Title	Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving Q2W chemotherapy regimen: A systematic review of efficacy, effectiveness, and safety (20190355)
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Marketing Authorization Holder(s)	*Amgen, Inc.*
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Research Question and Objectives	Among patients treated with biweekly chemotherapy regimens with high or intermediate risk for febrile neutropenia, systematically review the evidence regarding absolute or relative risk of - febrile neutropenia or grade 3 or 4 neutropenia - all-cause hospitalization - dose delays or dose reductions - adverse events, and - mortality for patients receiving prophylactic pegfilgrastim versus no prophylactic pegfilgrastim or prophylaxis with other granulocyte colony stimulating factor
Country(ies) of Study	*United States*

Author	[redacted] *Observational Research Manager* *Amgen Inc* [redacted] [redacted] *Director, US Medical,* *Amgen Inc* [redacted] [redacted] *Sylvester Cancer Center* *University of Miami* [redacted] [redacted] *Senior Medical Writer* *PharmaGenesis London* [redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	*Amgen, Inc*
MAH Contact Person	[redacted] *Amgen Inc.,* *One Amgen Center Drive* *Thousand Oaks, CA 91320* *Phone:* [redacted] *Email:* [redacted]

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1. ABSTRACT

- **Title**

Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving Q2W chemotherapy regimen: A systematic review of efficacy, effectiveness, and safety

- **Keywords**

Pegfilgrastim, Febrile Neutropenia, biweekly-chemotherapy, efficacy, effectiveness

- **Rationale and Background**

Febrile neutropenia (FN) following myelosuppressive chemotherapy is a potentially life-threatening complication and is associated with loss of treatment efficacy because of dose delays and dose reductions.[1-4] To prevent FN, the National Comprehensive Care Network (NCCN) guidelines recommend prophylactic use of granulocyte colony stimulating factor (G-CSF) for patients receiving chemotherapy regimen associated with high risk of developing FN (≥ 20%), or intermediate-risk of FN (10-20%) and have ≥ 1 patient-level risk factor.[5] Pegfilgrastim, a long-acting G-CSF, is administered once per cycle and is the most commonly used G-CSF in the US.[6] US prescribing information specifies pegfilgrastim should not be administered 14 days before or within 24 hours of administration of myelosuppressive chemotherapy.[7] This precludes the prophylactic use of pegfilgrastim with biweekly (Q2W) chemotherapy regimen in the US.

NCCN guidelines recommend at least 12 days between the dose of pegfilgrastim and the next cycle of chemotherapy, supporting the use of prophylactic pegfilgrastim in patients receiving Q2W regimens,[5] consistent wth the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC).[8]

However, there is a lack of systematic identification, appraisal, and synthesis of the existing evidence base from randomized clinical trials (RCTs) and observational studies that summarizes the efficacy, effectiveness, and safety of prophylactic pegfilgrastim to prevent FN among patients treated with Q2W chemotherapy regimen.

- **Research Question and Objectives**

Question: Is prophylactic pegfilgrastim efficacious, effective, and safe compared to no prophylactic pegfilgrastim or prophylaxis with other G-CSF in reducing the risk of FN among patients treated with Q2W chemotherapy regimens with high or intermediate risk for FN?

Objectives: Among patients treated with Q2W chemotherapy regimens with high or intermediate risk for FN, systematically review published evidence for the absolute or relative risk for FN or grade 3 or 4 neutropenia, all-cause hospitalization, dose delays or dose reductions, adverse events, or mortality, for patients receiving prophylactic pegfilgrastim versus no prophylactic pegfilgrastim or prophylaxis with other G-CSF.

- **Study Design**

Systematic literature review of RCTs, observational retrospective or prospective studies, and systematic reviews.

- **Setting**

An Ovid MEDLINE, Embase, and Cochrane Library literature search was executed to examine publications in English, between 01 January 2002 and 30 June 2019. Congress abstract literature search was conducted and limited to 30 June 2016 through 30 June 2019.

- **Subjects and Study Size, Including Dropouts**

Eligiblility was determined by the population, intervention, comparison, and outcomes (PICOS) criteria. The population were patients diagnosed with non-myeloid malignancy and treated with Q2W chemotherapy regimen, and studies in which the Q2W comparator was a Q3W chemotherapy regimen plus prophylactic pegfilgrastim. Interventions were Q2W chemotherapy regimens associated with a high (>20%) or intermediate (10–20%) risk of FN plus prophylactic pegfilgrastim. The comparisons included Q2W studies that compared pegfilgrastim to primary prophylaxis with other G-CSF, no prophylactic G-CSF or placebo, or Q2W compared to Q3W regimens with primary prophylactic pegfilgrastim. Excluded were single-arm trials without a comparator population, observational studies with no control or comparison group, studies in which the comparator was a Q3W regimen without prophylactic pegfilgrastim, studies of patients with myeloid malignancy, animal studies, abstracts or publications superceded by more recent publications, editorials or letters to the editors, and observational studies with <30 patients in the Q2W arm with primary prophylactic pegfilgrastim.

- **Variables and Data Sources**

Outcomes included FN, grade 3 or 4 neutropenia, all-cause hospitalization, dose delays or dose reductions, adverse events, or mortality. FN for RCTs was defined as ANC < 0.5×10^9/L or, < 1.0×10^9/L that was predicted to fall to < 0.5×10^9/L within 48 hours, with fever or clinical signs of sepsis; for observational studies, in-patient stay with a diagnosis for neutropenia, fever or infection; or where there was a variant of these definitions.

- **Results**

Of the 2258 identified publications, 13 studies satisfied eligibility criteria. Eight retrospective observational studies[9-16], one prospective cohort study[17], one phase I dose escalation study[18], and three RCTs were included.[19-21]

Six studies evaluated filgrastim versus pegfilgrastim[11,13,16-19], two studies evaluated placebo versus pegfilgrastim[20,21], one study evaluated filgrastim or not treated versus pegfilgrastim[10], and one study evaluated lipegfilgrastim versus pegfilgrastim[12]. Three studies evaluated patients receiving Q2W compared to Q3W regimens with prophylactic pegfilgrastim.[9,14,15]

The identified tumor types included breast, colon, rectal, gastric, pancreatic, esophageal, small bowel cancers, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma.

<u>FN (n=13 studies):</u>

- All three RCTs showed lower incidence of FN with pegfilgrastim compared with filgrastim or placebo. [16,19,20]
- Four of six non-RCT studies evaluating filgrastim versus pegfilgrastim showed lower or comparable incidence of FN with pegfilgrastim compared to filgrastim, or compared to filgrastim or not treated.[10,13,17,18]
- Two of three studies comparing Q2W regimens with pegfilgrastim to Q3W regimens with pegfilgrastim, found comparable rates of FN.[9,15]
- One study demonstrated higher incidence of FN in pegfilgrastim compared with lipegfilgrastim[12]

<u>Grade 1 - 4 neutropenia (n=9 studies)</u>:

- Of the two RCTs that evaluated neutropenia, both showed lower incidence of neutropenia with pegfilgrastim compared with placebo[20,21]
- Three of five non-RCT studies showed lower incidence of neutropenia with pegfilgrastim compared with filgrastim or not treated.[10,11,18]
- One study observed higher incidence of neutropenia with pegfilgrastim than with lipegfilgrastim.[12]
- In one study comparing Q2W regimens with pegfilgrastim to Q3W regimens with pegfilgrastim, the number of patients with grade ≥ 3 neutropenia was lower in Q2W patients.[9]

All-cause Hospitalization (n=6):

- No significant differences were observed in all-cause hospitalization.[10,14,15,17,19,20]

Dose delays (n=9):

- Two RCTs evaluated pegfilgrastim versus placebo; one found higher incidence of dose delays in patients with placebo compared to pegfilgrastim, while the other found lower incidence of dose delays in placebo compared to pegfilgrastim patients.[20,21]
- Three of four non-RCT studies showed lower or comparable incidence of dose delays with pegfilgrastim compared to filgrastim[11,13,16,17]
- Two of three studies comparing pegfilgrastim in Q2W patients with Q3W patients, found similar incidence of dose delays.[9,15]

Adverse Events (n=6):

- Three RCTs and 3 non-RCT studies evaluated adverse and safety events, and only small differences in the rates of adverse were reported between pegfilgrastim, placebo, filgrastim, or lipegfilgrastim.[9,12,18-21]

Mortality (n=2):

- No significant differences were reported in mortality data when comparing patients treated with pegfilgrastim to placebo.[20,21]

- **Discussion**

In this systematic literature review of patients receiving prophylactic pegfilgrastim versus no prophylactic pegfilgrastim or prophylaxis with other G-CSF following Q2W chemotherapy regimens, we did not observe differences in efficacy, effectiveness, or adverse event profiles. Thus, this systematic identification and appraisal of literature supports the current NCCN and EORTC guidelines on the use of prophylactic G-CSF in patients receiving Q2W chemotherapy regimens with intermediate or high risk for FN.

- **Marketing Authorization Holder(s)**

  Amgen, Inc

- **Names and Affiliations of Principal Investigators**

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