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Committee for Medicinal Products for Human Use CHMP)

Neulasta

pegfilgrastim

Procedure No EMEA/H/C/420/Article 45 051

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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INTRODUCTION

On 13 February 2008, the MAH submitted one completed paediatric study for Neulasta / Neupopeg (pegfilgrastim), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The clinical expert statement included in the renewal application in April 2007 briefly mentioned that a phase 2 paediatric clinical study data should be submitted as soon as it is available.

On 24 July 2008, the CHMP requested additional clarifications, which were submitted by the MAH in November 2008.

In addition, on 03 October 2008, the MAH also submitted the publication of an investigator-sponsored paediatric study (Wendelin at al, 2005).

No expert overview and no additional documentation were provided. The MAH did not propose any consequential regulatory action.

This assessment report relates to both submissions.

SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the clinical studies

Neulasta and Neupopeg are brand names for pegfilgrastim presented as 6mg/0.6ml solution for injection (10mg/ml) in either a pre-filled syringe or a pre-filled pen. Pegfilgrastim is a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) and monomethoxypolyethylene glycol that regulates the production and release of functional neutrophils from bone marrow.

There are no paediatric formulations for filgrastim or pegfilgrastim. For the trial, pegfilgrastim was packaged as single-use vials containing a 10mg/ml solution and filgrastim as single-use vials containing a 3mg/ml solution.

Non-clinical aspects

Not Applicable

Clinical aspects

Introduction

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

Until the presented study was undertaken, pegfilgrastim, with the decreased number of injections, was not available to paediatric patients. This study was designed to determine whether a single dose of pegfilgrastim per chemotherapy cycle was as effective and safe as daily filgrastim in paediatric subjects with sarcoma who were receiving myelosuppressive chemotherapy and to establish the appropriate

pegfilgrastim dose for the reduction of severe neutropenia in paediatric subjects. The clinical hypothesis of this study was that a single dose of pegfilgrastim per chemotherapy cycle in paediatric subjects with sarcoma who were receiving VAdriaC/IE chemotherapy would result in a duration of severe neutropenia, absolute neutrophil count (ANC) recovery profile, and safety profile similar to that observed with daily administration of filgrastim.

The MAH submitted one report for Study 990130: A study of single-dose-per-cycle filgrastim-SD/01 as an adjunct to VAdriaC/IE chemotherapy in paediatric sarcoma patients. The study was performed by Amgen in the United States and Australia.

Clinical study

Description

This was a multicenter, randomized, open-label study, in which paediatric subjects with sarcoma were randomized in a 6:1 allocation to receive either a single dose of pegfilgrastim 100 µg/kg or daily doses of filgrastim 5 µg/kg after the completion of VAdriaC/IE chemotherapy.

The study was divided into 2 parts. In part 1 of the study, 3 subjects were enrolled to receive 100 µg/kg pegfilgrastim to evaluate the safety of this dose in paediatric subjects. After establishing an acceptable safety profile in these 3 subjects, part 2 of the study was initiated. In part 2, an additional 18 subjects were randomized and stratified into each of 3 age groups (0 to 5, 6 to 11, and 12 to 21 years) in the first dose cohort.

Methods

Objectives:

Primary

The primary objective of this study was to assess the ANC profile after myelosuppressive chemotherapy followed by a single dose of pegfilgrastim or daily doses of filgrastim in paediatric subjects with sarcoma.

Secondary

The secondary objectives were the following:

• Assess the pharmacokinetic profile of a single dose of pegfilgrastim or daily filgrastim administered after myelosuppressive chemotherapy in paediatric subjects with sarcoma.

• Assess the safety profile of single dose administration of pegfilgrastim or daily filgrastim following myelosuppressive chemotherapy in paediatric subjects with sarcoma.

Diagnosis and main criteria for inclusion:

Inclusion Criteria

Eligible subjects had signed the informed consent form and met the following criteria:

• 0 to 21 years of age, inclusive

• confirmed sarcoma (including primitive peripheral neuroectodermal tumors)

• life expectancy of > 6 weeks with appropriate therapy

• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

• adequate renal and liver function (ie, < 2.5 times the upper limit of normal), including blood urea nitrogen (BUN), serum creatinine, total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)

• ANC ≥ 1 x 10 9/L and platelets ≥ 100 x109/L

Exclusion Criteria

Subjects were ineligible for the study if they fulfilled any of the following criteria:

• bone marrow involvement

• major surgery within two weeks prior to enrolment

• previous radiotherapy or chemotherapy

• evidence of hematologic malignancy or myelodysplasia, or other malignancies known HIV infection

• received antibiotics or anti-infectives for an active infection within the 72 hours before randomization

• received corticosteroids (oral or IV) or lithium within 1 week of study entry

• received cytokines within 2 weeks of initiation of chemotherapy or treatment with filgrastim within 1 week)

• concurrent enrolment in any other study with investigational drugs or devices

• psychiatric, addictive, or any disorder that compromises ability to give truly informed consent for participation in this study;

• known hypersensitivity to E coli-derived drugs (eg, filgrastim, HUMULIN® Insulin,

L-Asparaginase, HUMATROPE® Growth Hormone, INTRON® A)

• not using adequate contraceptive precautions

• girls of childbearing potential who were evidently pregnant (eg, positive human chorionic gonadotropin test) or breast feeding

• not available for follow-up assessment

• unable to comply with protocol procedures

Treatment

Subjects were randomized in a 6:1 ratio to receive 1 of the following 2 treatment assignments:

• single dose of pegfilgrastim 100 µg/kg approximately 24 hours after the completion of chemotherapy

• filgrastim 5 µg/kg/day beginning approximately 24 hours after completion of chemotherapy until ANC ≥ 10 x 10^9/L by day 21 of the chemotherapy cycle or until 24 hours before starting the next chemotherapy cycle

Duration of Treatment: Up to 12 weeks of treatment (subjects could receive up to

4 chemotherapy cycles, with each cycle expected to be 21 days), followed by follow-up visits at 1 and 3 months after the last on-study chemotherapy cycle, for a total of approximately 6 months on study per subject. At an expected accrual rate of 1 subject per month, the total study duration was expected to be approximately 4 years.

Study Endpoints

Pharmacodynamic/Efficacy:

• duration of severe neutropenia in cycles 1 and 3

• rates of febrile neutropenia by cycle and overall

• time to ANC recovery to ≥ 0.5 x 10^9/L in cycles 1 and 3

Pharmacokinetic:

• maximum observed serum concentration (Cmax)

• time to maximum observed serum concentration (tmax)

• area under the serum concentration time curve from time zero to the time of the last measurable concentration (AUC0-last)

• the area under the serum concentration time curve from time zero to infinity (AUC0-inf)

• the terminal half-life (t½)

• the apparent clearance after subcutaneous administration (CL/F)

Safety:

• the incidence of adverse events

Results

Recruitment/ Number analysed

Forty-four subjects were enrolled (n = 38 pegfilgrastim, 6 filgrastim) at 10 study centres in the United States and Australia. All but 1 subject received at least 1 dose of pegfilgrastim or filgrastim (37 pegfilgrastim, 6 filgrastim).

Thirteen subjects (12 pegfilgrastim, 1 filgrastim) were enrolled in the 0- to 5-year age group, 12 subjects (10 pegfilgrastim, 2 filgrastim) in the 6- to 11-year group, and 19 subjects (16 pegfilgrastim, 3 filgrastim) in the 12- to 21-year group.

All subjects who received at least 1 dose of investigational product were included in safety and efficacy analyses (37 pegfilgrastim, 6 filgrastim).

Sixty-three per cent of subjects in the pegfilgrastim group and 83% of subjects in the filgrastim group had 1 or more important protocol deviations. By subject incidence, the most common type of important protocol deviation was missing ANC, antibody, or pharmacokinetic data (55% pegfilgrastim, 50% filgrastim), followed by missed dose of investigational product (8% pegfilgrastim, 17% filgrastim), off-schedule study procedure (5% pegfilgrastim, 17% filgrastim), and eligibility violation (3% pegfilgrastim, 17% filgrastim).

Table 8-1. Subject Disposition (All Enrolled Subjects)

	Filgrastim	Pegfilgrastim	Overall Total
	5 µg/kg/day	100 µg/kg	
Enrolled	6	38	44
Received Investigational Product	6 (100%)	37 (97%)	43 (98%)
Cycles Started			
Cycle 1	6 (100%)	38 (100%)	44 (100%)
Cycle 2	4 (67%)	35 (92%)	39 (89%)
Cycle 3	4 (67%)	34 (89%)	38 (86%)
Cycle 4	3 (50%)	32 (84%)	35 (80%)
Early Termination of Investigational Product	3 (50%)	5 (13%)	8 (18%)
Treatment completed	3 (50%)	32 (84%)	35 (80%)
Study completed	3 (50%)	31 (82%)	34 (77%)

Table 8-2. Subject Disposition – Protocol-defined Age Groups (All Enrolled Subjects)

	Filgrastim	Pegfilgrastim	Overall Total
	5 µg/kg/day	100 µg/kg	
0 – 5 years			
Enrolled	1	12	13
Received Investigational Product	1 (100%)	12 (100%)	13 (100%)
Cycles Started			
Cycle 1	1 (100%)	12 (100%)	13 (100%)
Cycle 2	1 (100%)	12 (100%)	13 (100%)
Cycle 3	1 (100%)	11 (92%)	12 (92%)
Cycle 4	1 (100%)	10 (83%)	11 (85%)
Early Termination of Investigational Product	0 (0%)	2 (17%)	2 (15%)
Treatment completed	1 (100%)	10 (83%)	11 (85%)
Study completed	1 (100%)	10 (83%)	11 (85%)
6 – 11 years			
Enrolled	2	10	12
Received Investigational Product	2 (100%)	10 (100%)	12 (100%)
Cycles Started			
Cycle 1	2 (100%)	10 (100%)	12 (100%)
Cycle 2	1 (50%)	10 (100%)	11 (92%)
Cycle 3	1 (50%)	10 (100%)	11 (92%)
Cycle 4	1 (50%)	9 (90%)	10 (83%)
Early Termination of Investigational Product	1 (50%)	1 (10%)	2 (17%)
Treatment completed	1 (50%)	9 (90%)	10 (83%)
Study completed	1 (50%)	9 (90%)	10 (83%)
12 – 21 years			
Enrolled	3	16	19
Received Investigational Product	3 (100%)	15 (94%)	18 (95%)
Cycles Started			
Cycle 1	3 (100%)	16 (100%)	19 (100%)
Cycle 2	2 (67%)	13 (81%)	15 (79%)
Cycle 3	2 (67%)	13 (81%)	15 (79%)
Cycle 4	1 (33%)	13 (81%)	14 (74%)
Early Termination of Investigational Product	2 (67%)	2 (13%)	4 (21%)
Treatment completed	1 (33%)	13 (81%)	14 (74%)
Study completed	1 (33%)	12 (75%)	13 (68%)

Baseline data

The mean age was 9.8 years (SD 5.7 years) in the pegfilgrastim group and 10.8 years (SD 5.1 years) in the filgrastim group. In the pegfilgrastim group, 68% of subjects (28 boys) were male and 32% were female (16 girls).

In the filgrastim group, 33% of subjects were male and 67% were female. Most subjects in both treatment groups were white (79% pegfilgrastim, 83% filgrastim). Mean ANC at baseline was similar in the pegfilgrastim and filgrastim groups (5.018 x 10^9/L and 4.832 x 10^9/L, respectively).

Table 8-5. Summary of Demographics and Baseline Characteristics (All Subjects)

	Filgrastim 5 µg/kg/day (N=6)	Pegfilgrastim 100 µg/kg (N=38)
Sex		
Male	2 (33%)	26 (68%)
Female	4 (67%)	12 (32%)
Age (years)		
n	6	38
Mean	10.8	9.8
SD	5.1	5.7
Median	11.0	10.5
Q1, Q3	7.0, 14.0	5.0, 15.0
Min, Max	4, 18	0, 21
Race		
Asian	0 (0%)	0 (0%)
Black	0 (0%)	3 (8%)
Hispanic	1 (17%)	4 (11%)
Native American	0 (0%)	0 (0%)
Caucasian	5 (83%)	30 (79%)
Other	0 (0%)	1 (3%)
Baseline Weight (kg)		
n	6	38
Mean	46.29	42.19
SD	25.59	24.78
Median	46.65	44.55
Q1, Q3	20.05, 61.80	20.70, 54.00
Min, Max	17.8, 84.8	7.9, 119.2
Baseline ANC ($x10^9$/L)		
n	6	38
Mean	4.832	5.018
SD	1.896	2.913
Median	3.957	4.159
Q1, Q3	3.770, 5.256	2.886, 6.280
Min, Max	3.55, 8.50	1.27, 13.88

Table 8-6. Summary of Demographics and Baseline Characteristics – Protocol-defined Age Groups

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
0 – 5 years		
Sex		
Male	1 (100%)	10 (83%)
Female	0 (0%)	2 (17)
Age (years)		
n	1	12
Mean	4.0	3.1
SD	.	1.9
Median	4.0	4.0
Q1, Q3	4.0, 4.0	1.0, 5.0
Min, Max	4, 4	0, 5
Race		
Asian	0 (0%)	0 (0%)
Black	0 (0%)	1 (8%)
Hispanic	0 (0%)	0 (0%)
Native American	0 (0%)	0 (0%)
Caucasian	1 (100%)	11 (92%)
Other	0 (0%)	0 (0%)
Baseline Weight (kg)		
n	1	12
Mean	17.80	16.93
SD	.	6.03
Median	17.80	16.60
Q1, Q3	17.80, 17.80	11.65, 21.10
Min, Max	17.8, 17.8	7.9, 29.3
Baseline ANC ($x10^9$/L)		
n	1	12
Mean	3.810	4.938
SD	.	3.268
Median	3.810	4.005
Q1, Q3	3.810, 3.810	2.933, 6.119
Min, Max	3.81, 3.81	1.88, 13.88

Table 8-6. Summary of Demographics and Baseline Characteristics – Protocol-defined Age Groups

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
6 – 11 years		
Sex		
Male	0 (0%)	8 (80%)
Female	2 (100%)	2 (20%)
Age (years)		
n	2	10
Mean	8.0	9.4
SD	1.4	1.6
Median	8.0	10.0
Q1, Q3	7.0, 9.0	8.0, 11.0
Min, Max	7, 9	6, 11
Race		
Asian	0 (0%)	0 (0%)
Black	0 (0%)	1 (10%)
Hispanic	1 (50%)	1 (10%)
Native American	0 (0%)	0 (0%)
Caucasian	1 (50%)	7 (70%)
Other	0 (0%)	1 (10%)
Baseline Weight (kg)		
n	2	10
Mean	30.87	38.20
SD	15.31	11.09
Median	30.87	34.10
Q1, Q3	20.05, 41.70	33.50, 45.10
Min, Max	20.0, 41.7	20.7, 61.0
Baseline ANC ($x10^9$/L)		
n	2	10
Mean	6.302	4.159
SD	3.108	2.480
Median	6.302	3.696
Q1, Q3	4.104, 8.500	2.203, 6.280
Min, Max	4.10, 8.50	1.27, 8.91

Table 8-6. Summary of Demographics and Baseline Characteristics – Protocol-defined Age Groups

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
12 – 21 years		
Sex		
Male	1 (33%)	8 (50%)
Female	2 (67%)	8 (50%)
Age (years)		
n	3	16
Mean	15.0	15.2
SD	2.6	2.9
Median	14.0	15.0
Q1, Q3	13.0, 18.0	12.0, 17.5
Min, Max	13, 18	12, 21
Race		
Asian	0 (0%)	0 (0%)
Black	0 (0%)	1 (6%)
Hispanic	0 (0%)	3 (19%)
Native American	0 (0%)	0 (0%)
Caucasian	3 (100%)	12 (75%)
Other	0 (0%)	0 (0%)
Baseline Weight (kg)		
n	3	16
Mean	66.07	63.64
SD	17.01	20.06
Median	61.80	54.65
Q1, Q3	51.60, 84.80	51.40, 68.25
Min, Max	51.6, 84.8	46.2, 119.2
Baseline ANC ($x10^9$/L)		
n	3	16
Mean	4.193	5.615
SD	0.927	2.920
Median	3.770	5.304
Q1, Q3	3.552, 5.256	3.087, 7.320
Min, Max	3.55, 5.26	2.51, 12.99

CHMP comment

Number of studied patients is small and even smaller in each age subgroups.

Efficacy results

No consistent differences in the efficacy profile were observed between treatment groups.

In the first cycle of chemotherapy, the **mean duration of severe neutropenia** was 6.0 days in the pegfilgrastim group and 5.3 days in the filgrastim group, a difference that was neither clinically nor statistically significant.

Among subjects who received pegfilgrastim, the mean duration of severe neutropenia in cycle 1 was slightly longer in the younger age groups: 8.9, 6.0, and 3.7 days for subjects in the age groups of 0 to 5, 6 to 11, and 12 to 21 years, respectively.

In the third cycle of chemotherapy, the mean duration of severe neutropenia was 8.1 days in the pegfilgrastim group and 5.8 days in the filgrastim group. For the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the mean duration of severe neutropenia was 11.4, 9.0, and 4.7 days, respectively, for subjects who received pegfilgrastim.

The subject **incidence of febrile neutropenia** during cycle-1 chemotherapy was 57% in the pegfilgrastim group and 83% in the filgrastim group.

In the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the incidence of cycle-1 febrile neutropenia was 75%, 70%, and 33%, respectively, for subjects who received pegfilgrastim, and 100%, 50%, and 100%, respectively, for subjects who received filgrastim. The incidence of febrile neutropenia during cycle-3 chemotherapy was 44% in the pegfilgrastim group and 75% in the filgrastim group. In the age groups of 0 to 5, 6 to 11, and 12 to 21 years, the incidence of cycle-3 febrile neutropenia was 64%, 40%, and 31%, respectively, for subjects who received pegfilgrastim, and 100%, 100%, and 50%, respectively, for subjects who received filgrastim.

The **median time to ANC recovery** during the first cycle of chemotherapy was 14 days in both treatment groups. In the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the median times to ANC recovery were 15, 14, and 13 days, respectively, for subjects who received pegfilgrastim, and 16, 15, and 14 days, respectively, for subjects who received filgrastim.

In the third cycle of chemotherapy, the median time to ANC recovery was 14 days in the pegfilgrastim group and 15 days in the filgrastim group. In the age groups of 0 to 5, 6 to 11, and 12 to 21 years, the median times to ANC recovery were 17 days, 14 days, and 13 days, respectively, for subjects in the pegfilgrastim group, and 15, 17, and 15 days, respectively, for subjects in the filgrastim group.

Table 9-1. Duration of Severe Neutropenia in Cycle 1 (Efficacy Analysis Set With Protocol-specified Age Groups)

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
All Subjects in Efficacy Set		
Number of Subjects in Subset	6	37
Number of Subjects Started Cycle	6	37
Number (%) with Severe Neutropenia		
Yes	5 (83%)	35 (95%)
No	1 (17%)	2 (5%)
Duration of Severe Neutropenia (Days)		
N	6	37
Mean	5.3	6.0
Median	6.0	5.0
SD	3.1	3.9
Q1, Q3	4.0, 7.0	4.0, 7.0
Min, Max	0, 9	0, 24
Difference Between Filgrastim and Pegfilgrastim[a]		
Difference Between Means	-	0.67
SE of the Difference	-	1.69
95% Confidence Interval	-	(-2.75, 4.09)
0 to 5 years		
Number of Subjects in Subset	1	12
Number of Subjects Started Cycle	1	12
Number (%) with Severe Neutropenia		
Yes	1 (100%)	12 (100%)
No	0 (0%)	0 (0%)
Duration of Severe Neutropenia (Days)		
N	1	12
Mean	9.0	8.9
Median	9.0	8.0
SD	-	5.2
Q1, Q3	9.0, 9.0	6.5, 9.0
Min, Max	9, 9	4, 24

Severe neutropenia is the presence of observed or linearly interpolated ANC being $<0.5 \times 10^9$/L

[a] Differences calculated by subtracting the filgrastim mean duration of severe neutropenia from the pegfilgrastim mean duration of severe neutropenia.

Note: - indicates not applicable.

Table 9-1. Duration of Severe Neutropenia in Cycle 1 (Efficacy Analysis Set With Protocol-specified Age Groups)

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
6 to 11 years		
Number of Subjects in Subset	2	10
Number of Subjects Started Cycle	2	10
Number (%) with Severe Neutropenia		
Yes	1 (50%)	10 (100%)
No	1 (50%)	0 (0%)
Duration of Severe Neutropenia (Days)		
N	2	10
Mean	3.5	6.0
Median	3.5	6.0
SD	4.9	1.2
Q1, Q3	0.0, 7.0	5.0, 7.0
Min, Max	0, 7	4, 8
12 to 21 years		
Number of Subjects in Subset	3	15
Number of Subjects Started Cycle	3	15
Number (%) with Severe Neutropenia		
Yes	3 (100%)	13 (87%)
No	0 (0%)	2 (13%)
Duration of Severe Neutropenia (Days)		
N	3	15
Mean	5.3	3.7
Median	6.0	4.0
SD	1.2	2.2
Q1, Q3	4.0, 6.0	2.0, 5.0
Min, Max	4, 6	0, 7

Severe neutropenia is the presence of observed or linearly interpolated ANC being $<0.5x10^9/L$

[a] Differences calculated by subtracting the filgrastim mean duration of severe neutropenia from the pegfilgrastim mean duration of severe neutropenia.

Note: - indicates not applicable.

Table 9-5. Incidence of Febrile Neutropenia on Study (Efficacy Analysis Set)

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
Number of Subjects in Subset	6	37
Number (%) with Febrile Neutropenia		
Yes	5 (83%)	25 (68%)
No	1 (17%)	12 (32%)
Difference Between Filgrastim and Pegfilgrastim[a]		
Difference Between Percentages		-15.8
SE of the Difference		17.05
95% Confidence Interval[b]		(-50.2,18.67)
0 to 5 Years		
Number of Subjects in Subset	1	12
Number (%) with Febrile Neutropenia		
Yes	1 (100%)	10 (83%)
No	0 (0%)	2 (17%)
6 to 11 Years		
Number of Subjects in Subset	2	10
Number (%) with Febrile Neutropenia		
Yes	1 (50%)	8 (80%)
No	1 (50%)	2 (20%)
12 to 21 Years		
Number of Subjects in Subset	3	15
Number (%) with Febrile Neutropenia		
Yes	3 (100%)	7 (47%)
No	0 (0%)	8 (53%)

Febrile neutropenia was defined as the presence of ANC<0.5x10^9/L and oral or oral-equivalent temperature ≥ 38.2° C on the same day in a cycle
[a]Differences calculated by subtracting the Filgrastim FN percentage from the Pegfilgrastim FN percentage. Unknown is considered as no FN.
[b]Student t distribution approximation to Binomial distribution.

CHMP comment:

The primary objective was to assess the absolute neutrophil count (ANC) profile after myelosuppressive chemotherapy followed by single-dose administration of pegfilgrastim or daily filgrastim in paediatric subjects with sarcoma.

The mean (SD) duration of severe neutropenia was 6.0 (3.9) days in the pegfilgrastim group and 5.3 (3.1) days in the filgrastim group, a difference was neither clinically nor statistically significant. The mean duration of severe neutropenia in cycle-1 chemotherapy was longer in the younger age groups.

In cycle one the median duration of severe neutropenia was 3.5 days in the filgrastim arm and 6.0 days in the pegfilgrastim arm for the 6 to 11 years age group. But the number of subjects in the age group 6 to 11 years is small (2 subjects) in the filgrastim arm. Severe neutropenia seems to last longer in children compared to the pivotal study results in adults. The applicant is asked to comment.

Febrile neutropenia was also more frequent in pegfilgrastim arm (70%) compared to filgrastim arm (50%) in the same age group, but again the numbers are too small (one subject in the filgrastim arm) to draw definitive conclusions.

Incidence of febrile neutropenia in cycle 3 was more frequent in the filgrastim group in all age groups. Overall the incidence of febrile neutropenia was more common in the children compared to the results from earlier studies with adults. The applicant should comment on the difference between children and adults.

For all subjects in the efficacy set the median duration of severe neutropenia was 5.0 days in the pegfilgrastim group and 6.0 days in the filgrastim group in cycle one.

In the age group of younger children, the incidence of febrile neutropenia was more common compared to older children and adults in earlier studies. Also, duration of severe neutropenia was longer.

As the results might be dose-dependent in children, the CHMP recommends studying further the dose in children.

Pharmacokinetic results

Pharmacokinetic data were available for 36 subjects who received pegfilgrastim and 6 subjects who received filgrastim.

The maximum pegfilgrastim concentration was achieved approximately 24 hours postdose and was sustained until the ANC nadir occurred. As the ANC began to recover, the pegfilgrastim concentration declined rapidly.

During cycle 3, median exposures were lower than those in cycle 1 for each age group, potentially as a result of the expansion of neutrophils and neutrophils precursor mass with time. These observations are consistent with neutrophil-mediated clearance.

The pharmacokinetic profile was similar in the 2 older age groups and consistent with that in adults; the youngest age group appeared to have higher median exposure. The applicant presumes that the tendency toward a higher median exposure in the youngest age group may relate to the fact that these subjects had more severe neutropenia with a deeper ANC nadir and a longer duration of neutropenia, consistent with a neutrophil-mediated clearance mechanism.

Compared with the serum pegfilgrastim concentration profile, the median serum filgrastim concentration declined rapidly after the first dose. After repeated administration, the daily trough filgrastim concentration increased until the ANC nadir occurred and then decreased thereafter.

CHMP comment:

The youngest age group appeared to have higher median exposure. The company should be aware of the draft Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population

Safety results

Pegfilgrastim and filgrastim were well tolerated in the paediatric subjects enrolled in this study, with no consistent differences in the safety profiles observed between the treatment groups or across the protocol-specified age groups. The overall adverse event profile was generally consistent with the known effects and complications of cancer and its treatment. All subjects had 1 or more adverse events while on study.

Consistent with expectations for paediatric subjects with sarcoma who were receiving myelosuppressive chemotherapy, serious adverse events were relatively common, reported for 78% of subjects in the pegfilgrastim group and 83% of subjects in the filgrastim group. In the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the incidence of serious adverse events was 92%, 80%, and 67%, respectively, in the pegfilgrastim group and 100%, 50%, and 100%, respectively, in the filgrastim group. The incidence of serious adverse events was somewhat higher in the youngest age group (0 to 5 years) (92% pegfilgrastim, 100% filgrastim) than in the older age groups. This difference resulted primarily from a higher incidence of serious febrile neutropenia in the youngest age group (75% pegfilgrastim, 100% filgrastim), and it is not thought to be a treatment-related effect of pegfilgrastim or filgrastim.

It should be noted that the 0- to 5-year age group included only 1 subject who received filgrastim.

Most subjects (84% pegfilgrastim, 83% filgrastim) had 1 or more adverse events that were severe, life threatening, or fatal. Of these events, 1 was fatal (respiratory acidosis in a subject who received pegfilgrastim). One subject (3%) in the pegfilgrastim group withdrew because of an adverse event (disease progression).

Treatment-related adverse events were consistent with the known effects of pegfilgrastim and filgrastim and were reported for 22% of subjects who received pegfilgrastim and 33% of subjects who received filgrastim. Bone pain was the most common treatment-related adverse event (11% pegfilgrastim, 17% filgrastim). Treatment-related adverse events were primarily mild or moderate in severity. One subject in the pegfilgrastim group had serious adverse events (tachycardia, *Clostridium difficile* colitis, abdominal distension, and tachypnoea) that were considered by the investigator to be related to treatment.

No consistent differences were noted across the treatment or age groups in laboratory results.

Ten of 41 subjects (24%) tested positive for pre-existing antibodies against filgrastim or pegfilgrastim; 5 of these subjects were also positive for neutralizing antibodies to pegfilgrastim in the baseline sample. One subject (2%) developed transient postdose antibodies against filgrastim at a single time point after receiving pegfilgrastim. No consistent effects of the antibodies were noted in the clinical or pharmacokinetic profiles for these subjects.

Table 11-1. Summary of Adverse Events (Safety Analysis Set)

	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg
Number of Subjects in Subset	6	37
All adverse events	6 (100%)	37 (100%)
Fatal adverse events	0 (0%)	1 (3%)
Life-threatening, or fatal adverse events	1 (17%)	6 (16%)
Severe, life-threatening, or fatal	5 (83%)	31 (84%)
Related adverse events	2 (33%)	8 (22%)
Related fatal adverse events	0 (0%)	0 (0%)
Related life-threatening, or fatal	0 (0%)	0 (0%)
Related severe, life-threatening, or fatal	0 (0%)	1 (3%)
Serious adverse events	5 (83%)	29 (78%)
Related serious adverse events	0 (0%)	1 (3%)
Withdrawals due to adverse events	0 (0%)	1 (3%)

Deaths

One subject (3%) who received pegfilgrastim died while on study (ie, within 30 days of the last dose of investigational product).

The investigator reported the cause of death as renal failure secondary to acute tubular necrosis and worsening respiratory acidosis.

Withdrawals Due to Adverse Events

One withdrawal due to an adverse event of disease progression was reported for a subject who received pegfilgrastim

Serious Adverse Events

Serious adverse events were reported for 29 subjects (78%) who received pegfilgrastim and 5 subjects (83%) who received filgrastim. Serious adverse events reported for > 2 subjects in either treatment group were the following (pegfilgrastim, filgrastim): febrile neutropenia (24 subjects [65%], 5 subjects [83%]), dehydration (4 subjects [11%], 1 subject [17%]), neutropenia (0 subjects, 4 subjects [11%]), mucosal inflammation (3 subjects [8%], 0 subjects), vomiting (3 subjects [8%], 0 subjects), pyrexia (3 subjects [8%], 1 subject [17%]), and catheter-related infection (3 subjects [8%], 0 subjects).

Within the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the incidence of serious adverse events was 92%, 80%, and 67%, respectively, in the pegfilgrastim group and 100%, 50%, and 100%, respectively, in the filgrastim group. The incidence of serious adverse events was somewhat higher in the youngest age group (0 to 5 years) (92% pegfilgrastim, 100% filgrastim); however, this difference should be interpreted with caution because of the small number of subjects in the age groups. The primary difference in serious adverse events in the 0- to 5-year age group occurred in the incidence of serious febrile neutropenia (75% pegfilgrastim, 100% filgrastim); the

other serious adverse events reported for this age group were also associated with the effects and complications of cancer and its treatment.

One subject had serious adverse events considered by the investigator to be related to treatment with pegfilgrastim. No subject withdrew from treatment or the study because of a serious adverse event.

Table 11-2. Subject Incidence of Serious Adverse Events Reported for ≥ 2 Subjects in Either Treatment Group by Preferred Term in Descending Order of Frequency (Safety Analysis Set)

	Filgrastim 5 µg/kg/day (N = 6)	Pegfilgrastim 100 µg/kg (N = 37)
Preferred Term	n (%)	n (%)
Number of Subjects Reporting Serious Adverse Events	5 (83)	29 (78)
Febrile Neutropenia	5 (83)	24 (65)
Dehydration	1 (17)	4 (11)
Neutropenia	0 (0)	4 (11)
Catheter Related Infection	0 (0)	3 (8)
Mucosal Inflammation	0 (0)	3 (8)
Pyrexia	2 (33)	3 (8)
Vomiting	0 (0)	3 (8)
Colitis	0 (0)	2 (5)
Constipation	1 (17)	2 (5)
Platelet Count Decreased	0 (0)	2 (5)

Table 11-3. Subject Incidence of Serious Adverse Events Reported for ≥ 2 Subjects in Either Treatment Group Within the Protocol-defined Age Groups by Preferred Term in Descending Order of Frequency (Protocol-defined Age Groups) (Safety Analysis Set)

	Filgrastim 5 µg/kg/day (N = 6)	Pegfilgrastim 100 µg/kg (N = 37)
Preferred Term	n (%)	n (%)
0 – 5 Years		
Number of Subjects Reporting Serious Adverse Events	1 (100)	11 (92)
Febrile Neutropenia	1 (100)	9 (75)
Dehydration	0 (0)	3 (25)
Colitis	0 (0)	2 (17)
Constipation	0 (0)	2 (17)
Mucosal Inflammation	0 (0)	2 (17)
Neutropenia	0 (0)	2 (17)
6 – 11 years		
Number of Subjects Reporting Serious Adverse Events	1 (50)	8 (80)
Febrile Neutropenia	1 (50)	7 (70)
Vomiting	0 (0)	2 (20)
12 – 21 years		
Number of Subjects Reporting Serious Adverse Events	3 (100)	10 (67)
Febrile Neutropenia	3 (100)	8 (53)
Neutropenia	0 (0)	2 (13)
Pyrexia	0 (0)	2 (13)

Table 11-4. Subject Incidence of Adverse Events Occurring in ≥ 2 Subjects in Either Treatment Group (Safety Analysis Set)

Preferred Term	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg SC
Number of Subjects in Subset	6	37
Number of Subjects Reporting Adverse Events	6 (100%)	37 (100%)
Vomiting	5 (83%)	29 (78%)
Mucosal Inflammation	4 (67%)	27 (73%)
Febrile Neutropenia	5 (83%)	24 (65%)
Anaemia	2 (33%)	23 (62%)
Nausea	2 (33%)	21 (57%)
Constipation	3 (50%)	19 (51%)
Pain In Jaw	1 (17%)	16 (43%)
Headache	2 (33%)	15 (41%)
Diarrhoea	2 (33%)	13 (35%)
Rash	0 (0%)	13 (35%)
Alopecia	1 (17%)	12 (32%)
Back Pain	1 (17%)	11 (30%)
Pyrexia	2 (33%)	11 (30%)
Weight Decreased	3 (50%)	11 (30%)
Abdominal Pain	3 (50%)	10 (27%)
Cough	2 (33%)	10 (27%)
Pain In Extremity	1 (17%)	10 (27%)
Pain	0 (0%)	9 (24%)
Pharyngolaryngeal Pain	2 (33%)	9 (24%)
Fatigue	0 (0%)	8 (22%)
Flatulence	0 (0%)	8 (22%)
Rhinorrhoea	1 (17%)	8 (22%)
Stomatitis	0 (0%)	8 (22%)
Myalgia	0 (0%)	7 (19%)
Thrombocytopenia	0 (0%)	7 (19%)
Arthralgia	2 (33%)	6 (16%)

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Note: n (%) = Number and percentage of subjects reporting any adverse event in the preferred term

Table 11-4. Subject Incidence of Adverse Events Occurring in ≥ 2 Subjects in Either Treatment Group (Safety Analysis Set)

Preferred Term	Filgrastim 5 µg/kg/day	Pegfilgrastim 100 µg/kg SC
Bone Pain	1 (17%)	6 (16%)
Depression	0 (0%)	6 (16%)
Hypotension	2 (33%)	6 (16%)
Lethargy	0 (0%)	6 (16%)
Neutropenia	0 (0%)	6 (16%)
Pruritus	1 (17%)	6 (16%)
Anxiety	0 (0%)	5 (14%)
Chills	2 (33%)	5 (14%)
Decreased Appetite	0 (0%)	5 (14%)
Dehydration	2 (33%)	5 (14%)
Dyspepsia	0 (0%)	5 (14%)
Dysuria	0 (0%)	5 (14%)
Hypokalaemia	0 (0%)	5 (14%)
Oral Pain	0 (0%)	5 (14%)
Peripheral Sensory Neuropathy	0 (0%)	5 (14%)
Anorexia	2 (33%)	4 (11%)
Catheter Related Infection	0 (0%)	4 (11%)
Catheter Site Rash	1 (17%)	4 (11%)
Fluid Overload	0 (0%)	4 (11%)
Hypertension	0 (0%)	4 (11%)
Hypoaesthesia	0 (0%)	4 (11%)
Insomnia	0 (0%)	4 (11%)
Perianal Erythema	0 (0%)	4 (11%)
Rhinitis Allergic	0 (0%)	4 (11%)
Tachycardia	0 (0%)	4 (11%)
Vertigo	0 (0%)	4 (11%)
Abdominal Pain Upper	1 (17%)	3 (8%)
Erythema	1 (17%)	3 (8%)
Productive Cough	1 (17%)	2 (5%)
Epistaxis	2 (33%)	1 (3%)

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CHMP comment

Anaemia, nausea, rash, pain, fatigue etc. seem to be more frequent in the pegfilgrastim group compared to filgrastim group, but the number of patients in the filgrastim group is too small to draw comparisons between the filgrastim and pegfilgrastim groups.

The incidence of serious adverse events was higher in the youngest age group (0 to 5 years) (92% pegfilgrastim) compared to other age groups (80% in the age 6-11 and 67% in the age 12-21).

The safety profile is overall as expected from the adult studies; however the events were more frequent. The frequency of events might be dose-dependent, especially in younger children. It is recommended to carry further dose finding studies in paediatric population.

Treatment-related Adverse Events

Adverse events attributed by the investigators to treatment with investigational product were reported for 22% of subjects in the pegfilgrastim group and 33% of subjects in the filgrastim group. The only treatment-related adverse event reported for > 1 subject was bone pain, reported for 11% of subjects in the pegfilgrastim group and 17% of subjects in the filgrastim group. In the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the incidence of treatment-related adverse events was 25%, 50%, and 0%, respectively, for subjects who received pegfilgrastim and 0%, 50%, and 33%, respectively, for subjects who received filgrastim. With the exception of severe Clostridium difficile and

tachypnoea reported for a subject who received pegfilgrastim, all treatment-related events were mild to moderate in severity.

Antibodies

The incidence of postdose antibody development was 2% (1 of 41 subjects with available samples); 1 subject developed transient postdose antibodies to filgrastim at a single time point after receiving pegfilgrastim. Ten subjects (10 of 41, 24%) had pre-existing binding antibodies to pegfilgrastim, filgrastim, or both, and 5 (5 of 41, 12%) of these subjects tested positive for neutralizing antibodies to pegfilgrastim at baseline. All 10 subjects tested negative after receiving investigational product. It is unknown whether the increased incidence of pre-existing antibodies observed in this study relates to the underlying diagnosis of sarcoma in these subjects or to the more diverse immune repertoire of the paediatric population. A review of data for the subjects with pre-existing antibodies and single subject with transient postdose antibodies did not reveal an altered safety profile in these subjects.

CHMP comment:

One (of 41) subject developed transient postdose antibodies to filgrastim. The number of studies subjects is too small to show the real frequency.

Discussion on clinical aspects

The MAH has submitted the clinical study report of study 990130 as part of the obligation to submit paediatric data to the CHMP.

The overall mean duration of severe neutropenia in cycle 1 was 6.0 days in the pegfilgrastim group and 5.3 days in the filgrastim group (consistent with previous data), a difference between treatment groups that was neither clinically nor statistically significant. The mean duration of severe neutropenia in cycle-1 chemotherapy tended to be longer in the younger age groups: 8.9, 6.0, and 3.7 days for subjects who received pegfilgrastim in the age groups of 0 to 5, 6 to 11, and 12 to 21 years, respectively.

Severe neutropenia in cycle 3 was reported for 97% of subjects in the pegfilgrastim group and 75% of subjects in the filgrastim group, with a mean duration of 8.1 days in the pegfilgrastim group and 5.8 days in the filgrastim group. For the protocol-specified age groups of 0 to 5, 6 to 11, and 12 to 21 years, the mean duration of severe neutropenia was 11.4, 9.0, and 4.7 days, respectively, among subjects who received pegfilgrastim.

The pharmacokinetics of pegfilgrastim was generally consistent with that in adults. The neutrophil-mediated clearance mechanism previously observed in adults was evident in this study, including in the youngest subjects (0 to 5 years of age). The maximum pegfilgrastim concentration was achieved at approximately 24 hours postdose and was sustained until the ANC nadir occurred. As ANC started to recover, the pegfilgrastim concentration declined rapidly.

The pharmacokinetic profile was similar in the 2 older age groups and consistent with that in adults; the youngest age group appeared to have higher median exposure.

The overall adverse event profile was consistent with the known effects of filgrastim and pegfilgrastim and the complications of cancer and its treatment.

Rapporteur's Overall Conclusion and Recommendation

Overall pegfilgrastim seems to have similar efficacy and safety to filgrastim; however the number of subjects in each age group was too small to robustly compare filgrastim and pegfilgrastim. No new safety trends or concerns emerged from this review. The types of reported events are consistent with what has been observed in adults.

The incidence of serious adverse events was higher in the youngest age group (0 to 5 years) (92% pegfilgrastim) compared to other age groups (80% in the age group 6-11 and 67% in the age group 12-21).

The obligation to submit paediatric data for Neupogen/Neulasta is fulfilled for the current submission, however the CHMP recommends studying further the adequate dose for paediatric population as the incidence of serious adverse events was higher, the duration of severe neutropenia was longer and the frequency of serious adverse events more common in the younger children compared to older age groups and to results from adult studies

Recommendation

☒ Not fulfilled:

Based on the data submitted, the MAH should provide additional clarifications as part of this procedure P45 (see section IV "Additional clarifications requested").

Additional clarifications requested

1. As the first years of life is associated with major changes in the processes affecting the absorption, distribution, metabolism and excretion of drugs, the applicant is asked to present efficacy and pharmacokinetic results for the first years of life (years 0-5 should be divided) as classified in the ICH and CPMP guidelines (Guideline on the Role of Pharmacokinetic in the Development of Medicinal Products in the Paediatric Population): preterm newborn infants, term newborn infants (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 – 5 years in this study).
2. Overall the incidence of febrile neutropenia was more common in the children compared to the results from earlier studies with adults. The applicant should comment the difference in results between children and adults.
3. Severe neutropenia seems to last longer in children compared to the pivotal study results in adults. The applicant is asked to comment.
4. The incidence of serious adverse events was higher in the youngest age group (0 to 5 years) (92% pegfilgrastim) compared to other age groups (80% in the age 6-11 and 67% in the age 12-21). The applicant should present the safety results of age group 0-5 years old more detailed in age groups (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 – 5 years).

Assessment of the responses to the request for additional clarifications

Question Nr. 1

As the first years of life is associated with major changes in the processes affecting the absorption, distribution, metabolism and excretion of drugs, the applicant is asked to present efficacy and pharmacokinetic results for the first years of life (years 0-5 should be divided) as classified in the ICH and CPMP guidelines (Guideline on the Role of Pharmacokinetic in the Development of Medicinal Products in the Paediatric Population): preterm newborn infants, term newborn infants (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 – 5 years in this study).

MAH's response

Within the 0-5 year age category, 13 subjects were enrolled, 12 were randomized to the pegfilgrastim arm and 1 subject was randomized to the Filgrastim arm. In this study, no subjects were enrolled in the first two age categories (preterm newborn infants or term newborn infants).

Table 1. Patient Disposition for the First years of Life as Classified by ICH and CPMP Guidelines

Age Category	Pegfilgrastim (100 μg/kg) Number of Subjects	Filgrastim (5 μg/kg/day) Number of Subjects
Preterm newborn infants	0	0
Term newborn infants (0-27 days)	0	0
Infants and toddlers (28 days – 23 months)	4	0
Children (2-5 years)	8	1

The statistical analysis plan prespecified analyses by three age categories, 0-5 years, 6-11 years, and 12-21 years. Individual efficacy and PK data are presented for each individual subject within the 0-5 age category. Due to the small numbers of subjects in each of the subgroups within the 0-5 year age category, summary statistics were not calculated. PK data were not collected for one subject, 713401 who was in the 28 days - 23 months age category.

Assessment of the MAH's response

The MAH briefly presented individual efficacy and PK data for all enrolled patients in the 0-5 years age category. PK data for one enrolled patient was not presented due to non-collection of such data during this study.

In general, the duration of severe neutropenia and incidence of febrile neutropenia were greater in cycles 1 and 3, as these cycles were associated with administration of more myelotoxic chemotherapy regimes than cycles 2 and 4.

For both duration of severe neutropenia and incidence of febrile neutropenia, there was little evidence or suggestion of a difference between the two subgroups; infants and toddlers (28 days – 23 months) and children (2-5 years) (No patients were enrolled in younger age categories). However, the small patient numbers preclude any conclusion that infants and toddlers do not have a higher incidence of febrile neutropenia or duration of severe neutropenia than children aged 2-5 years.

PK data for the two subgroups described the same phenomenon demonstrated in the adult studies where improvements in ANC were accompanied by falls in the serum pegfilgrastim concentration, reflecting increasing neutrophil mediated uptake of pegfilgrastim.

The limited efficacy and PK data presented on the small number of patients within the (28 days – 23 months) and (2-5 years) subgroups do not demonstrate increased duration of severe neutropenia and incidence of febrile neutropenia in infants compared to children. However, the small patient numbers preclude any conclusions being drawn from these data.

Point resolved

Question Nr. 2

Overall the incidence of febrile neutropenia was more common in the children compared to the results from earlier studies with adults. The applicant should comment the difference in results between children and adults.

MAH's response

Incidence of febrile neutropenia is directly proportional to the duration of severe neutropenia resulting from the myelotoxicity of the regimen, disease involvement of the bone marrow compartment, and specific patient-related factors (such as co-morbidities, previous anti-cancer therapy, organ function-including absorption, distribution, metabolism and excretion of drugs, and use of growth factor). The study chemotherapy, VAdriaC/IE (vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide), is a long-accepted and widely-utilized treatment for paediatric sarcoma. The regimen however, is associated with significant myelotoxicity with a median duration of severe neutropenia of 9 days without growth factor (Wexler et al, 1996) requiring treatment dose-delays and dose-reductions. In curative-setting treatment protocols, maintenance of dose intensity is an important factor in treatment outcome (Smith et al, 1991). Therefore, Filgrastim has often been incorporated in the administration of dose-intensive VAdriaC/IE with a reduction in the duration of severe neutropenia by approximately 3-4 days (Unpublished data, POB/NCI/NIH). Considering the study chemotherapy regimen, the desired dose-intensity of administration and the age-specific patient characteristics, the duration of severe neutropenia and incidence of febrile neutropenia in both the Filgrastim and pegfilgrastim treated subjects is as expected.

The rate of febrile neutropenia in this study was 54% in cycle 1 and 42% in cycle 3 (cycles 2 and 4 incorporated less myelotoxic chemotherapy administration). A higher rate of febrile neutropenia was concentrated in the 0-5 and 6-11 year age categories, where less mature drug metabolism and excretion would be expected to translate into an increased duration of severe neutropenia and accordingly, an increased incidence of febrile neutropenia

While the incidence of febrile neutropenia in this paediatric study is higher than in a number of earlier studies in adult populations, this is due to the chemotherapy regimens employed and the differing degrees of myelosuppression. A comparison of these data with the pivotal phase III study of Filgrastim in adults reveals a similar rate of febrile neutropenia: the Filgrastim study, in adult small cell lung cancer patients receiving cyclophosphamide, doxorubicin, and etoposide, reported a febrile neutropenia rate with Filgrastim support of 40% across all cycles (Crawford et al, 1991).

Assessment of the MAH's response

The point raised by the MAH concerning the significant myelotoxicity associated with VAdriaC/IE therapy is acknowledged

The overall rate of febrile neutropenia in patients administered pegfilgrastim in the submitted study report was 57% in cycle 1 and 44% in cycle 3, not 54% and 42% quoted in the MAH's response.

The MAH acknowledges that a higher rate of febrile neutropenia was seen in patients in the 0-5 years and 6-11 years categories; however, attributes this age related rate difference to less effective cytotoxic drug clearance by the younger patients, resulting in greater levels of immunosupression. Whilst this appears to be a logical explanation, the MAH did not provide any references or other information to support its assertion.

The MAH also attributes the rate differences seen between this study and the adult studies to the different chemotherapeutic regimens used. To illustrate this assertion the MAH highlights similar rates (40% across all cycles (Crawford et al)) of febrile neutropenia in adult small cell lung cancer patients who participated in a phase III study of filgrastim and received similarly myelosuppressive chemotherapy.

Whatever the aetiology of the higher rates of febrile neutropenias seen in patients in this study compared to adult patients enrolled in earlier studies of filgrastim and pegfilgrastim, it is important that both prescribers and patients are made aware of the data from this study to help inform treatment decisions and choices for paediatric patients for whom treatment with pegfilgrastim is being considered.

Therefore, the MAH is invited to submit a type II variation to update various sections of the SmPC with safety and efficacy data from this study

Point resolved subject to submission of the requested variation

Question Nr. 3

Severe neutropenia seems to last longer in children compared to the pivotal study results in adults. The applicant is asked to comment.

MAH's response

As shown below, the duration of severe neutropenia in this study is consistent with that observed in other paediatric studies using VAdriaC/IE chemotherapy with growth factor support.

The duration of severe neutropenia observed in this study is also consistent with that observed in two pivotal studies of Filgrastim. In these studies, patients with small cell lung cancer received cyclophosphamide, doxorubicin, and etoposide with or without G-CSF support. Those randomised to the Filgrastim group experienced a median duration of severe neutropenia across all cycles of 6 days (Trillet-Lenoir et al, 1993; Crawford et al., 1991).

Table 2 Duration of Neutropenia Associated with VAdriaC/IE Chemotherapy

	Regimen	Dose	Median Duration of Neutropenia
Wexler	Vincristine	2.0 mg/m^2	GM-CSF arm

(n = 37)	Doxorubicin Cyclophosphamide Ifosfamide Etoposide ± GM-CSF (beg in cycle 3)	35 mg/m^2 900 mg/m^2 1800 mg/m^2 100 mg/m^2 5 to 15 mcg/kg/day	< 0.5 x 10^9/L 7 days < 1 x 10^9/L 7 days
POB/NCI/NIH (n = 12)	Vincristine Doxorubicin Cyclophosphamide Ifosfamide Etoposide Filgrastim	2.0 mg/m^2 35 mg/m^2 900 mg/m^2 1800 mg/m^2 100 mg/m^2 5 mcg/kg/day	Mean duration of neutropenia (first 4 cycles) < 0.5 x 10^9/L 5 days < 1 x 10^9/L 6.3 days
Study 990130 (n = 44)	Vincristine Doxorubicin Cyclophosphamide Ifosfamide Etoposide Pegfilgrastim	2.0 mg/m^2 75 mg/m^2 1200 mg/m^2 1800 mg/m^2 100 mg/m^2 5 mcg/kg/day	< 0.5 x 10^9/L Mean cycle 1 5.8 days Median cycle1 5.0 days Mean cycle 3 7.8 days Median cycle 3 7.0 days

Assessment of the MAH's response

The point raised by the MAH concerning the duration of severe neutropenia associated with VAdriaC/IE therapy + growth factor support in other paediatric studies and in the adult pivotal studies of filgrastim is acknowledged.

However, it is noted that for patients allocated to the pegfilgrastim cohort within this study, the mean duration of severe neutropenia appears longest in the youngest age category, with a trend towards decreasing duration of severe neutropenia with increasing age: 8.9, 6.0 and 3.7 days for patents in the following respective subgroups; 0-5, 6-11 and 12-21 years.

Regardless of the aetiology, it is important that both prescribers and patients are made aware of the data from this study to help inform treatment decisions and choices for paediatric patients for whom treatment with pegfilgrastim is being considered.

Therefore, the MAH is invited to submit a type II variation to update various sections of the SmPC with safety and efficacy data from this study

Point resolved subject to submission of the requested variation

Question Nr. 4

The incidence of serious adverse events was higher in the youngest age group (0 to 5 years) (92% pegfilgrastim) compared to other age groups (80% in the age 6-11 and 67% in the age 12-21). The applicant should present the safety results of age group 0-5 years old more detailed in age groups (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 – 5 years).

MAH's response

As stated in the response to question 1, within the 0-5 year age category, 13 subjects were enrolled, 12 were randomized to the pegfilgrastim arm and 1 subject was randomized to the Filgrastim arm. Of these, 4 subjects were in the 28 day to 23 month age category (all pegfilgrastim), and 9 were in the 2-5 year age category (8 pegfilgrastim, 1 Filgrastim); no subjects were enrolled in the first two age categories (preterm newborn infants or term newborn infants).

Considering the pegfilgrastim group alone, serious adverse events occurred in a total of 11 subjects. The most common serious adverse event for both age categories was febrile neutropenia.

Table 3 Adverse Events for those in the 0-5 Age Category

Age Category	Infants and toddlers (28 days – 23 months) n = 4	Children (2-5 years) n = 8
Number of subjects with a serious adverse event	4	7
Number of total serious adverse events	22	37
Number of subjects with febrile neutropenia	3	7
Number of febrile neutropenia events	7	14

Individual data are presented for all 12 subjects (11 pegfilgrastim and 1 Filgrastim).

Assessment of the MAH's response

The MAH presented SAE data for individual patients within the pre-defined groups, as requested. The majority of SAEs were febrile neutropenias and other serious infections, which occurred more frequently in the 0-5 years age category than in other age groups. The points made earlier by the MAH regarding the increased susceptibility of this sub group to infections in this respect are acknowledged.

The incidence of non-infectious SAEs did not appear to be increased in the 0-5 years subgroup compared to older children enrolled in the study. However, the small patient numbers and the small number of non-infectious SAEs recorded preclude any conclusions being drawn

Point resolved

Assessment of the additional publication

The following **publication** has been submitted:

Once-per-cycle pegfilgrastim versus daily filgrastim in paediatric patients with Ewing sarcoma. Wendelin, G. et al.

Journal of Paediatric Hematology/Oncology. 2005;27(8):449 5

Method

The study was conducted from September 2003 to September 2005 in one single centre in Germany.

Five male patients, aged 10-15 years, received cytotoxic chemotherapy for Ewing sarcoma. It consisted of 6 preoperative induction cycles of VIDE (vincristine, ifosfamide, doxorubicin, etoposide) and/or postoperative cycles of either VAI (vincristine, actinomycin D, ifosfamide) or VAC (vincristine, actinomycin D, cyclophosphamide). They were alternatively treated with a single subcutaneous 100 µg/kg pegfilgrastim dose on day 4 after chemotherapy and with daily subcutaneous doses of 10 µg/kg filgrastim starting on day 4 after chemotherapy until an absolute neutrophil count above 1 x 10^9/L after the chemotherapy-induced nadir was reached.

A sixth female patient was withdrawn after the 4th preoperative cycle due to life-threatening neutropenia lasting more than 10 days while on filgrastim; she was subsequently switched to continuous 24-hour intravenous infusion of rhG-CSF.

Overall, 29 cycles with each treatment were studied (see table below).

Chemotherapy	VIDE	VAI	VAC	All
Cycles with Pegfilgrastim, no.	9	14	6	29
Cycles with Filgrastim, no.	9	12	8	29
Total no. of cycles	18	26	14	58
Filgrastim Injections/Cycle, median	9	6	5	6
Range	6–10	4–9	3–7	3–10

Results

The duration of severe neutropenia, the incidence and duration of febrile neutropenia were comparable with both treatments (see table below).

Chemotherapy	VIDE G-CSF/PEG	VAI G-CSF/PEG	VAC G-CSF/PEG	All G-CSF/PEG
Duration grade 4 neutropenia, days (mean)	5,9/6,1	0,9/0,6	0,9/0,3	2,5/2,2
Incidence febrile neutropenia, percent	56/78	8/0	0/0	21/24
Duration febrile neutropenia, days (mean)	1,3/1,4	0,1/0	0/0	0,5/0,5

Abbreviations: G-CSF = Filgrastim, PEG = Pegfilgrastim.

Bone pain associated with pegfilgrastim was noted in one patient after one cycle. No other adverse effects were attributed to the use of pegfilgrastim or filgrastim. Maximum leukocyte counts, platelet and red blood cell (RBC) recovery and the need for platelet and RBC transfusions were similar.

CHMP comment:

Although limited to 5 children, these results suggest comparable efficacy between one injection of 100 µg/kg pegfilgrastim and a course of filgrastim administered at twice the dose usually recommended.

CHMP's Overall Conclusion and recommendation

Overall conclusion

The MAH has provided the requested information regarding Study 990130 and the issues are considered resolved subject to submission of the requested variation. It is acknowledged that such a paediatric trial is difficult to conduct for all the reasons noted by the MAH. The enrolment of 4 infants and 9 children less than 6 years old is itself considered to be of significant value. Further, the MAH has indicated that it would not be feasible to "initiate further study (of pegfilgrastim) in the paediatric population". This is considered reasonable and acceptable at present

Although limited, the information generated by this trial and by the publication of a cross-over trial supports the use of pegfilgrastim as an alternative to filgrastim in children treated with cytotoxic chemotherapy. However, the results suggest that the outcomes in infants and young children (less than 6 years old) are slightly inferior to those observed in older children, which is likely to be due to their higher sensitivity to cytotoxic chemotherapy. Simultaneously, higher serum levels of pegfilgrastim are measured, a finding consistent with its receptor mediated clearance.

Based on the data provided, the CHMP considers the obligation fulfilled but recommends that a type II variation should be submitted by the MAH within 3 months in order to update the SmPC.

Recommendation

The CHMP recommends the update of various sections of the SmPC with safety and efficacy data from the paediatric study within 3 months

☒ Fulfilled:

Type II variation to be requested from the MAH by April 2009.