Title: Risk factors For Bone Pain among Neulasta® users

Neulasta

Amgen Study Number 20120320

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Date:	27 January 2014
Version:	*3.0*

STUDY GLOSSARY

Term	Definition
AE	Adverse Event
ANC	Absolute Neutrophil count
Chemotherapy cycle	Begins with chemotherapy administration and ends at either the next chemotherapy cycle or end of chemotherapy
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHOP-R	Cyclophosphamide, doxorubicin , vincristine , prednisone and rituximab
CI and 95%CI	Confidence Interval and 95% Confidence Interval
CRF	Case Report Form
CIN	Chemotherapy-induced neutropenia
EC	Ethics Committee
FN	Febrile Neutropenia, defined as fever in the presence of neutropenia
GCSF	Granulocyte-colony stimulating factor
GEE	Generalized Estimating Equations
NSCLC	Non-small Cell Lung Cancer
NHL	Non-Hodgkin Lymphoma
RDI	Relative Dose Intensity
ARDI	Average Relative Dose Intensity
OR	Odds Ratio
WBC	White blood cell

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STUDY SYNOPSIS

Study Title: Risk factors for bone pain among Neulasta® users	
Objectives	To identify risk factors for bone pain among patients treated with myelosuppressive chemotherapy and Neulasta® .
Study Design	A cohort study using patient data from randomized clinical trials (RCTs) sponsored by Amgen.
Study Population	Adults enrolled in the clinical trials who were diagnosed with non-myeloid malignancies treated with myelosuppressive chemotherapy at risk of developing febrile neutropenia (FN).
Inclusion Criteria	Amgen sponsored pegfilgrastim trials conducted in adult patients diagnosed with non-myeloid malignancy are eligible to be included in the study. Patients who received pegfilgrastim for primary prophylaxis per label (i.e. 24 hours following administration of cytotoxic chemotherapy) in the eligible trials will be included in the analysis.
Exclusion Criteria	Trials will be excluded from the analysis in the presence of any one of the following criteria: 1) Trials conducted in pediatric population (age less than 18 years old); 2) Trials conducted in patients with myeloid malignancy; 3) Trials conducted in patients receiving peripheral blood stem cell (PBSC or PBPC) transplant; 4) Trials collected only serious adverse drug reactions rather than adverse events; 5) Phase I trial in healthy subjects; or 6) Cross over trials. Patients in the eligible trials will be further excluded from the analysis in the presence of any one of the following criteria: 1) Patients who did not receive pegfilgrastim (in the filgrastum or non G-CSF use treatment arm); 2) patients who received pegfilgrastim for non primary prophylactic use (e.g. secondary prophylaxis or treatment); or 3) Patients who received pegfilgrastim and chemotherapy on the same day.
Definitions of Key Study Variables	The primary endpoint is the occurrence of moderate to severe bone pain (grade 2+) in cycle 1 of the study treatment chemotherapy, captured as part of AE reporting. Secondary endpoints: moderate to severe bone pain across study treatment cycles (up to and including 6 cycles of chemotherapy); bone pain of all grades in cycle 1 and bone pain of all grades across cycles of chemotherapy
Statistical Considerations	Risk of bone pain (grade 2+ and all grades) will be estimated by patient demographic and clinical characteristics. Logistic regression models will be used to identify risk factors that are associated with the occurrence of moderate to severe bone pain and bone pain of all grades in cycle 1, of chemotherapy, and across cycles 1–6.

Rationale for Study	It is useful to understand and characterize which patients are more likely to develop bone pain, in particular severe bone pain, following pegfilgrastim use for the timely prevention and management of this toxicity. No risk factors have been identified that predict which cancer patients receiving chemotherapy will develop bone pain after pegfilgrastim use. Previous descriptive studies have speculated that certain factors (e.g. age) may predict bone pain, but these observations remain to be confirmed.

1. OBJECTIVES

1) To identify risk factors for developing moderate to severe bone pain (grade 2+) in the first cycle, of chemotherapy, among patients treated with myelosuppressive chemotherapy who received pegfilgrastim for primary prophylaxis

2) To identify risk factors for developing bone pain of any grade in the first chemotherapy cycle among patients who received pegfilgrastim for primary prophylaxis

3) To identify risk factors for developing moderate to severe bone pain across chemotherapy cycles (up to and including 6 cycles)

4) To identify risk factors for developing bone pain of any grade across chemotherapy cycles (up to and including 6 cycles)

5) To describe demographic and clinical characteristics of patients treated with pegfilgrastim who experienced bone pain

2. BACKGROUND AND RATIONALE

2.1 Disease and Therapeutic Area

Chemotherapy-induced neutropenia (CIN) is a common side effect of myelosuppressive chemotherapy and a significant risk factor for infection (febrile neutropenia [FN]). FN is generally defined as fever with grade 3/4 neutropenia. FN can lead to chemotherapy dose delays, reductions, and treatment discontinuations, thereby affecting the optimal delivery of therapy. FN is associated with early morbidity, lengthy hospitalizations and early mortality (Kuderer 2006, Crawford, 2008, Lyman 2010). G-CSFs have been shown to reduce the severity and duration of CIN and the risk of developing FN (Crawford et al. 2002, Aapro et al. 2006). Filgrastim (Neupogen®) was the first G-CSF to receive FDA approval in 1991. Subsequently, pegfilgrastim (Neulasta®), a pegylated form of G-CSF, received FDA approval in 2002. Compared to filgrastim, pegfilgrastim has a longer duration of action and is administered as a single dose injection once per chemotherapy cycle. Clinical practice guidelines recommend primary prophylactic use of a colony-stimulating factor (CSF) when FN risk, based on chemotherapy and patient risk factors, is approximately 20% or greater, and recommend consideration of G-CSF prophylaxis when FN risk is 10%–20%(NCCN guidelines 2010, Smith et al. 2006).

2.2 Scientific Rationale for Planned Study

Filgrastim and pegfilgrastim are well tolerated with the most common adverse event reported being bone pain. Amgen recently conducted a retrospective analysis to evaluate the incidence and severity of bone pain across Amgen-supported pegfilgrastim clinical trials. (Gregory, et al. 2010) The study reported that in pegfilgrastim versus filgrastim randomized clinical trials, the incidence proportions (95% CI) of bone pain of any grade were 62% (57%–67%) and 66% (61%–71%) in the pegfilgrastim and filgrastim groups, respectively, for the first four cycles of chemotherapy. Severe (grade 3/4) bone pain was infrequent, with incidence proportions of 7% (4%–10%) and 8% (5%–11%), respectively. Furthermore, the study reported findings from a second analysis that evaluated incidence proportions of bone pain in pegfilgrastim versus no G-CSF randomized clinical trials. In this analysis, the incidence proportions of bone pain of any grade were 33% (30%–36%) and 23% (21%–26%) in the pegfilgrastim and no G-CSF groups, respectively, in the first chemotherapy cycle. Severe bone pain was infrequent, with incidence proportions of 3% (2%–5%) and 2% (1%–3%), respectively.

Moreover, a third analysis was performed to evaluate incidence proportions of bone pain in over 1,800 pegfilgrastim-treated patients from CIN studies. In this analysis, the incidence proportions of bone pain of any grade and grade 3/4 bone pain were 50% (47%–52%) and 6% (5%–7%), respectively. No formal statistical testing was performed in this retrospective study. However, descriptive analyses showed that the incidence proportion of any grade bone pain was higher in younger patients (< 65 years) and those who received taxane-based regimens, but these findings were not confirmed with severe bone pain. Tumor type also appeared to be associated with bone pain (Gregory, et al. 2010).

Other groups have investigated the incidence of bone pain associated with pegfilgrastim use in clinical trials or clinical practice. However, studies to identify risk factors for developing pegfilgrastim associated bone pain are limited. In a survey conducted in 100 patients in a large clinical oncology practice, 35% and 24% of patients experienced moderate and severe bone pain, respectively, following their first dose of pegfilgrastim (Kirshner et al, 2007). Although the study attempted to find correlates of bone pain, it was too small to be conclusive. Other studies also had too few patients to be able to identify predictors of pegfilgrastim-associated bone pain (Kubista et al. 2003, Green et al. 2010) Moreover, risk factors associated with the incidence and severity of pegfilgrastim-induced bone pain were not identified in a clinical trial that evaluated naproxen for the prevention of pegfilgrastim-induced pain (Kirshner et al. 2010, Kirshner et al. 2012). However, an unplanned analysis revealed a higher incidence of pegfilgrastim-induced pain in African Americans as compared to Europeans.

To our knowledge, no risk factors have been identified that predict which cancer patients receiving chemotherapy and pegfilgrastim will develop bone pain. Previous descriptive studies, particularly the exploratory study by Gregory and colleagues (Gregory, et al. 2010) have speculated that certain factors (e.g. age), but these observations remain to be confirmed. Therefore, we plan to conduct a retrospective study, using data from Amgen-sponsored pegfilgrastim clinical trials to better understand the characteristics of patients who experience bone pain after pegfilgrastim use. This will help identify patients with high risk of developing bone pain who should be targeted for education and NSAID therapy.

2.3 Statistical Inference (Estimation / Hypotheses)

Estimation

We will estimate the relationship between clinical factors including specific tumor types, certain co-morbid conditions(e.g. arthritis, hypercholesteremia, anemia), cancer metastasis, chemotherapy regimens and the odds of moderate to severe (grade 2+) bone pain (as well as bone pain of all grades) occurring in the first chemotherapy cycle among patients who received pegfilgrastim for primary prophylaxis. Odds ratios and 95% confidence intervals will be estimated for these potential risk factors in association with developing bone pain in the first chemotherapy cycle as well as across cycles (up to and including 6 cycles).

3. STUDY DESIGN

3.1 Study Source Population

This cohort study includes data from pegfilgrastim clinical trials sponsored by Amgen that enrolled adult patients with non-myeloid malignancies who received myelosuppresive chemotherapy regimens and were at risk of developing FN.

3.2 Study and Source Data

This is a cohort study using patient data from Amgen sponsored pegfilgrastim clinical trials. A full description of data elements collected in the trials is provided in Appendix A. A full description of clinical trials on file (Neulasta data mart) is provided in the Appendix B and Appendix C.

3.3 Selection of Participants

3.3.1 Inclusion (Eligibility) Criteria

Amgen sponsored pegfilgrastim trials conducted in adult patients diagnosed with non myeloid malignancy will be included in the study. (Appendix B: Description of trials to be included in the analysis). Patients in the eligible trials who received pegfilgrastim for primary prophylaxis per label, i.e. 24 hours following administration of cytotoxic chemotherapy will be included in the analysis.

3.3.2 Exclusion Criteria

Trials will be excluded from the study in the presence of any one of the following criteria:

1) Trials conducted in pediatric population (less than 18 years old)
2) Trials conducted in patients with myeloid malignancy
3) Trial conducted in patients receiving peripheral blood stem cell (PBSC or PBPC) transplant
4) Trials collected only serious adverse drug reactions rather than adverse events
5) Phase I trials conducted in healthy subjects
6) Cross–over trials

Therefore, of the 34 Amgen sponsored-supported pegfilgrastim trials identified, 11 trials will be excluded from the present study based on the study population evaluated or study design (Appendix C: Description of trials to be excluded from the analysis).

Patient data from the remaining 23 eligible trials (Appendix D: Figure 1. Study Schema) will be further excluded from the analysis in the presence of any one of the following criteria: 1) patients who did not receive pegfilgrastim (i.e. patients recruited in the filgrastim arm or patients recruited in the non-GCSF treatment arm); 2) patients who received pegfilgrastim for non primary prophylactic use (i.e. secondary prophylaxis or treatment); or 3) patients who received pegfilgrastim and chemotherapy on the same day.

Definition of Exposure, Outcome, and Other Study Variables

3.3.3 Exposure

All study participants received pegfilgrastim (100 µg/kg or 6-mg fixed dose) for primary prophylaxis per label in 23 eligible trials will be included in the analysis.

3.3.4 Study Endpoints

Primary Endpoint

- Moderate to severe bone pain (grade 2+) in cycle 1, captured as part of AE reporting

Secondary Endpoints:

- All grade bone pain in cycle 1, captured as part of AE reporting
- Moderate to severe (grade 2+) bone pain across cycles (up to and including 6 cycles), captured as part of AE reporting
- All grade bone pain across cycles (up to and including 6 cycles), captured as part of AE reporting

Bone pain is identified based on the adverse events reported in the clinical trials. Adverse events reported in original trials were coded or re-coded using the Medical Dictionary for Regulatory Activities (MedDRA) and updated according to the most recent version (15.1). Bone pain severity was recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) as reported by the investigators of the original studies (graded as 0=none, 1=mild, 2=moderate, 3=severe). If a patient had multiple reported AEs with PTs considered “bone pain” in a cycle, the severity of the AE with the highest CTCAE grade was taken as the bone pain severity for that cycle.

The restrictive preferred terms in the bone pain EOI (Event of Interest) will be used to define bone pain for main analysis in the present study. (Appendix E: List of restrictive preferred terms).

3.3.5 Predictors of Study Outcome

Patient's demographic characteristics, patient clinical and co-morbid conditions (from medical history) were collected at baseline. Available data collected in the trials will be used to evaluate patients' risk profile prior to receipt of pegfilgrastim including co-morbid conditions, cancer and treatment history.

Patient -demographic characteristics:

Patient characteristics that will be considered in this analysis include age, race/ethnicity, region, sex, weight, height, and body surface area (Appendix A)

Patient co-morbid conditions:

Patients' medical histories were collected at baseline in the trials using Amgen standard Medical History Collection form. The free text terms were read by professional medical coders and re-coded using the Medical AE preferred terms (PTs). There are several co-morbidities that have an a priori reason to be associated with bone pain, such as osteoporosis, arthritis including osteoarthritis, anemia, sickle cell disease, thalasemia, allergies (e.g. drug allergies, asthma). Other co-morbid conditions of interest to be studied as part of an exploratory analysis, include diabetes, diabetes with end organ damage, hypertension, cardiovascular diseases, moderate to severe liver disease (hepatitis, cirrhosis), moderate to severe renal failure, autoimmune conditions (RA, SLE, MS), thyroid disorder (including autoimmune thyroiditis), peptic ulcer disease, dementia, osteoarthritis, connective tissue disease, HIV infection, and previous history of infections (e.g. pneumonia, sepsis). (Appendix A)

Cancer, chemotherapy and treatment characteristics:
Cancer type (including histology type), cancer stage at diagnosis, metastatic status, previous use of radiation therapy, and surgical procedures will be assessed at baseline (prior to randomization). (Appendix A) Patients' performance status (ECOG) was available in several trials.

Chemotherapy regimen and dose were collected by treatment cycle in the original trials. For each original trial, chemotherapy dose and relative dose intensity (RDI, calculated) were previously calculated prior to this analysis.

All subjects are considered to have received cycle 1 treatment on time. For the subsequent cycles, a subject is considered to have experienced a dose delay if the day 1 of the corresponding cycle is more than 3 days late from the expected administration date based their chemotherapy schedule from the day 1 of the previous cycle.

3.4 Validation of Study Variables

Data and study variables collected in the original trials were validated in terms of completeness and accuracy by the Data Management Teams when conducting original trials. Moreover, data elements from original trials were validated and cross-checked by the trial analysts prior to this study.

Datasets and variables created in the Neulasta datamart are validated through formal programming QC process. All newly created datasets and variables for this project will be further validated by the project team.

3.4.1 Outcome Validation

The outcome of moderate to severe bone pain (grade 2+) and all grade bone pain will be retrieved from the trial database. As described in section 3.4.2, bone pain related preferred terms were reviewed by three independent physicians and predetermined before this study.

3.5 Study Follow-up Period, Exposure Time, and Time at Risk from

Each patient included in the original trials was followed to the first of loss to follow up, the end of trial conduction period, or death.

4. STUDY SIZE

An estimate of 1860 patients enrolled in the Amgen sponsored clinical trials that met inclusion criteria will be included in the analysis. The incidence of moderate to severe bone pain (grade $\geq$2) in the first cycle is about 20% based on published clinical trials. (Gregory, et al. 2010) Assuming a prevalence of 20% for the presence of potential risk factors, 95% confidence intervals are 0.91-1.58 for an odds ratio (OR) of 1.2 and 1.56-2.57 for an odds ratio of 2.0. (Table 1) Multivariate adjustment is not considered for estimating 95% confidence intervals in the table below.

Table 1. 95% Confidence Intervals for potential odds ratios (Targeted type I error=0.05)

	95%Confidence Intervals		
	Prevalence of potential risk factors		
Odds Ratios	10%	15%	20%
1.2	0.84-1.72	0.89-1.63	0.91-1.58
1.4	0.99-1.99	1.04-1.88	1.08-1.82
1.6	1.14-2.25	1.20-2.13	1.24-2.07
1.8	1.29-2.51	1.36-2.39	1.40-2.32
2.0	1.44-2.78	1.52-2.64	1.56-2.57

5. STATISTICAL ANALYSIS

5.1 Exploratory and Descriptive Analysis

Characteristics of the study population, by presence of bone pain will be evaluated. Statistics such as mean, median, percentiles, and standard deviations will be estimated for continuous variables. Proportions will be estimated for categorical variables.

5.2 Statistical Modeling

Primary analyses will be conducted for bone pain defined by restrictive preferred terms. Crude incidence of moderate to severe and any grade bone pain in cycle 1 and across cycles will be summarized by patients' demographic and baseline clinical characteristics. The relationship between exposure variables and bone pain will be studied in logistic regression models. Both unadjusted (bivariate) and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) will be estimated from the logistic regression model. Multivariable logistic regression models will be used to estimate adjusted odds ratios and will include adjustment for age, sex, cancer type, chemotherapy regimens, presence of metastases (bone, other site), cycle number, year of cancer diagnosis and chemotherapy, geographic location (region), and presence of co-morbid conditions (e.g. sickle cell disease, thalasemia, anemia, allergies, arthritis, osteoporosis and hypercholesterolemia). In order to reduce residual confounding, continuous covariates will be smoothed by using functions of natural cubic splines.(Benedetti and Abrahamowicz, 2004). Categorical variables will be modeled as indicator variables. All analyses will be conducted using the Statistical Analysis System (SAS), version 9.2.

5.3 Missing Data

This study will use data from pegfilgrastim clinical trials conducted by Amgen. Clinical trials in which important covariates were not collected will be excluded for the purpose of this study. We expect to have missing data on some covariates. The percent of missing data for each covariate will be recorded. Multiple imputations will be used if appropriate.

5.4 Subgroup and Sensitivity Analysis

Sensitivity analyses will be conducted for bone pain defined by broad preferred terms. The broad preferred terms were described in a previous publication (Gregory, et al. 2010):

1) Pain related PTs in the Musculoskeletal and Connective Tissue Disorders system organ class (SOC) such as bone pain, back pain, neck pain, pain in hip, pain in shoulder, aching in limb, and pain in extremity.
2) Pain related PTs in the Respiratory, Thoracic and Mediastinal Disorders SOC such as rib pain
3) Toothache in the Gastrointestinal Disorders SOC.

Ordinal logistic regression models (PROC CATMOD, SAS) will also be used to assess the associations between variables of interest and the severity of bone pain.

A sensitivity analysis will be conducted after exclusion of patients who develop at any time the following: bone fracture or other skeletal related event, osteoporosis, osteonecrosis, or bone metastasis.

6. STUDY LIMITATIONS

There are several other potential sources of bias that should be considered for this study.

6.1 Internal Validity of Study Design

6.1.1 Selection Bias and Confounding Bias

A range of covariates included in this analysis will be obtained from the clinical trial databases. Since Amgen sponsored pegfilgrastim clinical trials were not originally designed for the purpose of this study, information on certain covariates such as the presence of bone metastasis, and prior history of medication use for bone related disorders may not always be available. Another important source of selection bias in the context of a cohort study relates to the problem of differential loss to follow up. However we do not anticipate that, conditional on covariates, loss to follow-up will be associated with bone pain.

There may be residual confounding due to inaccuracies associated with some covariates, the lack of information on others, and potential model misspecification.

6.1.2 Information Bias

Patients' medical histories were evaluated using Amgen standard Medical History Collection Questionnaire and were re-coded by professional medical coders. Adverse events reported in original trials were re-coded using the Medical AE preferred terms. All bone pain related terms were adjudicated by three independent physicians who were blinded to other information in the trials. All preferred terms were and will be determined before the current analysis. Thus, there is little reason to assume that there will be a significant differential measurement bias. However, because no variable is measured without error, there is likely to be non-differential measurement error which is likely to bias odds ratio estimates toward the null.

6.1.3 Generalizability

Patients included in clinical trials form a special group who may be unlike the general population in several ways. To the extent that included patients are similar to the general population of cancer chemotherapy patients who receive growth factor, the results of this study will be generalizable.

6.1.4 Reliability and Validity

Bone pain related preferred terms were reviewed by two independent physicians. Any inconsistencies were resolved by the third physician. Measurements and evaluations were standardized and consistent across all trials included in this study. The presence of bone pain and grade of bone pain have been predetermined before the current analysis.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

This is a secondary analysis of previously published clinical trials. Information on adverse events have been reported and published. Reporting of adverse events in association with Amgen products are therefore not applicable in this study.

8. ETHICAL AND REGULATORY OBLIGATIONS

8.1 Protection of Human Subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy.

8.2 Informed consent

Individual consent forms have been obtained in the original trials. No additional informed consent will be needed for the purpose of this study. No personal identification data is extracted, ensuring full anonymity and confidentiality of the information collected.

8.3 Investigator responsibility

8.3.1 Confidentiality

By signing this protocol, the study team members affirm to the company that information furnished to the Investigators by the company will be maintained in confidence and will be only revealed to study collaborators, affiliated institution(s) and employees under an appropriate understanding of confidentiality with such study collaborators, affiliated institution(s) and employees. The Investigators agree that, subject to local regulations and ethical considerations, a company representative or any regulatory agency have the right of access to the main study database at any time in order to verify data entry.

8.3.2 Compliance to Protocol and Law

By signing this protocol, the study team members agree to conduct the study in an efficient and diligent manner in accordance with this protocol and local laws, rules and regulations.

9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1 Study Amendments and Study Termination

Any considerable changes to this protocol and substantial amendment(s) that arise during the study must be accepted by the Study Team. All parties involved in the study should be notified in writing of the study's completion or early termination. Else, the study is considered terminated upon the publication of study results.

9.2 Study Documentation and Archive

Retention of study-related documents is governed by Amgen Policy CCD024r03, "RECORDS AND INFORMATION MANAGEMENT POLICY".

10. COMMUNICATION OF STUDY RESULTS

Authorship should follow the guidelines proposed by the International Committee of Medical Journal Editors (2004). All authors will meet the criteria for authorship, and all people who meet the criteria should be authors. Potential conflicts of interest will be disclosed. All authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; and (3) approved the version to be published. Each author will meet all of these conditions. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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12. APPENDICES

12.1 Appendix A: Data elements collected in the data mart

Variables	Baseline	Repeated assessment
Socio-demographic	✓	NA
Age	✓	NA
Sex	✓	NA
Region	✓	NA
Height	✓	NA
Weight	✓	✓
BSA	✓	✓
Medical history		
Prior history of bone pain	✓	NA
Osteoporosis	✓	NA
Hypercholesteremia	✓	NA
Anemia	✓	NA
Sickle cell disease	✓	NA
Allergy (inc. drug allergies, hay fever, atopy, asthma, etc.)	✓	NA
Prior history of neutropenia/FN	✓	NA
Cancer related		
Prior history of chemotherapy	✓	NA
Prior history of radiotherapy	✓	NA
Time since cancer (baseline)	✓	NA
Metastasis involvement (baseline)	✓	NA
Cancer histology type	✓	NA
Cancer stage	✓	X
Chemotherapy dose and regimen	✓	✓
RDI	✓	✓
ARDI	✓	✓
Dose delayed	NA	✓
Growth factor dose		
Previous growth factor use and dose	X	X
Current growth factor use and dose	✓	✓

Appendix A: Data elements collected in the data mart (continued)

Variables	Baseline	Repeated assessment
Neutropenia/FN		
Grade 3/4 neutropenia (cycle specific)	NA	✓
Grade 4 neutropenia/FN	NA	✓
Hospitalization		
Duration (start date, end date)	NA	✓
Reason for hospitalization	NA	✓
Neutropenia related	NA	✓
Adverse events (classified by organ systems, including bone pain)	NA	✓
Bone pain	NA	✓
Degree of bone pain	NA	✓

Appendix A: Data elements collected in the data mart (continued)

Variables	Baseline	Repeated assessment
Lab measurements		
Vital signs	✓	✓
Temperature	✓	✓
Blood pressure	✓	✓
Pulse	✓	✓
ALBUMIN	✓	✓
ALK. PHOS	✓	✓
ALT (SGPT)	✓	✓
AST (SGOT)	✓	✓
BICARBONATE	✓	✓
BUN	✓	✓
CALCIUM	✓	✓
CHLORIDE	✓	✓
CREATININE	✓	✓
GLUCOSE	✓	✓
LDH	✓	✓
MAGNESIUM	✓	✓
PHOSPHORUS	✓	✓
POTASSIUM	✓	✓
SODIUM	✓	✓
BILIRUBIN	✓	✓
TOTAL PROTEIN	✓	✓
URIC ACID	✓	✓
SERUM UREA	✓	✓
ABSOLUTE NEUTROPHIL COUNT	✓	✓
ATYPICAL LYMPHOCYTES	✓	✓
BANDS/STABS	✓	✓
BASOPHILS	✓	✓
BLASTS	✓	✓
DELAYED TYPE HYPERSENSITIVITY (CELL INFLAMMATORY responses)	✓	✓

Appendix A: Data elements collected in the data mart (continued)

Variables	Baseline	Repeated assessment
EOSINOPHILS	✓	✓
GRANULOCYTES	✓	✓
HEMATOCRIT	✓	✓
HEMOGLOBIN	✓	✓
IMMATURE CELLS	✓	✓
JUVENILE CELLS	✓	✓
LYMPHOCYTES	✓	✓
METAMYELOCYTES	✓	✓
MID-CELL FRACTION	✓	✓
MONOCYTES	✓	✓
MYELOBLASTS	✓	✓
MYELOCYTES	✓	✓
NEUTROPHILS	✓	✓
NUCLEATED RBC	✓	✓
OTHER DIFFERENTIAL CELLS	✓	✓
PLAMSA CELLS	✓	✓
PLATELETS	✓	✓
PROMYELOCYTES	✓	✓
RBC	✓	✓
RETICULOCYTES	✓	✓
SEG. NEUTROPHILS	✓	✓
WBC	✓	✓

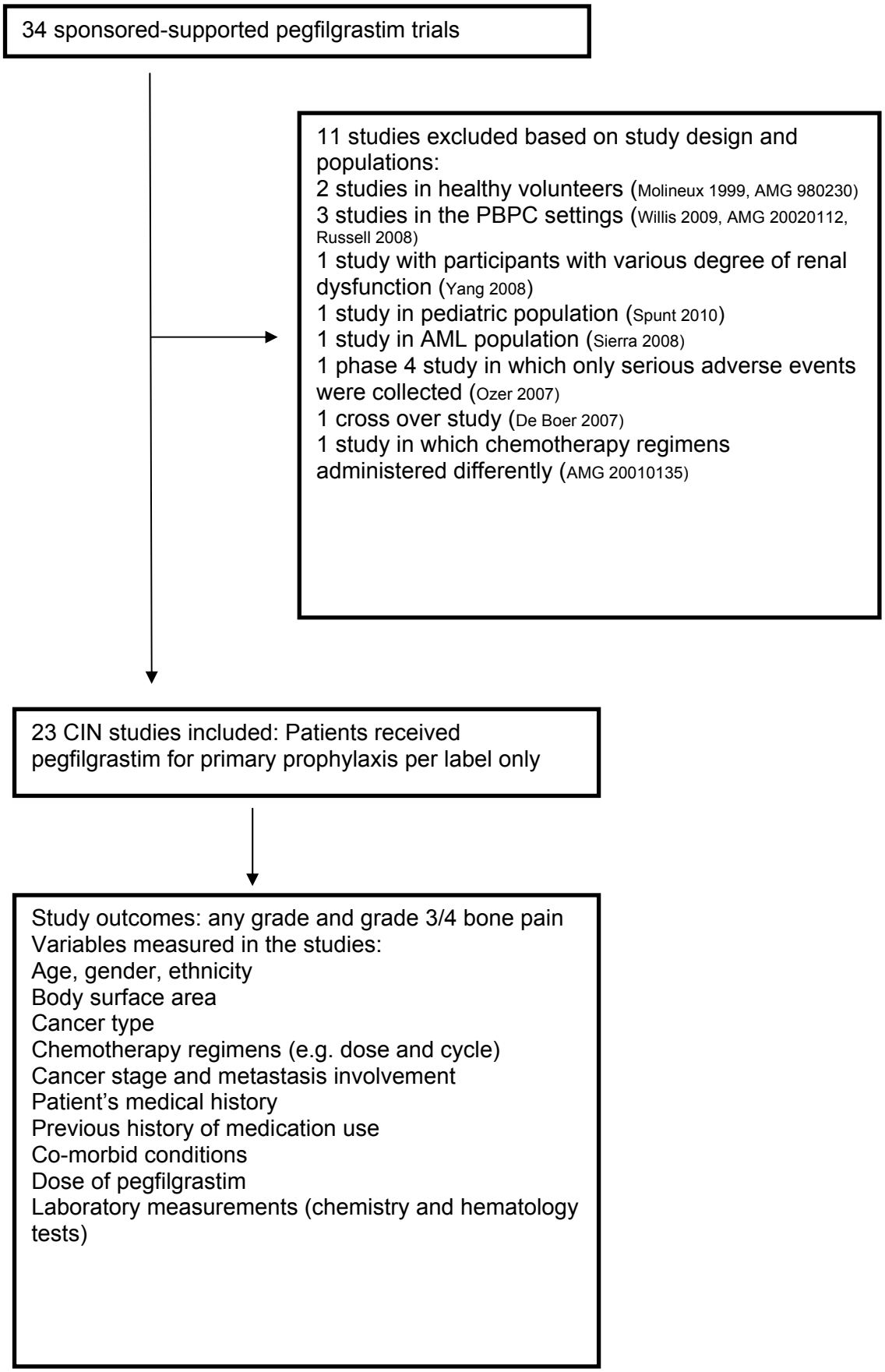
12.2 Appendix B: Description of Studies to be included in the analysis

Study	Study phase	Study population	Chemotherapy regimen
Pegfilgrastim vs filgrastim RCTs			
Holmes et al, 2002	II	Breast	Doxorubin+docetaxel
Holmes et al, 2002	III	Breast	Doxorubin+docetaxel
Green et al, 2003	III	Breast	Doxorubin+docetaxel
Grigg et al, 2003	II	NHL	CHOP
Lopez et al, 2004	II	NHL	CHOP-R
Vose et al, 2003	II	NHL	ESHAP
Johnston et al, 2000	II	NSCLC	Carboplatin+paclitaxel
Pegfilgrastim vs no G-CSF RCTs			
Vogel et al 2005	III	Breast	Docetaxel
Romieu et al 2007	II	Breast	FEC-100
Hecht et al 2010	II	Colorectal	FOIL, FOLFOX4, FOLFIRI
Smith et al 2005	IV	NSCLC	Carboplatin+paclitaxel+docetaxel
Balducci et al 2007	IV	NHL, lung, breast, ovarian	Various
Same day vs next day studies (only next day arm will be included)			
Engert et al 2006	II	Hodgkin's lymphoma	BEACOPP
Burris et al 2010	II	NHL, breast, ovarian, lung	Various
Single-arm studies			
Mattioli et al 2009	II	Breast	CMF
George et al 2003	II	NHL	CHOP
Wolf et al 2006	II	NHL	CHOP
Pirker et al 2006	II	SCLC	ACE
AMG 990736 (data on file)	II	Mixed	Various
AMG 20010137 (data on file)	II	Breast	Various

12.3 Appendix C: Description of studies to be excluded from the analysis

Study	Study phase	Study population	Chemotherapy regimen	Reason for exclusion
Molineux et al 1999	I	Healthy	None	Healthy
AMG 980230 (data on file)	I	Healthy	None	Healthy
Yang et al 2008	I	Various degree of renal function impairment	None	Various degree of renal function impairment
Spunt et al 2010	II	Pediatric sarcoma	VDC/IE	Pediatric
Willis et al 2009	II	Solid tumors/PBPC	Carboplatin+paclitaxel	PBPC
AMG 20020112 (data on file)	II	NHL, Hodgkin's lymphoma/PBPC	Various	PBPC
Russell et al 2008	II	NHL/PBPC	ICE	PBPC
Sierra et al 2008	II	AML	Idarubicin+cytarabine	Myeloid malignancy
Ozer et al 2007	IV	Various	Various	Only severe adverse events reported
AMG 20010135 (data on file)	II	Breast,lung,NHL	Various	Different regimens
De Boer et al 2007	II	Breast	AC-T	Cross over

12.4 Appendix D: Study Schema



Appendix E: List of Restrictive Preferred Terms to define bone pain (EOI terms)

Arthralgia
Arthritis
Arthropathy
Back disorder
Back pain
Bone pain
Chest discomfort
Coccydynia
Costochondritis
Hip pain
Limb discomfort
Monarthritis
Musculoskeletal chest pain
Musculoskeletal discomfort
Musculoskeletal pain
Myalgia
Myalgia intercostal
Neck pain
Non-cardiac chest pain
Osteoarthropathy
Osteochondritis
Pain
Pain in extremity
Pain in jaw
Pain in sternum
Pelvic pain
Periarthritis
Periarticular disorder
Periostitis
Sacroiliitis
Scapular pain
Skull pain
Spinal pain