomized controlled trial in order to evaluate the comparative efficacy of pegfilgrastim in

preventing FN and its tolerability after autologous PBSC transplantation for lymphoma and myeloma. Extensive data on use of resources were collected in order to perform a comparative economic evaluation.

Methods

Patients

Eligible patients had to be at least 18 years old, with a diagnosis of myeloma or lymphoma requiring HDC-SCT. Conditioning was achieved without total body irradiation. Patients undergoing a second HDC-SCT were eligible if their first such treatment was more than 100 days preceding enrolment. All patients had to have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, a platelet count $\geq 100 \times 10^9$/L and at least 2×10^6 cryopreserved CD34 cells/kg before conditioning. Patients were hospitalized in the participating center during treatment and until their ANC reached $>0.5 \times 10^9$/L. Patients were not eligible if they had an acquired immunodeficiency syndrome or a known intolerance to any component of the G-CSF administered. All patients gave written informed consent before any study-related tests were performed.

Study design

This study was a multicenter, open-label, not blinded, randomized phase II to assess the safety, efficacy and cost-effectiveness of a single pegfilgrastim injection *versus* daily filgrastim injections.

Study drugs and G-CSF treatment procedures

Pegfilgrastim (Neulasta® – AMGEN Europe B.V.) and filgrastim (Neupogen® – AMGEN Europe B.V.) are produced by recombinant DNA technology and are

expressed in *Escherichia coli*. Pegfilgrastim comprises the protein filgrastim to which a 20-kDa polyethylene-glycol (PEG) molecule is covalently bound.

Pegfilgrastim and filgrastim were administered subcutaneously; Pegfilgrastim was given as a single 6mg injection 5 days after the PBSC reinfusion. Filgrastim was given at 5µg/kg/day from day 5 post-transplantation until resolution of neutropenia (ANC $>0.5x10^9$/L). Supportive care was provided according to the standard procedures of each participating institution.

Study data collection

Patients were screened during the week preceding transplantation. They were randomized immediately after having undergone autologous hematopoietic stem cell transplantation (D0). Patients were followed up from D0 to D100±10.

Clinical data: Complete blood counts (CBCs) were performed daily during hospitalization, twice weekly after hospitalization until platelet and neutrophil recovery (respectively $>100x10^9$/L and $>1.5x10^9$/L), then every two weeks and at D100±10. Patients' temperature was taken four times daily (at intervals of at least four hours) from D0 to the end of the first period of hospitalization. Use of anti-infectives was recorded from medical reports during the first period of hospitalization and from patients' note books at each subsequent visit. Transfusions were recorded from medical reports from D0 to the end of the study. Grade ≥3 adverse events (AE), related or not to the study drugs, were assessed using NCI-CTCAE v.3.0.

Economic data: Alongside the clinical trial, data on consumption of resources (length of hospital stay, number of transfusions, quantity of anti-infectives and G-CSFs

administered) were collected prospectively from D0 until discharge from the bone marrow unit.

The cost of hospital resources was taken as the mean unit cost across the 10 participating centers. For each patient, lengths of stay were multiplied by the daily unit cost, which covered personnel, medications (except growth factors and anti-infectious therapies), medical devices, laboratory tests, depreciation of equipment and overheads. The prices of anti-infectives and the G-CSFs were taken as the mean purchase price for the centres involved. Transfusions were costed according to the official 2009 French tariffs[19]. Center effect was tested by the calculation, for both arms, of the mean of the average total costs of each center. All costs are presented in 2009 euros (2009 annual exchange rate: 1.39 US dollar/euro).

Sample size

The primary endpoint was the mean duration of FN defined as an ANC <0.5 G/L and temperature >38°C at least once a day. Assuming a mean duration of FN of 4 days (standard deviation (SD) 3.7), 75 patients were needed in the pegfilgrastim arm in order to estimate the mean duration of FN with a precision of 0.85 day anda two-sided 95% confidence interval. Given a 1:1 randomisation ratio, a total of 150 patients had to be included in the study. Randomization, stratified by pathology (myeloma *vs* lymphoma) and participating center, used a block method (with block size of 2 and 4) and was centralized by way of a specific website.

No formal comparison between arms was planned for the primary endpoint. The randomization was intended to afford a substantial degree of reassurance that the control value chosen to plan the sample size was appropriate.

Statistical analyses

All analyses were performed in the intent-to-treat population, which included all randomly assigned patients. Baseline characteristics of the two arms were described and compared using the non parametric Wilcoxon rank sum test or Fisher's exact test to verify that treatment groups were well-balanced.

Clinical outcomes

The mean duration of FN (the primary outcome was calculated for each arm with its 95% confidence interval and was adjusted for potential imbalance in baseline characteristics in multivariate analysis.

Secondary endpoints included the duration of treatment in the filgrastim arm, the duration of hospitalization from stem cell transplantation, the duration of neutropenia, thrombopenia and fever (defined as temperature >38°C once or more per day) and the number of red blood cell and platelet transfusions. They are presented for each arm as mean and SD.

Toxicity profiles (grade ≥ 3 adverse events, related or not to the study drugs) and the occurrence of documented infections are also reported as frequencies and percentages.

All clinical statistical analyses were performed using SAS software (version 9.2 SAS institute, Cary, NC).

Economic outcomes

Cost-effectiveness analysis: The ICER, defined as $\frac{\overline{C}_{pegfi\lg rastim} - \overline{C}_{fi\lg rastim}}{\overline{E}_{pegfi\lg rastim} - \overline{E}_{fi\lg rastim}}$, was determined on the basis of the mean total costs in pegfilgrastim *vs* filgrastim arms. The efficacy outcome used was the mean duration of FN from D0 until discharge

from the bone marrow unit. The ICER was expressed as the cost per day of FN prevented.

Sensitivity analysis: One-way sensitivity analyses were conducted by varying across the range of the purchase prices of pegfilgrastim and filgrastim paid by the participating centers. The uncertainty surrounding the ICER was captured by a probabilistic sensitivity analysis. One thousand replications were obtained by nonparametric bootstrap methods. A graphical representation of the sampling uncertainty associated with the ICER on the cost-effectiveness (CE) plane is shown in figure 1. The four quadrants of the CE plane are as follows: northeast, i.e pegfilgrastim more costly and more effective than filgrastim; southeast (pegfilgrastim less costly, more effective); northwest (more costly, less effective) and southwest (less costly, less effective). The probability that the true ICER falls in each quadrant was expressed as a percentage. Confidence regions were assessed and are represented by ellipses. The outer ellipse defines the confidence region at the 95% level, and the inner ellipse at the 50%level[20]. All economic analyses were performed using STATA software (version 10.0) and Gauss software (version 9.0).

Results

Patient characteristics

From October 2008 to September 2009, 151 patients were enrolled by ten French centers (80 patients with lymphoma and 71 patients with myeloma). All patients except one were evaluable for the primary outcome. Patient characteristics at baseline are summarized in **Table 1**. Disease characteristics, treatment history,

conditioning protocols and number of stem calls reinfused were similar in the two groups. Median age was greater in the pegfilgrastim arm (59 years *vs* 55, Wilcoxon test, p = 0.021).

Efficacy

In the filgrastim arm, the median number of treatment days was 7 (range 4 to 15 days.) In the pegfilgrastin arm, there was a mean of 3.07 days of FN (SD 1.96) compared with a mean of 3.29 (SD 2.54) in the filgrastim arm. After adjustment for age, the mean values were 3.00 days (SD 2.27) and 3.35 days (SD 2.26) respectively. In the pegfilgrastin arm, among 39 patients with lymphoma, FN occurred in 38 (97.4%) with a mean duration of 3.49 days (SD 1.92]). FN occurred in 36 of the 40 lymphoma patients (90.0%) in the filgrastim arm, with a mean duration of 4.15 days (sd 2.85). Of patients with myeloma, 31 of 35 (88.6%) experienced FN in the pegfilgrastim arm, with a mean duration 2.60 days (SD 1.93). The corresponding figures in the filgrastim arm were 30 of 36 patients (83.3%), with a mean duration of 2.33 days (SD 1.72).

Table 2 shows related outcomes according to therapy arm.

Blood lymphocyte counts at D100 were similar in the two arms: 1.23G/L (SD 0.64) for pegfilgrastim versus 1.28G/L (SD 0.76)) for filgrastim even when analyzed in subgroups (1.23G/L (SD 0.69) *vs* 1.29G/L (SD 0.90) and 1.24G/L (SD 0.59) *vs* 1.26G/L (SD 0.59) for lymphoma and myeloma respectively).

Toxicity

No grade 3 or 4 adverse event related to pegfilgrastim or filgrastim were reported. A comparable rate of grade 3 or 4 chemotherapy related toxicity events was reported (52% in the pegfilgrastim arm and 52.6% in the filgrastim arm). Severe mucositis was observed in 25% of patients receiving pegfilgrastim versus 20% for those receiving filgrastim. Four patients died: one from pneumonia at D39 in the pegfilgrastim arm and three in the filgrastim arm (deaths at D120 from cardiorespiratory failure, at D65 from neuropathy with tetraplegia and respiratory failure and at D45 from pneumonia and pulmonary embolism). No death was related to the study drugs.

Costs

Table 3 reports the costs according to study treatment from D0 to discharge from the transplant unit. Mean total costs reached €23,256 ($32,326) and €25,448 ($35,373) for pegfilgrastim and filgrastim arms respectively. Mean costs were also somewhat higher in the filgrastim arm when broken down into costs for hospitalisation, for transfusions, for use of anti-infectives, and for growth factors. Mean total costs weighted according to patient inclusion rate by centers, i.e. centers effect, were €22,978 ($31,939) and €26,075 ($36,244) for pegfilgrastim and filgrastim arms respectively (Wilcoxon test, $p = 0.414$).

Incremental cost-effectiveness ratio

Based on the primary endpoint of FN, economic analysis suggested that pegfilgrastim was less costly and more effective than filgrastim, i.e. pegfilgrastim strictly dominates filgrastim (**Table 4**). When handling uncertainty, since the origin of the cost-effectiveness plane was included in the inner 95% confidence ellipse, the probabilistic sensitivity analysis did not allow to conclude this with certainty

(**Figure 1**).However, as Figure 1 also shows, the probability that the true ICER fell in the southeast quadrant (i.e. pegfilgrastim is less costly and more effective compared to filgrastim) is 62%. The probability that pegfilgrastim is more effective and more costly than filgrastim is 8%; and the probability that it is less effective and less costly 22%. The probability that pegfilgrastim is less effective and more costly than filgrastim is only 6%. Taking into account the minimum and maximum prices of pegfilgrastim paid by participating centres did not change the study's conclusions.

Discussion

Despite many randomized controlled trials[21-27], the use of myeloid growth factors in the post-transplant setting remains controversial. Indeed, while the ASCO guidelines strongly recommend their systematic use at D1 or D5 from the date of PBSC reinfusion[5], this strategy is not accepted in the recent ESMO guidelines[28]. Although involving only small numbers of patients, most conclude that the use of G-CSF hastens neutrophil recovery, shortens hospital stay by 1 to 2 days and decreases the rate of documented infections. Other clinical outcomes such as need for transfusion and antibiotics are not significantly influenced. The absence of convincing health economic and quality of life studies contributes to the difficulties in interpreting these data. However, most physicians consider that the additional costs related to G-CSF are probably largely balanced by a shorter duration of hospitalization and reduced risk for patients.

With a longer half life, a single dose of pegfilgrastim is as effective as repeated doses of filgrastim in reducing the duration of neutropenia in cancer patients including those experiencing intensive chemotherapy prior to PBSC transplantation. In recent studies

of autologous stem cell transplantation for myeloma[29;30] and lymphoma[31], pegfilgrastim is associated with more rapid engraftment and shorter hospitalization when compared with a historical cohort of patients treated with filgrastim.

To date, four randomized controlled trials[18;32-34] had compared pegfilgrastim *versus* filgrastim in the post-transplant setting. They included between 37 and 101 patients with lymphoma or myeloma. In all of them growth factors started at D1. Pegfilgrastim and filgrastim produced similar results on the main outcomes. No prospective cost-effectiveness analysis was performed. In one study, only the costs of growth factors were considered[33].

The present study is a large, multicentre, randomized trial including 150 patients undergoing autologous transplantation for myeloma or lymphoma. Based on previous data and usual policy in participating institutions, pegfilgrastim or filgrastim were started at D5 after the PBSC reinfusion [35;36]. Our results confirm the feasibility, safety and efficacy of this strategy and shows that use of the two agents leads to comparable results on the main outcome measures. No severe side effect related to the drugs was observed.

We did not observe any difference in the late lymphocyte reconstitution in the pegfilgrastim arm as had been suggested in a small nonrandomized study in myeloma[15]. A low D15 lymphocyte count in patients transplanted for lymphoma would be associated with a poorer survival[37]. More biological data are needed to compare the kinetics of immune reconstitution with the two drugs and to identify any potentially clinically important differences.

This prospective cost-effectiveness analysis of pegfilgrastim *versus* filgrastim is the first based on a randomized interventional study. Despite the recommendation that cost-benefit analysis be part of trials, this is rarely done, and had not before been included in any study of HDC-SCT and not had been addressed until now for HDC followed by PBSC;.even if the User's Guide to the Medical Literature suggests that costs should be considered in the application of all study result[38]]. As Allan et al. shows based on 6 majors general medical journal (188 randomised controlled trials (RCTs)), health care cost were mentioned in only 28% of RCTs of pharmaceutical therapy[39]. Our data suggest with a quite high probability that pegfilgrastim dominates filgrastim for the primary endpoint of the trial. These results complement those of studies that have examined both G-CSF strategies in patients undergoing standard chemotherapy where pegfilgrastim has a favourable ICER and position in the cost-effectiveness plane. In the study of Lyman et al in patients with aggressive non Hodgkin lymphoma, the ICER of pegfilgrastim versus 6-day filgrastim as primary prophylaxis was $2,167 per FN event avoided. The cost per Quality Adjusted Life Year (QALY) varied from $1,677 to $6,190 depending on the assumptions of the model[40]. Moreover, Eldar-Lissai et al. also showed in adult cancer patients receiving chemotherapy that pegfilgrastim dominates filgrastim: the mean cost saving associated with pegfilgrastim was $2,195 and the mean difference in effectiveness 0.269 Quality Adjusted Life Day (QALD)[41]. Pegfilgrastim has been also evaluated on an outpatient basis for autologous transplantation in 38 patients with myeloma[42]. This approach is feasible, safe and associated with a rehospitalisation rate of only 12%. Further clinical trials are needed to identify a well-defined subset of patients who might be safely considered for transplant on an outpatient basis with

pegfilgrastim support. A single injection is associated with optimum compliance, a saving in nurses' time and less inconvenience for patients.

As this study was based on French costs data, results are relevant within the French health care system. Then, before the routine use of pegfilgrastim in the setting of autologous transplantation, further health economics, quality of life and biologic studies are needed.

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Table 1: Characteristics of the 151 patients

	Pegfilgrastim arm	Filgrastim arm
Number of patients	75	76
Median age (range)	59 (19-73)	55 (20-75)
Sex (M/F)	45/30	41/35
Disease, n (%)		
Multiple myeloma	35 (47)	36 (47)
Non-Hodgkin lymphoma	33 (44)	32 (42)
Hodgkin lymphoma	7 (9)	8 (11)
ABMT indication, n (%)		
First line	37 (49)	39 (51)
Second line	32 (43)	29 (38)
> 2nd line	6 (8)	8 (11)
Disease status, n (%)		
CR or near CR	29 (39)	30 (39)
PR	35 (47)	46 (61)
SD or PD	4 (5)	0 (0)
Not evaluable	7 (9)	0 (0)
Conditioning regimen, n (%)		
Melphalan	30 (40)	34 (45)
BEAM	33 (44)	32 (42)
Zevaline/BEAM	6 (8)	4 (5)
Others	6 (8)	6 (8)
Median CD34 reinfused 10^6 / kg (range)	3.63 (1.3-15)	3.72 (1.2-29)
Prior transplantation, n (%)	9 (12)	7 (9)

Table 2. Primary endpoint and related variables

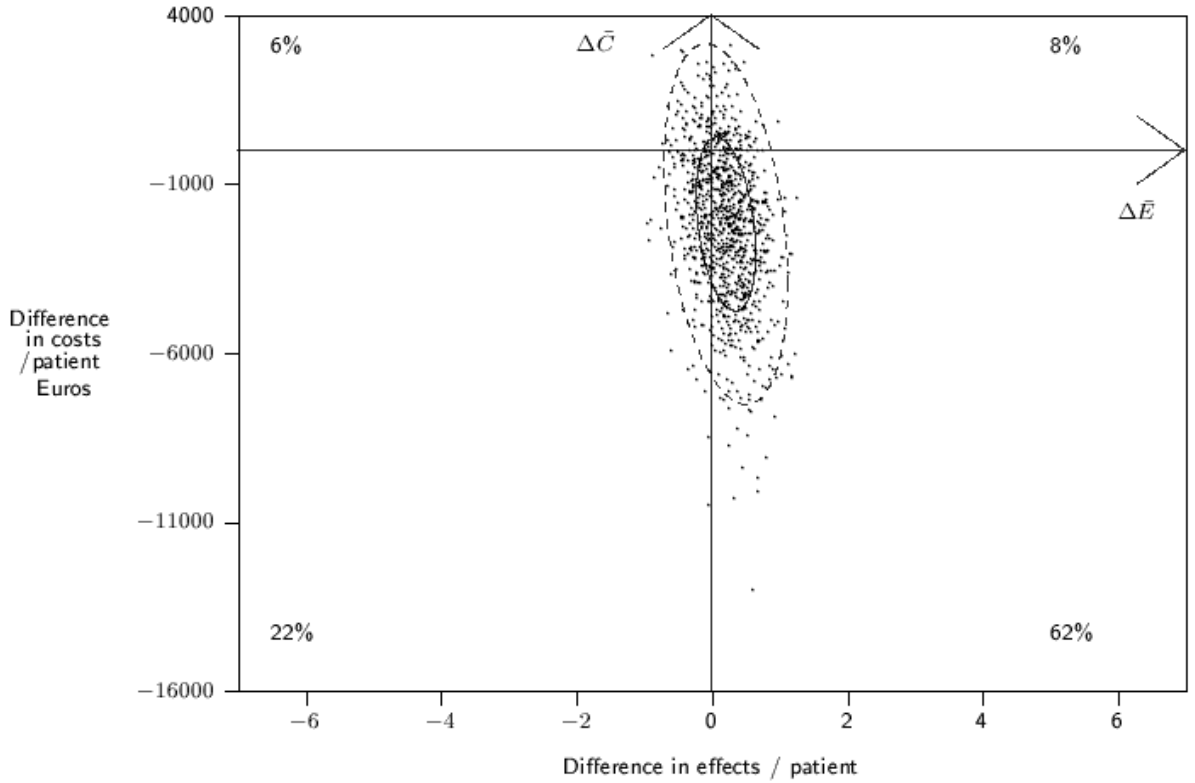
	Pegfilgrastim arm				Filgrastim arm			
	Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
Mean days of febrile neutropenia	3,07	1,96	0,00	8,00	3,29	2,54	0,00	10,00
Day of ANC <0.5g/l	7,43	3,96	3,00	31,00	7,17	2,94	2,00	17,00
Days of ANC < 1g/l	10,05	6,50	5,00	38,00	11,99	8,81	4,00	51,00
Days with platelets < 20g/l	3,19	4,14	0,00	25,00	3,61	7,79	0,00	62,00
Days with fever	5,65	4,21	0,00	18,00	7,12	7,51	0,00	40,00
Number of Red Blood Cell transfusions	2,01	2,51	0,00	14,00	2,57	5,55	0,00	45,00
Number of platelet transfusions	3,43	3,49	1,00	24,00	3,99	7,64	0,00	62,00
Duration of hospital stay since reinjection of stem	15,48	4,82	11,00	40,00	16,64	9,54	11,00	67,00
Days of antibiotic therapy	5,42	6,11	0,00	40,00	9,86	34,90	0,00	286,00
	n		%		n		%	
Number of patients with Red Blood Cell transfusions	46		61,3		45		60,8	
Number of patients with platelets transfusions	75		100		72		97,3	
Number of documented infections								
at least 1 infection	73		97,3		73		96,1	
Fever of unknown origin	47		64,38		47		64,38	
Infection with no identified germ without fever	13		17,8		19		26,03	
Infection with identified germ with or without	37		50,68		37		50,68	

Table 3. Costs of treatment alternatives

Costs (in € 2009)	Pegfilgrastim (n=74)				Filgrastim (n=76)			
	Mean	(SD)	Min	Max	Mean	(SD)	Min	Max
Hospitalisation	20,725	(6,427)	14,695	53,436	22,236	(12,748)	14,695	89,505
Transfusion	1,029	(1,017)	216	7,752	1,312	(2,596)	0	21,642
Anti infectious	863	(1,368)	6	6,663	1,138	(2,828)	0	20,141
Antifungal	471	(1,156)	0	6,217	774	(2,433)	0	16,576
Antibiotics	340	(397)	0	2,004	311	(479)	0	3,531
Antiviral	52	(51)	0	278	53	(46)	0	296
Growth factors	639	(89)	629	1,396	762	(230)	262	1,396
Total	23,256	(7,897)	15,871	64,726	25,448	(17,077)	16,180	131,986

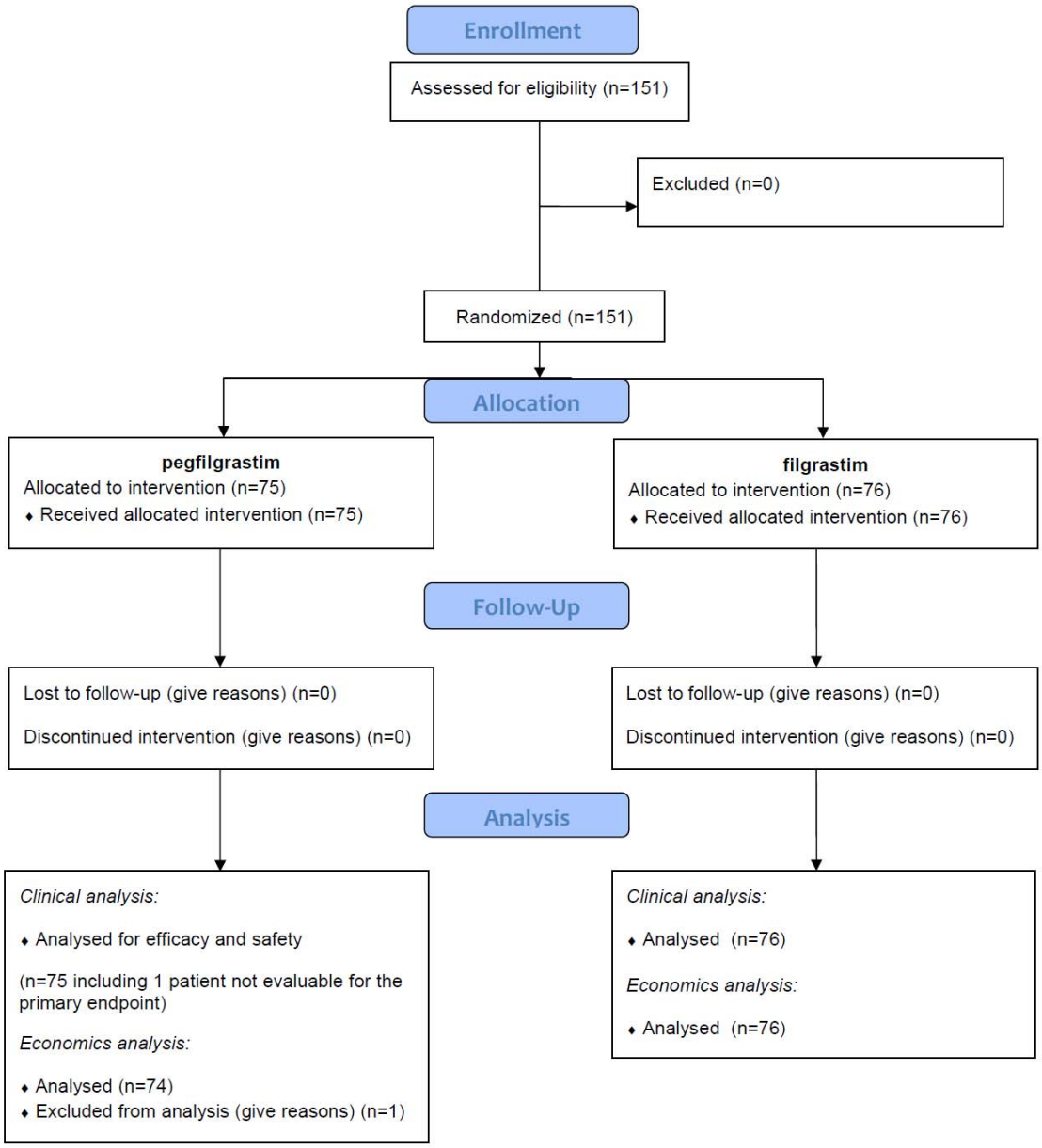
Table 4. Incremental cost-effectiveness analysis comparing treatment alternatives

Intervention	Costs (€, 2009)	Effectiveness (days with FN)	Incremental cost (ΔC)	Incremental effectiveness (ΔE)	ICER (ΔC/ΔE)
Pegfilgrastim	23,256	3.07	_	_	
Filgrastim	25,448	3.29	2,192	-0.22	Dominated



$\Delta\bar{C}$ is the difference in average total costs. $\Delta\bar{E}$ is the difference in average effectiveness. The scatter of points corresponds to 1000 nonparametric bootstrap replications of the pairs $(\Delta\bar{C}, \Delta\bar{E})$. In each quadrant, the percentages quantify the probability that the true incremental cost-result ratio is in the quadrant. The external ellipse defines the confidence region at level 95%, and the internal ellipse that of level 50%.

Figure 1: Probabilistic analysis of the ICER: scatter of points and confidence ellipses


Enrollment
Assessed for eligibility (n=151)
Excluded (n=0)
Randomized (n=151)
Allocation
pegfilgrastim
Allocated to intervention (n=75)
♦ Received allocated intervention (n=75)
filgrastim
Allocated to intervention (n=76)
♦ Received allocated intervention (n=76)
Follow-Up
Lost to follow-up (give reasons) (n=0)
Discontinued intervention (give reasons) (n=0)
Lost to follow-up (give reasons) (n=0)
Discontinued intervention (give reasons) (n=0)
Analysis
Clinical analysis:
♦ Analysed for efficacy and safety
(n=75 including 1 patient not evaluable for the primary endpoint)
Economics analysis:
♦ Analysed (n=74)
♦ Excluded from analysis (give reasons) (n=1)
Clinical analysis:
♦ Analysed (n=76)
Economics analysis:
♦ Analysed (n=76)

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