Summary Table of Study Protocol

Title	A Prospective Observational Study to Estimate the Incidence of Febrile Neutropenia (FN) Among Subjects With Non-myeloid Malignancies at High Risk for FN and Receiving Neulasta® (pegfilgrastim) Onpro® kit or Other Physician Choice Options for Prophylaxis of FN
Protocol number	20170758
Date of last version of the protocol	19 June 2018
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Neulasta® (pegfilgrastim) Onpro® kit
Medicinal Product	Neulasta (pegfilgrastim) Onpro kit
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	**Research Question**: What is the risk of febrile neutropenia (FN) over first four myelosuppressive chemotherapy cycles among subjects with non-myeloid malignancies at high risk of FN and receiving Neulasta® (pegfilgrastim) Onpro® kit or other physician choice options for prophylaxis of FN? **Primary Objective**: The primary objective of the study is: • to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis Subjects will be classified in subgroups of FN prophylaxis (Neulasta Onpro kit versus other physician choice options for FN prophylaxis) based on the first cycle administration. The Neulasta Onpro kit with every administered chemotherapy cycle group will be a subset of the group defined as Neulasta Onpro kit.

Research Question and Objectives (Continued)	**Secondary Objectives**: The secondary objectives are to: • to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis, in the curative setting • to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis, in the palliative setting • to compare granulocyte-colony stimulating factor (G-CSF) persistence in subjects who received Neulasta Onpro kit with subjects who received other physician choice options for FN prophylaxis • to compare chemotherapy delivery in subjects who received Neulasta Onpro kit and in subjects who received other physician choice options for FN prophylaxis • to describe adverse events in subjects treated with Neulasta Onpro kit and other physician choice options for FN prophylaxis • to compare G-CSF compliance in subjects who received Neulasta Onpro kit with subjects who received pegfilgrastim prefilled syringe (PFS) or pegfilgrastim biosimilar PFS for FN prophylaxis • to estimate the relative risk of FN in subjects who received Neulasta Onpro kit with subjects who received other physician choice options for FN prophylaxis overall, in the curative setting, and in the palliative setting • to estimate the relative risk of FN in subjects who received Neulasta Onpro kit in every administered chemotherapy cycle with subjects who received other physician choice options for FN prophylaxis overall, in the curative setting, and in the palliative setting **Exploratory Objectives:** • explore the impact of FN events on subject-reported health-related quality of life (HRQoL) • describe G-CSF support, utilization, and access for all study subjects
Country of Study	United States
Author	PPD [redacted]

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen
MAH Contact	NA

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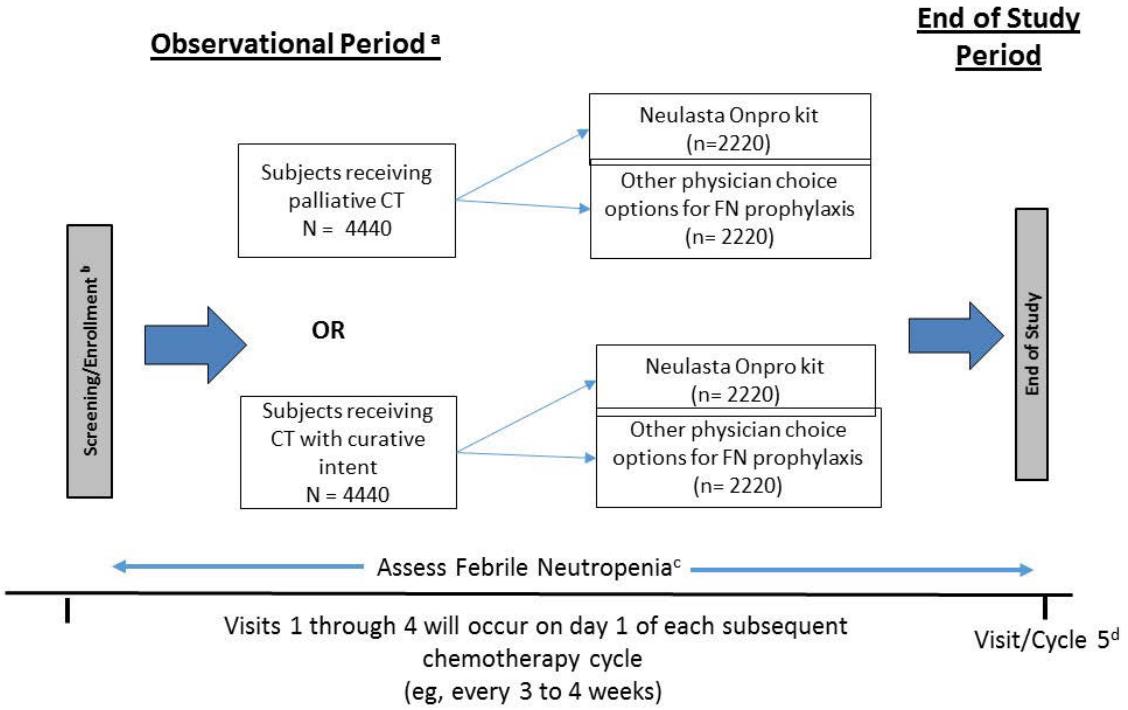
Investigator's Agreement

I have read the attached protocol entitled A Prospective Observational Study to Estimate the Incidence of Febrile Neutropenia (FN) among Subjects with Non-myeloid Malignancies at High Risk for FN and receiving Neulasta® (pegfilgrastim) Onpro® kit or Other Physician Choice Options for Prophylaxis of FN, dated 19 June 2018, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator <<*Coordinating Investigator*>>	Date (DD Month YYYY)

Study Design Schema



CT = chemotherapy; EOS = end of study; FN = febrile neutropenia; G-CSF = Granulocyte-colony stimulating factor

[a] Each subject will be followed during the observational period from the screening/enrollment visit 1/cycle 1 (day 1) through visit 4 on day 1 of each subsequent chemotherapy cycle (a chemotherapy cycle can range from 3 to 4 weeks in duration). If the subjects' chemotherapy was delayed for any reason, study visits can be delayed to coincide with day 1 (± 7 days) of the subjects chemotherapy cycle. Subject enrollment into each of the 4 subgroups will be stopped once 2220 subjects have been enrolled.

[b] Subjects diagnosed with breast cancer, lung cancer, non-Hodgkin lymphoma, or prostate cancer and receiving CT regimen with FN risk > 20% or 10% to 20% with 1 risk factor for FN. Enrollment will occur at the same time as visit 1/cycle 1/day 1. Subjects who received chemotherapy up to 1 week prior to enrollment are eligible to participate in the study.

[c] Subjects who experience FN can receive Neulasta Onpro kit or other physician choice options (eg, Neulasta PFS, pegfilgrastim biosimilar PFS [ie, Neulasta biosimilar], filgrastim, tbo-filgrastim, filgrastim-sndz or no prophylaxis).

[d] Subjects who discontinue chemotherapy, start radiation therapy or withdraw from the study, will be assessed for the final study visit 21 to 30 days (± 3 days) after the last scheduled visit. Subjects who discontinue chemotherapy, switch to a regimen not specified in Appendix E prior to completing 4 cycles, start radiation therapy or withdraw from the study will be assessed for the final study visit 21 to 30 days (± 3 days) after the last visit scheduled study visit where the subject received originally planned chemotherapy regimen. Subject follow-up will continue for a total of 4 cycles if chemotherapy dose is reduced, or the regimen is switched to 1 listed in Appendix E. Regimen discontinuation is defined as discontinuation of all chemotherapy or switch to a non-protocol specified regimen (regimen not listed in Appendix E). The EOS period (visit 5) will occur up to 21 to 30 days (± 3 days) after visit 4 for subjects who have received 4 cycles of chemotherapy. For subjects who receive 5 cycles of chemotherapy treatment, the final study visit will be on day 1 of visit 5 (± 3 days). Attempts will be made to bring subjects for EOS visit or gather additional information using telephonic interview in case of loss to follow-up or withdrawal of consent.

Table 1. Schedule of Activities

Schedule Procedure		**Observational Period[a] (± 7 days)**			**EOS Period (or early withdrawal)[b] (± 3 days)**
	Screening/ Enrollment/ Visit 1/Cycle 1 (day 1)[c]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Informed consent[d]	X				
Demographics[e]	X				
Medical history[f]	X				
Physical measurements[g]	X				
Health plan information[h]	X				
Substance use[i]	X				
Physical examination	X	X	X	X	X
Vital signs[j]	X	X	X	X	X
Hematology (if available)[k]	X	X	X	X	
Chemistry (if available)[k]	X				
ECOG performance status	X	X	X	X	X
Concomitant medications[l]	X	X	X	X	X
Call to IVR/IWR system[m]	X				X
Chemotherapy administration[n]	X	X	X	X	X
G-CSF administration[o]	X	X	X	X	X
Emergency room visit/hospitalization[p]		X	X	X	X
Adverse events[q]	X	X	X	X	X
SF-12	X	X	X	X	X

Footnotes on next page.

CMP = comprehensive metabolic profile; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; G-CSF = granulocyte-colony stimulating factor; IVR = interactive voice response; IWR = interactive web response; SF-12 = short form health survey

[a] Each subject will be followed during the observational period from the screening/enrollment visit 1/cycle 1 (day 1) through visit 4 on day 1 of each subsequent chemotherapy cycle (a chemotherapy cycle can range from 3 to 4 weeks in duration). If the subjects' chemotherapy was delayed for any reason, study visits can be delayed to coincide with day 1 (± 7 days) of the subjects chemotherapy cycle. At each visit, determination should be made if chemotherapy was discontinued or interrupted, chemotherapy dose was reduced or modified to a different regimen prior to the completion of 4 cycles, or the subject' was lost to follow-up or withdrew consent.

[b] Subjects who discontinue chemotherapy, switch to a regimen not specified in Appendix E prior to completing 4 cycles, start radiation therapy or withdraw from the study will be assessed for the final study visit 21 to 30 days (± 3 days) after the last visit scheduled study visit where the subject received originally planned chemotherapy regimen. Subject follow-up will continue for a total of 4 cycles if chemotherapy dose is reduced, or the regimen is switched to 1 listed in Appendix E. Regimen discontinuation is defined as discontinuation of all chemotherapy or switch to a non-protocol specified regimen (regimen not listed in Appendix E). The EOS period (visit 5) will occur up to 21 to 30 days (± 3 days) after visit 4 for subjects who have received 4 cycles of chemotherapy. For subjects who receive 5 cycles of chemotherapy treatment, the final study visit will be on day 1 of visit 5 (± 3 days). Attempts will be made to bring subjects for EOS visit or gather additional information using telephonic interview in case of loss to follow-up or withdrawal of consent.

[c] Subjects who received chemotherapy up to 1 week prior to enrollment are eligible to participate in the study. Visit 1/cycle 1 is to coincide with day 1 (± 7 days) of the subjects' chemotherapy treatment. Subjects who started chemotherapy prior to protocol enrollment should have their initial study visit within 7 days of being identified as protocol eligible. Data collection should be retroactive to day 1/visit 1/cycle 1.

[d] Prior to any data collection, eligibility must be verified and all subjects or their legally authorized representative must sign and personally date the informed consent form. Subjects who initiated chemotherapy up to 1 week prior to enrollment (visit 1/cycle 1 is to coincide with day 1 [± 7 days] of the subjects' chemotherapy treatment) and meet the inclusion and exclusion criteria at selected sites will be enrolled.

[e] To include age, sex, and race.

[f] To include medical conditions, malignancy for which subject is receiving chemotherapy, malignancy characteristics (eg, malignancy histology, date of initial malignancy diagnosis, stage at diagnosis, current malignancy stage, any previous cancer therapy [radiation, surgery or chemotherapy]), concurrent chronic medical conditions, and history of other malignancies except for non-melanoma skin cancer.

[g] To include height in centimeters and weight in kilograms.

[h] Obtain the following health plan information at study enrollment: no insurance, Medicare, Medicaid, dual eligible, commercial insurance (eg, Aetna, Anthem, Blue Cross Blue Shield).

[i] Collect tobacco history and/or use.

[j] The following measurements will be recorded: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. The investigator is to collect all fever episodes from the subject since the last office visit.

[k] During the subject's chart review, will be collected if available.

[l] Prior and concomitant medications will be collected up to 30 days prior to the initial visit through the EOS.

[m] Study staff are to call the IVR/IWR system to enroll eligible subjects into the study and receive a unique subject identification number.

[n] The following must be collected for chemotherapy regimens (eg, curative, palliative) that are administered: drug name, dosage, and date(s) administered. At visit 2 and beyond, if chemotherapy regimen has changed the following must be collected: change in dose and reason for change.

[o] If G-CSF is administered the following must be collected: name of G-CSF used including dose and date(s) administered.

[p] Collect and record 1 of the following if applicable on the appropriate electronic case report form (eCRF): emergency room visit led to hospitalization, emergency room visit led to discharge home, or hospitalization without emergency room visit. If subject was seen in the emergency room or was hospitalized the investigator will obtain these records and record the following: fevers, complete blood count (CBC) data collection, and any antibiotic use (including name of antibiotic used).

[q] Adverse events (refer to Appendix G for adverse events that will not be collected throughout the study) and product complaints will be reported from the screening/enrollment visit (day 1) until EOS.

1. Table of Contents

List of Tables

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2. List of Abbreviations

Abbreviation	Definition
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BP	bodily pain
CBC	complete blood count
CHF	congestive heart failure
CI	confidence Interval
CIS	carcinoma in situ
C_{max}	maximum (or peak) serum concentration that a drug achieves in a specific test area of the body
COPD	chronic obstructive pulmonary disease
CTCAE	Common Terminology for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMR	electronic medical record
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
FDA	Food and Drug Administration
FN	febrile neutropenia
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GEE	generalized estimating equations
GH	general health
HCPCS	Healthcare Common Procedure Coding System
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IV	intravenous
IVR	Interactive Voice Response
IWR	Interactive Web Response
LDH	lactate dehydrogenase

Abbreviation	Definition
LLN	lower limit of normal
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MH	mental health
MS	multiple sclerosis
MSM	marginal structural model
NCCN	National Comprehensive Cancer Network
NHL	non–Hodgkin Lymphoma
OBI	on-body injector
PF	physical functioning
PFS	prefilled syringe
RA	rheumatoid arthritis
RDI	relative dose intensity
RE	role-emotional
RP	role-physical
SD	standard deviation
SEC	Self-Evident Corrections
SF	social functioning
SF-12	short form health survey
SLE	Systemic Lupus Erythematosus
SN	severe neutropenia
SOPs	standard operating procedures
ULN	upper limit of normal
US	United States
USPI	US package insert
VT	vitality
WBC	white blood cell

3. Responsible Parties

Amgen will identify appropriate sites in the United States (US) and initiate the protocol at these sites after contract finalization.

4. Abstract

- **Study Title:**

A Prospective Observational Study to Estimate the Incidence of Febrile Neutropenia (FN) among Subjects with Non-myeloid Malignancies at High Risk for FN and receiving Neulasta® (pegfilgrastim) Onpro® kit or Other Physician Choice Options for Prophylaxis of FN

- **Study Background and Rationale:**

Severe neutropenia (SN) and febrile neutropenia (FN) are major chemotherapy toxicities and are associated with increased morbidity and mortality, as well as dose reductions and delays, which can compromise treatment efficacy. Severe neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an ANC < 1000 neutrophils/mcL with a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours. Neutropenia can develop into FN (> 38.3°C orally or > 38°C over a 1-hour period), which is typically a reason for dose limiting chemotherapy and often requires hospitalization and broad spectrum antibiotic administration (Crawford et al, 2017).

Prevention for SN and FN has focused on granulocyte-colony stimulating factor (G-CSF) drugs such as filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. These drugs have been studied in the context of primary and secondary FN prevention with an emphasis on primary prevention. Meta-analyses of clinical studies have confirmed the efficacy of G-CSF in decreasing rates of infection and risk of neutropenia (Mhaskar et al, 2014; Kuderer et al, 2007; Sung et al, 2007; Clark et al, 2005). Pegfilgrastim is highly effective at reducing FN risk by 94% in breast cancer patients receiving docetaxel 100 mg/m^2 every 3 weeks (Vogel et al, 2005). Febrile neutropenia continues to be a significant clinical problem in the US despite the availability of multiple G-CSF agents. There were approximately 91 000 hospitalizations secondary to FN in the US in 2012 (Tai et al, 2017). The reasons for the continued high incidence of FN are multi-factorial and are likely related to inadequate use of G-CSF therapy, challenging healthcare economics, and the logistical burden associated with G-CSF therapy.

The Neulasta (pegfilgrastim) Onpro kit with its innovative on-body injector (OBI) technology was designed to eliminate the need for next-day travel requirement associated with other forms of G-CSF. The OBI administers the full dose of pegfilgrastim automatically to the patient approximately 27 hours after chemotherapy. A safety and pharmacokinetic randomized equivalence study of pegfilgrastim administered via the OBI compared to pegfilgrastim administered via the prefilled syringe (PFS) revealed comparable pegfilgrastim pharmacokinetics between the delivery methods (Yang et al, 2015).

Little is known about the real-world risk of FN among subjects receiving Neulasta (pegfilgrastim) Onpro kit or other physician choice options (ie, Neulasta PFS, pegfilgrastim biosimilar PFS or short-acting filgrastim molecules or no G-CSF for prophylaxis of FN). There is limited real world information on whether the improved convenience from the Neulasta Onpro kit provides improved subject persistence and compliance with G-CSF prophylaxis. Retrospective exploration of claims based on real world data has been unsuccessful at comparing the efficacy of Neulasta Onpro kit, as an FN prevention tool, to other FN prevention strategies. There are 2 reasons for the failure of retrospective claims-based data in answering this question: the lack of ICD-9/ICD-10 code for FN and the lack of a separate Healthcare Common Procedure Coding System (HCPCS) code that differentiates the Neulasta Onpro kit from the Neulasta PFS.

This prospective observational cohort study is designed to estimate the risk of FN among subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered cycle, and other physician choice options FN prophylaxis in subjects who are at high risk for FN while receiving myelosuppressive chemotherapy.

- **Research Question and Objectives:**
- **Research Question**

  What is the risk of febrile neutropenia (FN) over first 4 myelosuppressive chemotherapy cycles among subjects with non-myeloid malignancies at high risk of FN and receiving Neulasta® (pegfilgrastim) Onpro® kit or other physician choice options for prophylaxis of FN?

- **Primary Objective**

  The primary objective of the study is:

  - to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis.

Subjects will be classified in subgroups of FN prophylaxis (Neulasta Onpro kit versus other physician choice options for FN prophylaxis) based on the first cycle administration. The Neulasta Onpro kit with every administered chemotherapy cycle group will be a subset of the group defined as Neulasta Onpro kit.

- **Secondary Objectives**

  The secondary objectives are to:

  - to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis, in the curative setting
  - to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis, in the palliative setting
  - to compare granulocyte-colony stimulating factor (G-CSF) persistence in subjects who received Neulasta Onpro kit with subjects who received other physician choice options for FN prophylaxis
  - to compare chemotherapy delivery in subjects who received Neulasta Onpro kit and in subjects who received other physician choice options for FN prophylaxis
  - to describe adverse events in subjects treated with Neulasta Onpro kit and other physician choice options for FN prophylaxis
  - to compare G-CSF compliance in subjects who received Neulasta Onpro kit with subjects who received pegfilgrastim prefilled syringe (PFS) or pegfilgrastim biosimilar PFS for FN prophylaxis
  - to estimate the relative risk of FN in subjects who received Neulasta Onpro kit with subjects who received other physician choice options for FN prophylaxis overall, in the curative setting, and in the palliative setting
  - to estimate the relative risk of FN in subjects who received Neulasta Onpro kit in every administered chemotherapy cycle with subjects who received other physician choice options for FN prophylaxis overall, in the curative setting, and in the palliative setting

- **Exploratory Objectives**
  - explore the impact of FN events on subject-reported health-related quality of life (HRQoL)
  - describe G-CSF support, utilization, and access for all study subjects
- **Hypothesis(es)/Estimation**

This is an estimation study and no hypothesis will be tested in this study. We will estimate the incidence proportion and 95% confidence interval (CI) for FN during the chemotherapy course (up to 4 cycles) among subjects receiving Neulasta Onpro Kit, Neulasta Onpro Kit in every administered cycle, and other physician choice options for prophylaxis of FN, in high risk subjects receiving myelosuppressive chemotherapy for the treatment of breast cancer, lung cancer, prostate cancer, and non-Hodgkin lymphoma (NHL).

- **Study Design/Type**

This is a multicenter, prospective, observational cohort study in subjects receiving myelosuppressive chemotherapy for a non-myeloid malignancy and are considered at high risk for developing FN.

- **Study Population and Data Resource**

This study will be conducted in subjects diagnosed with biopsy-proven confirmed breast cancer, lung cancer, NHL, or prostate cancer, who are receiving myelosuppressive chemotherapy and are at “high risk” for FN.

Subjects at “high risk” for FN will be defined as subjects receiving high risk chemotherapy regimens with FN risk > 20%, or intermediate risk chemotherapy regimen with FN risk between 10% to 20% and 1 additional risk factor for FN.

Subject enrollment is expected to take approximately 18 months. Each subject will be followed for approximately 4 months from time of enrollment to the end of study (EOS).

The study data will be captured using the study electronic case report form (eCRF), which will contain information collected directly about the subjects and their treatment/outcomes from the healthcare study research personnel. The data to be entered into the eCRF will be obtained from paper records or electronic medical records depending on the technology used by individual sites. The short form health survey (SF-12) HRQoL instrument will be used for HRQoL outcomes.

A steering committee will be formed to monitor the study conduct and data.

- **Summary of Subject Eligibility Criteria**

Subjects with biopsy-proven breast cancer, lung cancer, NHL or prostate cancer starting myelosuppressive chemotherapy in the neoadjuvant/adjuvant or first line advanced/metastatic setting with at least 4 anticipated chemotherapy cycles. Subjects must be at high risk for getting FN and have adequate hepatic and renal function.

- **Follow-up**

Subjects will be followed from study enrollment until the earliest of loss to follow-up, withdrawal of consent, death, EOS, premature discontinuation of chemotherapy regimen prior to 4 cycles, or termination of study by the sponsor.

- **Variables**

Primary Endpoint:

- FN during the study period: defined as ANC < 1000 x 10^6/L and 1 of the following occurring within 24 hours of decreased ANC: temperature > 38°C (100.4°F), use of specific oral antibiotics (eg, ciprofloxacin, levofloxacin, moxifloxacin, amoxicillin-clavulanate), or intravenous (IV) antibiotic use

Secondary Endpoints:

- FN during the study period for subjects receiving chemotherapy with curative intent
- FN during the study period for subjects receiving chemotherapy with palliative intent
- persistence with G-CSF therapy
    - consistent G-CSF support for all chemotherapy cycles (consistent G-CSF support is defined as 1 Neulasta Onpro kit per cycle, 1 Neulasta PFS per cycle, 1 pegfilgrastim biosimilar PFS per cycle, or 10 short acting G-CSF injections per cycle) regardless of timing G-CSF administration
- chemotherapy delivery
    - discontinuation (cessation of the planned chemotherapy regimen on or before cycle 4)
    - dose delays (extension of the time between planned chemotherapy cycles on or before cycle 4)
    - dose reductions (reduction in the dose of the planned chemotherapy on or before cycle 4)
- adverse events
- compliance with pegfilgrastim therapy
    - pegfilgrastim administered on the day after the last day of chemotherapy administration

Exploratory Endpoints:

- SF-12 scores
- Neulasta Onpro kit denial by payer as measured by eCRF questionnaire
- type of G-CSF administered and date administered

- **Exposure Assessment**
  - type of prophylaxis for FN: exposure of interest is whether a subject received Neulasta Onpro kit FN prophylaxis or other therapy physician choice options for FN prophylaxis with each chemotherapy cycle. For all chemotherapy cycles record if the subject received Neulasta Onpro kit or other physician choice options for FN prophylaxis (eg, Neulasta PFS, pegfilgrastim biosimilar PFS, filgrastim, tbo-filgrastim, filgrastim-sndz or no G-CSF prophylaxis).
  - timing of prophylaxis for FN: record the date, dose, and cycle for subjects who received Neulasta Onpro kit FN prophylaxis. Record the date, dose, and cycle for subjects who received other physician choice options for FN prophylaxis (eg, Neulasta PFS, pegfilgrastim biosimilar PFS, filgrastim, tbo-filgrastim, filgrastim-sndz or no G-CSF prophylaxis). For subjects who do not receive FN prophylaxis, this will be recorded into the eCRF along with the reasons for omission. Febrile neutropenia prophylaxis administration information will be collected for up to 4 cycles of chemotherapy.
  - exposures of interest include myelosuppressive chemotherapy regimens, chemotherapy drugs used and the days the chemotherapy drugs were administered. Chemotherapy regimens and doses will be repeatedly collected for a maximum of 4 cycles of chemotherapy. Chemotherapy regimens will be classified as “high risk” (> 20% risk of developing FN), or “intermediate risk” (10% to 20% risk of developing FN) as listed in Appendix E. Name(s), dose(s), and date(s) of administration of any concomitant targeted therapy agent(s) administered along with chemotherapy will also be recorded.
- **Covariates**

The following factors are baseline covariates believed to be potential risk factors for FN that are potential confounders in examining the association of FN prophylaxis (Neulasta Onpro kit versus other physician choice options) and the onset of FN, and therefore, will be considered in the analyses.

- tumor type (breast cancer, lung cancer, NHL, prostate cancer)
- chemotherapy regimen
- age in years
- sex (male, female)
- health plan information
- Eastern Cooperative Oncology Group (ECOG) performance status
- comorbidities (eg, hypertension, coronary artery disease, congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD], renal dysfunction, diabetes mellitus)

- baseline laboratory measurements (hemoglobin, ANC, white blood cell [WBC], platelets, lactate dehydrogenase [LDH], and alkaline phosphatase)
- history of any other malignancy except non-melanoma skin cancer
- prior surgery within 6 months prior to study enrollment
- bone marrow involvement
- antibiotic use prior to initiation of chemotherapy
- prior history of chemotherapy within 6 months prior to study enrollment
- prior history of radiation therapy within 6 months prior to study enrollment

- **Study Sample Size**

The target sample size is 2000 subjects receiving Neulasta Onpro kit and 2000 subjects receiving other physician choice options for FN prophylaxis, for a total of 4000 subjects. Due to the requirement to capture adequate data in subjects receiving chemotherapy with palliative as well as curative intent, 4000 subjects are required in each chemotherapy cohort, for a total of 8000 subjects. Accounting for drop-out, a final overall sample size of 8880 is anticipated.

- **Data Analysis**

The first interim analysis will be performed after 1000 subjects have been enrolled and the second interim analysis will be performed after 2000 subjects have been enrolled. Data on baseline subject characteristics, chemotherapy treatment, G-CSF prophylaxis use (including discontinuation within the Neulasta Onpro kit subjects), and incidence of FN and extent of missing covariate in the overall subject population will be summarized. No formal comparison of FN outcomes between Neulasta Onpro kit and other physician choice options subjects will be performed at either of the interim analyses. However, compliance and persistence will be described at each of the 2 interim analyses. G-CSF support, utilization and access data will also be described at the 2 interim analyses.

5. Amendments and Updates

None.

6. Milestones

Milestone	Planned date
Start of data collection	Q4 2018
Interim Analysis 1	will occur when 1000 subjects have been enrolled
Interim Analysis 2	will occur when 2000 subjects have been enrolled
End of data collection	Q4 2020
Final Observational Research Study Report	within 12 months of the end of data collection

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Severe neutropenia (SN) and febrile neutropenia (FN) are major chemotherapy toxicities and are associated with increased morbidity and mortality, as well as dose reductions and delays, which can compromise treatment efficacy. Severe neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an ANC < 1000 neutrophils/mcL with a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours. Neutropenia can develop into FN (> 38.3°C orally or > 38°C over a 1-hour period), which is typically a reason for dose limiting chemotherapy and often requires hospitalization and broad spectrum antibiotic administration (Crawford et al, 2017).

Approximately 25% to 40% of chemotherapy-naïve patients develop FN when exposed to common chemotherapy regimens (Dale et al, 2003). A number of factors have been shown to be associated with increased risk of developing SN or FN, including age, chemotherapy regimen (Lalami et al, 2006), performance status, and baseline blood cell counts (Ray-Coquard et al, 2003). These and other factors have been systematically studied with the goal of predicting the risk of a specific patient to develop SN or FN (Lyman et al, 2011).

Prevention for SN and FN has focused on G-CSF drugs such as filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. These drugs have been studied in the context of primary and secondary FN prevention with an emphasis on primary prevention. Meta-analyses of clinical studies have confirmed the efficacy of G-CSF in decreasing rates of infection and risk of neutropenia (Mhaskar et al, 2014; Kuderer et al, 2007; Sung et al, 2007; Clark et al, 2005). Pegfilgrastim is highly effective at reducing FN risk by 94% in breast cancer patients receiving docetaxel 100 mg/m^2 every 3 weeks (Vogel et al, 2005). Hospitalization and anti-infective use were decreased. Pegfilgrastim has been compared with daily filgrastim in breast cancer patients receiving a regimen consisting of epirubicin and either docetaxel or paclitaxel. Febrile neutropenia rates were similar in patients who received pegfilgrastim versus filgrastim (Schippinger et al, 2006). The main toxicity associated with G-CSF treatment is mild to moderate bone pain, which can affect 10% to 30% of patients. This is typically controlled with non-narcotic analgesics (Crawford et al, 2017).

Febrile neutropenia continues to be a significant clinical problem in the United States (US) despite the availability of multiple G-CSF agents. There were approximately

91 000 hospitalizations secondary to FN in the US in 2012 (Tai et al, 2017). The reasons for the continued high incidence of FN are multi-factorial and are likely related to inadequate use of G-CSF therapy, challenging healthcare economics, and the logistical burden associated with G-CSF therapy. G-CSF therapy is inadequately used when fewer than 10 filgrastim injections are given per cycle, or in the case of pegfilgrastim, when it is used on a day other than the day after chemotherapy administration or stopped prematurely (Weycker et al, 2006; Weycker et al, 2017a; Weycker et al, 2017b). Filgrastim, tbo-filgrastim and filgrastim-sndz all have short half-lives and are administered for multiple days following chemotherapy. Pegfilgrastim is longer acting than filgrastim, therefore making it possible to be administered as a single subcutaneous injection of 6 mg per chemotherapy cycle. The introduction of pegfilgrastim reduced the need for repeated office visits associated with the use of filgrastim, tbo-filgrastim and filgrastim-sndz. However, filgrastim, pegfilgrastim, filgrastim-sndz, and tbo-filgrastim are all associated with the logistical burden for next-day administration. A recent study demonstrated that next day pegfilgrastim administration resulted in an extra 33 minutes and 23-mile travel burden when administered the day after chemotherapy (Stephens et al, 2017). The logistical burden associated with next day administration may result in skipped or inappropriately timed G-CSF following chemotherapy (Hauber et al, 2018). Skipped or inappropriately timed doses of G-CSF may result in increased FN risk (Lyman et al, 2017). Despite the availability of multiple agents, 40% of first cycle high/intermediate risk chemotherapy is not supported by G-CSF (Amgen internal data). A recent retrospective analysis demonstrated that patients who received pegfilgrastim on the same day as chemotherapy had increased FN risk compared to patients who received pegfilgrastim day after chemotherapy (Weycker et al, 2017a; Weycker et al, 2017b). These factors demonstrate the need for patient focused and convenient therapy that will not result in additional logistical and travel burden for critical G-CSF administration. The Neulasta Onpro kit can help to overcome the logistical challenges posed by the traditional methods of G-CSF administration. As described below, Neulasta Onpro kit is applied the same day as chemotherapy administration and administers pegfilgrastim 27 hours later. Because it can be applied the same day as chemotherapy, the Neulasta Onpro kit overcomes the challenge of next day travel for pegfilgrastim administration. It also helps overcome the issue of pegfilgrastim administration occurring on the wrong day, by automatically administering the agent 27 hours after it is placed on the body. These properties of the Neulasta Onpro kit allow

for its use with every administered chemotherapy cycle, where appropriate per the prescribing Information.

7.2 Product Background

7.2.1 Neulasta (pegfilgrastim) Onpro Kit

Information on the safety and activity of Neulasta (pegfilgrastim) and the Neulasta (pegfilgrastim) Onpro kit may be found in the US package insert (USPI).

On 31 January 2002, the US Food and Drug Administration (FDA) approved Neulasta (pegfilgrastim). On 23 December 2014, the FDA approved (pegfilgrastim) Onpro kit which includes an on-body injector (OBI) device and a prefilled syringe (PFS) containing pegfilgrastim. The PFS is used to load the OBI with pegfilgrastim. The OBI is applied on patients by a healthcare provider on the same day as chemotherapy, which automatically administers the pegfilgrastim dose 27 hours after placement. The Neulasta (pegfilgrastim) Onpro kit with its innovative OBI technology was designed to eliminate the need for next-day travel requirement associated with other forms of G-CSF. The OBI administers the full dose of pegfilgrastim automatically to the patient approximately 27 hours after chemotherapy. A safety and pharmacokinetic randomized equivalence study of pegfilgrastim administered via the OBI compared to pegfilgrastim administered via the PFS revealed comparable pegfilgrastim pharmacokinetics between the delivery methods (Yang et al, 2015). The mean area under the curve $(AUC)_{0\text{-inf}}$ values for the OBI and manual injection were 10 900 and 11 100 ng/mL, respectively, mean maximum (or peak) serum concentration that a drug achieves in a specific test area of the body (C_{max}) values were 248 and 262 ng/mL, respectively. The least squares geometric mean ratios were 0.97 for C_{max} and 1.00 for $AUC_{0\text{-inf}}$ with 90% CI within pre-specified range indicating comparable pharmacokinetics.

7.3 Rationale

Little is known about the real-world risk of FN among subjects receiving Neulasta (pegfilgrastim) Onpro kit or other physician choice options (ie, Neulasta PFS, pegfilgrastim biosimilar PFS or short-acting filgrastim molecules, or no G-CSF for prophylaxis of FN). There is limited real world information on whether the improved convenience from the Neulasta Onpro kit provides improved subject persistence and compliance, with G-CSF prophylaxis. Retrospective exploration of claims based on real world data has been unsuccessful at comparing the efficacy of Neulasta Onpro kit, as an FN prevention tool, to other FN prevention strategies. There are 2 reasons for the failure of retrospective claims-based data in answering this question: the lack of

ICD-9/ICD-10 code for FN and the lack of a separate HCPCS code that differentiates the Neulasta Onpro kit from the Neulasta PFS.

Current National Comprehensive Cancer Network (NCCN) guidelines recommend G-CSF based FN prophylaxis for subjects receiving regimens with > 20% FN risk or subjects receiving regimens with 10% to 20% FN risk and 1 additional subject risk factor for FN (Crawford et al, 2017). Despite these guidelines on FN prophylaxis, 40% of eligible subjects do not receive G-CSF with the first cycle of chemotherapy (Amgen unpublished data). Randomized comparative clinical studies have shown that the rate of SN (defined as ANC < 0.5 x 10^9/L) is similar in subjects treated with a mean of 10 to 11 daily filgrastim doses per chemotherapy cycle or subjects treated with 1 pegfilgrastim dose per chemotherapy cycle (Holmes et al, 2002; Green et al, 2003). In routine clinical practice, filgrastim prophylaxis is often administered for fewer than 10 to 11 days and is associated with increased incidence of FN and FN-related hospitalizations compared to pegfilgrastim prophylaxis (Morrison et al, 2007; von Minckwitz et al, 2008; Weycker et al, 2009; Tan et al, 2011; Naeim et al, 2013). Current other physician choice options for FN prophylaxis can include Neulasta PFS, pegfilgrastim biosimilar PFS, filgrastim, filgrastim-sndz, tbo-filgrastim, or no treatment. There is no published report evaluating the real-world risk of FN among high risk subjects receiving other physician choice options for FN prophylaxis.

Results from a prospective study that estimates the risk of FN following use of Neulasta Onpro kit, Neulasta Onpro kit in every administered cycle, and other physician choice options (ie, Neulasta PFS, pegfilgrastim biosimilar PFS, short-acting G-CSF prophylaxis or no G-CSF prophylaxis) will be important scientific evidence to add to the existing evidence in the peer-reviewed literature. Robust clinical data will be collected to present incidence proportion and 95% confidence intervals of FN for each sub-group standardized to the overall population .

This prospective observational cohort study aims to collect detailed information on the risk of FN among subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered cycle, and other physician choice options for FN prophylaxis in subjects who are at high risk for FN while receiving myelosuppressive chemotherapy. This study is designed to estimate the risk of FN over the chemotherapy course (up to 4 cycles) with measures of precision among subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered cycle, and other physician choice options for FN prophylaxis. Based on currently available retrospective data, best clinical practice for FN

prophylaxis is pegfilgrastim administered the day after chemotherapy administration for all chemotherapy cycles (Weycker et al, 2006; Weycker et al, 2017a; Weycker et al, 2017b). However, prospective data estimating the risk of FN among subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered cycle, and other physician choice options for FN prophylaxis are not available. Additionally, the study is designed to describe actual clinical practice patterns.

The study population will be stratified into 2 separate groups. The first group will comprise of subjects who are receiving chemotherapy with a curative intent and the second group will comprise of subjects who are receiving chemotherapy with palliative intent. This stratification is necessary because these are 2 very different subject populations. For example, there can be more chemotherapy dose reductions and chemotherapy dose delays in subjects receiving chemotherapy with palliative intent. Therefore, a decision was made to stratify the overall study population into 2 groups based on chemotherapy intent.

7.4 Statistical Inference (Estimation or Hypothesis)

This is an estimation study and no hypothesis will be tested in this study. We will estimate the incidence proportion and 95% Confidence Interval (CI) for FN during the chemotherapy course (up to 4 cycles) among subjects receiving Neulasta Onpro Kit, Neulasta Onpro Kit in every administered cycle, and other physician choice options for prophylaxis of FN, in high risk subjects receiving myelosuppressive chemotherapy for the treatment of breast cancer, lung cancer, prostate cancer, and non-Hodgkin lymphoma (NHL).

8. Research Question and Objectives

What is the risk of febrile neutropenia (FN) over first 4 myelosuppressive chemotherapy cycles among subjects with non-myeloid malignancies at high risk of FN and receiving Neulasta® (pegfilgrastim) Onpro® kit or other Physician Choice Options for Prophylaxis of FN?

8.1 Primary Objective

The primary objective of the study is:

- to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis

Subjects will be classified in subgroups of FN prophylaxis (Neulasta Onpro kit versus other physician choice options for FN prophylaxis) based on the first cycle

administration. The Neulasta Onpro kit with every administered chemotherapy cycle group will be a subset of the group defined as Neulasta Onpro kit.

8.2 Secondary Objectives

The secondary objectives are to:

- to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis, in the curative setting
- to estimate the incidence of FN among subjects treated with myelosuppressive chemotherapy for the treatment of non-myeloid malignancies and receiving Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, or other physician choice options for FN prophylaxis, in the palliative setting
- to compare granulocyte-colony stimulating factor (G-CSF) persistence in subjects who received Neulasta Onpro kit with subjects who received other physician choice options for FN prophylaxis
- to compare chemotherapy delivery in subjects who received Neulasta Onpro kit and in subjects who received other physician choice options for FN prophylaxis
- to describe adverse events in subjects treated with Neulasta Onpro kit and other physician choice options for FN prophylaxis
- to compare G-CSF compliance in subjects who received Neulasta Onpro kit with subjects who received pegfilgrastim prefilled syringe (PFS) or pegfilgrastim biosimilar PFS for FN prophylaxis
- to estimate the relative risk of FN in subjects who received Neulasta Onpro kit with subjects who received other physician choice options for FN prophylaxis overall, in the curative setting, and in the palliative setting
- to estimate the relative risk of FN in subjects who received Neulasta Onpro kit in every administered chemotherapy cycle with subjects who received other physician choice options for FN prophylaxis overall, in the curative setting, and in the palliative setting

8.3 Exploratory Objectives

- explore the impact of FN events on subject-reported health-related quality of life (HRQoL)
- describe G-CSF support, utilization, and access for all study subjects

9. Research Methods

9.1 Study Design

This is a multicenter, prospective, observational cohort study in subjects receiving myelosuppressive chemotherapy for a non-myeloid malignancy and are considered at high risk for developing FN.

Subjects who meet the eligibility criteria (Section 9.2.3.1 and Section 9.2.3.2), have signed the informed consent form and will be initiating their first cycle of chemotherapy (eg, every 3 week or every 4 week regimens) or have recently initiated chemotherapy (within 1 week of study enrollment), will be enrolled into the study at visit 1/cycle 1 (eg, enrollment/screening period [day 1]). Interactive Voice Response (IVR)/Interactive Web Response (IWR) system will be used to facilitate enrollment.

Investigators will record the chemotherapy that is administered to the subject; and whether chemotherapy is being administered curative intent or palliative intent. Subjects will be enrolled and followed in 2 separate cohorts based on chemotherapy intent (ie, curative or palliative). Permitted chemotherapy regimens for visit 1/cycle 1 (day 1) must have an estimated FN risk ≥ 20% OR ≥ 10% (refer to Appendix E) and 1 additional subject risk factor for FN (refer to Appendix F). Chemotherapy dose modifications are not allowed except as specified in Appendix E. Investigators will decide on the type of FN prophylaxis to be administered to the subjects.

The type of FN prophylaxis and the dates of administration will be recorded in the eCRF. The primary endpoint of the study is FN. For analytical purposes, the subjects will be divided into 3 subgroups: Neulasta Onpro kit prophylaxis subgroup, which is defined as subjects receiving Neulasta Onpro kit with the first cycle of chemotherapy Neulasta Onpro kit on-label prophylaxis subgroup, which is defined as subjects receiving Neulasta Onpro kit with every administered chemotherapy cycle (up to 4 cycles), and other physician choice FN prophylaxis subgroup defined as subjects receiving Neulasta PFS, pegfilgrastim biosimilar PFS, daily short-acting filgrastim (Filgrastim, tbo-filgrastim, filgrastim-sndz, or other filgrastim biosimilar) or no G-CSF for FN prophylaxis with the first cycle of chemotherapy.

The FN incidence over the chemotherapy course (up to 4 cycles) will be estimated in these 3 subgroups. There is a separate secondary objective where FN incidence over the chemotherapy course (up to 4 cycles) will be estimated in these three subgroups for subjects receiving chemotherapy with curative intent. In another separate secondary objective, FN incidence over the chemotherapy course (up to 4 cycles) will be estimated in these three subgroups for subjects receiving chemotherapy with palliative intent.

Each subject will be followed during the observational period from the screening/enrollment visit 1/cycle 1 (day 1) through visit 4 on day 1 of each subsequent chemotherapy cycle (a chemotherapy cycle can range from 3 to 4 weeks in duration). If the subjects' chemotherapy was delayed for any reason, study visits can be delayed to

coincide with day 1 (± 7 days) of the subjects chemotherapy cycle. At each visit, a determination should be made if chemotherapy was discontinued or interrupted, chemotherapy dose was reduced or modified to a different regimen prior to the completion of 4 cycles, or if the subject was lost to follow-up or withdrew consent.

The EOS period (visit 5) will occur up to 21 to 30 days (± 3 days) after visit 4 for subjects who have received 4 cycles of chemotherapy. For subjects who receive 5 cycles of chemotherapy treatment, the final study visit will be on day 1 of visit 5 (± 3 days). Attempts will be made to bring subjects for EOS visit or gather additional information using telephonic interview in case of loss to follow-up or withdrawal of consent. The EOS visit can occur up to 30 days following loss to follow-up or withdrawal of consent.

Subjects who discontinue chemotherapy, switch to a regimen not specified in Appendix E prior to completing 4 cycles, start radiation therapy, or withdraw from the study, will be assessed for the final study visit 21 to 30 days (± 3 days) after the last visit scheduled study visit (refer to Table 1 for assessments) where the subject received originally planned chemotherapy regimen. Subject follow-up will continue for a total of 4 cycles if the chemotherapy dose is reduced or regimen is switched to 1 listed in Appendix E and the subject does not meet the criteria for regimen switch or regimen discontinuation. Regimen discontinuation is defined as discontinuation of all chemotherapy or switch to a non-protocol specified regimen (not listed in Appendix E).

Subjects who discontinue will not be replaced.

All data will be collected during routine visits and will be entered into the eCRF.

9.2 Setting and Study Population

The study population will consist of subjects diagnosed with biopsy-proven confirmed breast cancer, lung cancer, NHL, or prostate cancer, who are receiving myelosuppressive chemotherapy and are at “high risk” for FN.

Subjects at “high risk” for FN will be defined as subjects receiving high risk chemotherapy regimens with FN risk > 20%, or intermediate risk chemotherapy regimen with FN risk between 10% to 20% and 1 additional risk factor for FN. The investigator will evaluate the regimen (Appendix E) and subject risk factors (Appendix F) and certify that the subject meets the criteria for being classified as high risk for FN. All eligible subjects will be identified and categorized by the investigator by treatment (palliative chemotherapy or chemotherapy with curative intent).

9.2.1 Study Period

Subject enrollment is expected to take approximately 18 months. Each subject will be followed for approximately 4 months from time of enrollment to the EOS.

Subjects will be enrolled on a continuous basis at participating sites, and each subject will be seen at the study clinic at day 1 of each treatment cycle.

9.2.2 Selection and Number of Sites

Approximately 150 sites will be selected to participate in this study in the US. If study sites do not enroll subjects within approximately 3 months they may be closed to enrollment. Study enrollment will be closely monitored on a frequent basis. Subject enrollment into each of the 4 subgroups will be stopped once 2220 subjects have been enrolled.

Approximately 8880 subjects will be enrolled and stratified into 2 groups:

- approximately 4440 subjects in the palliative chemotherapy group with approximately 2220 subjects receiving Neulasta Onpro kit and approximately 2220 receiving other physician choice options for FN prophylaxis and
- approximately 4440 subjects in the chemotherapy with curative intent group with approximately 2220 subjects receiving Neulasta Onpro kit and approximately 2220 receiving other physician choice options for FN prophylaxis

9.2.3 Subject/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

1. Subject ≥ 18 years of age at the time of signing the informed consent form.
2. Subject with biopsy-proven breast cancer, lung cancer, NHL or prostate cancer starting myelosuppressive chemotherapy in the neoadjuvant/adjuvant or first line advanced/metastatic setting with at least 4 anticipated chemotherapy cycles.
3. Life expectancy > 6 months
4. Subject is starting or has recently (within the past 7 days) started myelosuppressive chemotherapy regimen with every 3 or 4-week cycle with a high FN risk > 20%, OR intermediate FN risk 10% to 20% risk (refer to Appendix E [only regimens listed within this appendix are allowed for enrollment]) and at least 1 risk factor for FN per Appendix F. Addition of non-cytotoxic targeted agents (eg, monoclonal antibodies, anti-angiogenic agents, and kinase inhibitors) to the listed chemotherapy regimens is permitted.
5. Subject who is starting adjuvant chemotherapy, neoadjuvant chemotherapy or first line chemotherapy in the metastatic setting and will be receiving at least 4 cycles of planned chemotherapy.

9.2.3.2 Exclusion Criteria

1. Subject initiating chemotherapy regimen with < 14 days between cytotoxic and G-CSF drug dosing.
2. Planned chemotherapy dose reduction for cycle 1.
3. Known history of serious allergic reactions to pegfilgrastim or filgrastim.
4. Contraindication to short acting G-CSFs, Neulasta PFS, pegfilgrastim biosimilar PFS, or Neulasta Onpro kit.
5. Currently receiving treatment in another investigational device or drug study, or ≤ 28 days before screening/enrollment since ending treatment on another investigational device or drug study(ies).
6. Subject who started first line chemotherapy for metastatic disease who completed adjuvant/neoadjuvant chemotherapy < 6 months prior to study enrollment.
7. Subject who has received radiation < 2 weeks prior to study enrollment.
8. Any co-morbidity (refer to Appendix H) in the opinion of investigator will prevent the subject from receiving chemotherapy.
9. Subject has significant abnormalities on the most recent laboratory test prior to screening/enrollment per the Investigator including but not limited to the following:
    - white blood cell (WBC) < 4, ANC < lower limit of normal (LLN), hemoglobin < 10 g/dL, hematocrit < 30%, platelet count < 100,000, creatinine ≥ 1.5 or glomerular filtration rate < 30 (as calculated by Cockcroft-Gault Equation), total Bilirubin ≥ 2.0, aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≥ 3 x upper limit of normal (ULN), and a subject without liver metastasis or AST/ALT ≥ 5 ULN in a subject with liver metastasis
10. Known human immunodeficiency virus (HIV) infection by history.
11. History of solid organ or stem cell transplant.
12. Concurrent primary cancers except non-melanoma skin cancer, or adequately treated carcinoma in situ (CIS).

9.2.4 Matching

Not applicable.

9.2.5 Baseline Period

After signing the informed consent form, data collection will start at visit 1/cycle 1 (screening/enrollment [day 1]; subjects who received chemotherapy up to 1 week prior to enrollment are eligible to participate in the study). Visit 1/cycle 1 is to coincide with

day 1 (± 7 days) of the subjects' chemotherapy treatment and data collection should be retroactive and start from day 1/visit 1/cycle 1 of chemotherapy. Entries will be recorded during a subject's medical chart review to obtain information on demographic factors, malignancy characteristics (eg, malignancy histology, date of initial malignancy diagnosis, stage at diagnosis, current malignancy stage, any previous cancer therapy [radiation, surgery or chemotherapy]), relevant co-morbidities, laboratory data, and relevant concomitant therapies.

Subjects' socio-demographic and clinical characteristics will be collected on the date of enrollment and include age, sex, geographic region, health plan information, socioeconomic status (employment status), body surface area, and tobacco use. Detailed clinical information and laboratory information will be collected. This includes the subjects' medical and treatment history including co-morbid conditions and history of any other malignancies (including any treatment received for these other malignancies).

9.2.6 Study Follow-up

Subjects will be followed from study enrollment until the earliest of loss to follow-up, withdrawal of consent, death, EOS, premature discontinuation of chemotherapy regimen prior to 4 cycles, or termination of study by the sponsor.

9.3 Variables

9.3.1 Exposure Assessment

- type of prophylaxis for FN: exposure of interest is whether a subject received Neulasta Onpro kit FN prophylaxis or other therapy physician choice options for FN prophylaxis with each chemotherapy cycle. For all chemotherapy cycles record if the subject received Neulasta Onpro kit or other physician choice options for FN prophylaxis (eg, Neulasta PFS, pegfilgrastim biosimilar PFS, filgrastim, tbo-filgrastim, filgrastim-sndz or no G-CSF prophylaxis).
- timing of prophylaxis for FN: record the date, dose, and cycle for subjects who received Neulasta Onpro kit FN prophylaxis. Record the date, dose, and cycle for subjects who received other physician choice options for FN prophylaxis (eg, Neulasta PFS, pegfilgrastim biosimilar PFS, filgrastim, tbo-filgrastim, filgrastim-sndz or no G-CSF prophylaxis). For subjects who do not receive FN prophylaxis, this will be recorded into the eCRF along with the reasons for omission. Febrile neutropenia prophylaxis administration information will be collected up to for 4 cycles of chemotherapy.
- exposures of interest include myelosuppressive chemotherapy regimens, chemotherapy drugs used and the days the chemotherapy drugs were administered. Chemotherapy regimens and doses will be repeatedly collected for a maximum of 4 cycles of chemotherapy. Chemotherapy regimens will be classified as "high risk" (> 20% risk of developing FN), or "intermediate risk" (10% to 20% risk of developing FN) as listed in Appendix E. Name(s), dose(s), and date(s) of administration of any concomitant targeted therapy agent(s) administered along with chemotherapy will also be recorded.

9.3.2 Outcome Assessment

9.3.2.1 Primary Endpoint

- FN during the study period: defined as ANC < 1000 x 10^6/L and 1 of the following occurring within 24 hours of decreased ANC: temperature > 38°C (100.4°F), use of specific oral antibiotics (eg, ciprofloxacin, levofloxacin, moxifloxacin, amoxicillin-clavulanate), or intravenous (IV) antibiotic use

9.3.2.2 Secondary Endpoints

- FN during the study period for subjects receiving chemotherapy with curative intent
- FN during the study period for subjects receiving chemotherapy with palliative intent
- persistence with G-CSF therapy
    - consistent G-CSF support for all chemotherapy cycles (consistent G-CSF support is defined as 1 Neulasta Onpro kit per cycle, 1 Neulasta PFS per cycle, 1 pegfilgrastim biosimilar PFS per cycle, or 10 short acting G-CSF injections per cycle) regardless of timing G-CSF administration
- chemotherapy delivery
    - discontinuation (cessation of the planned chemotherapy regimen on or before cycle 4)
    - dose delays (extension of the time between planned chemotherapy cycles on or before cycle 4)
    - dose reductions (reduction in the dose of the planned chemotherapy on or before cycle 4)
- adverse events
- compliance with pegfilgrastim therapy
    - pegfilgrastim administered on the day after the last day of chemotherapy administration

9.3.2.3 Exploratory Endpoints

- SF-12 scores
- Neulasta Onpro kit denial by payer as measured by eCRF questionnaire
- type of G-CSF administered and date administered

9.3.3 Covariate Assessment

The following factors are baseline covariates believed to be potential risk factors for FN that are potential confounders in examining the association of FN prophylaxis (Neulasta Onpro kit versus other physician choice options) and the onset of FN, and therefore, will be considered in the analyses.

- tumor type (breast cancer, lung cancer, NHL, prostate cancer)
- chemotherapy regimen

- age in years
- sex (male, female)
- health plan information
- Eastern Cooperative Oncology Group (ECOG) performance status
- comorbidities (eg, hypertension, coronary artery disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), renal dysfunction, diabetes mellitus)
- baseline laboratory measurements (hemoglobin, ANC, WBC, platelets, LDH, and alkaline phosphatase)
- history of any other malignancy except non-melanoma skin cancer
- prior surgery within 6 months prior to study enrollment
- bone marrow involvement
- antibiotic use prior to initiation of chemotherapy
- prior history of chemotherapy within 6 months prior to study enrollment
- prior history of radiation therapy within 6 months prior to study enrollment

9.3.4 Validity and Reliability

The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making for a subject's care. Abstractors will be trained on the eCRF to ensure that data entered are accurate.

9.4 Data Sources

The study data will be captured using the eCRF, which will contain information collected directly about the subjects and their treatment/outcomes from the healthcare study research personnel. Data will be entered into the eCRF by research coordinators at the individual sites. The data to be entered into the eCRF will be obtained from paper records or electronic medical records depending on the technology used by individual sites. The short form health survey (SF-12) HRQoL instrument will be used for HRQoL outcomes.

A steering committee will be formed to monitor the study conduct and data. The steering committee will be unblinded to FN outcomes by treatment group at the 2 interim analyses. Enrollment and design adjustments will be considered if the baseline FN rate is not approximately 10% in the other physician choice options group at each interim analysis. The steering committee can recommend a design and enrollment adjustments depending on FN rates at the 2 interim analyses. Enrollment target and study enrollment period will both be increased if the baseline FN rate in the control group is < 7%. The curative chemotherapy cohort is expected to accrue faster than the palliative chemotherapy cohort due to the nature of the chemotherapy regimens that are allowed

in the inclusion criteria. Enrollment in the palliative chemotherapy cohort may be discontinued if only < 25% of the total subjects are being enrolled in this group. Amgen will be blinded to FN incidence in the 2 subgroups at both interim analyses. Amgen will not have access to FN incidence by Neulasta Onpro kit and other physician choice options subgroups. However, compliance and persistence will be described at each of the 2 interim analyses. Early study discontinuation will be considered if < 1000 subjects are enrolled after all the study sites have been active for at least 3 months or if baseline FN incidence in other physician choice options FN prophylaxis subgroup is < 5%. If the study is stopped early or the required sample size is not reached, a formal analysis will be completed with the available data if deemed appropriate by the steering committee.

9.5 Study Size

An internal analysis was performed to assess the incidence of FN in a real-world population of breast, colorectal and lung cancer and NHL subjects ([n = 2294]; Amgen; GHE Supportive Care Study, 2018), which showed that 9.4% of subjects experienced FN during their chemotherapy course. In this dataset, 32% and 11% had received primary and secondary FN prophylaxis support respectively, with a slightly higher use of filgrastim compared to pegfilgrastim.

Table 2 below shows the expected precision for estimating the proportion of subjects with FN, as assessed by the half-width of the 95% CI, for a range of sample sizes and varying assumptions of FN incidence.

Table 2. Expected 95% Confidence Interval Half-widths for FN Incidence

Sample Size (N)	Proportion of Subjects with FN								
	0.06 (6%)	0.065 (6.5%)	0.07 (7%)	0.075 (7.5%)	0.08 (8%)	0.085 (8.5%)	0.09 (9%)	0.095 (9.5%)	0.1 (10%)
1000	0.015	0.015	0.016	0.016	0.017	0.017	0.018	0.018	0.019
1500	0.012	0.012	0.013	0.013	0.014	0.014	0.014	0.015	0.015
2000	0.010	0.011	0.011	0.012	0.012	0.012	0.013	0.013	0.013
2500	0.009	0.010	0.010	0.011	0.011	0.011	0.011	0.011	0.012
3000	0.008	0.009	0.009	0.009	0.010	0.010	0.010	0.010	0.011
3500	0.008	0.008	0.008	0.009	0.009	0.009	0.009	0.009	0.010
4000	0.007	0.008	0.008	0.008	0.008	0.009	0.009	0.009	0.009

For example, in estimation terms, a sample size of 1000 subjects would ensure that the half-width of the 95% CI for an observed proportion of subjects with FN of ≤ 10% would be no larger than 2 percentage points.

A comparison of the estimated 95% CIs for the incidence of FN in each prophylaxis group can further demonstrate the expected precision that a given sample size in each group would provide. Based on assumptions for observed FN incidences of 7.5% and 10% for subjects receiving Neulasta Onpro kit and other physician choice options for FN prophylaxis respectively, with 2000 subjects in each group, the 95% CIs are not expected to overlap:

Neulasta Onpro Kit:	7.5%, 95% CI [6.35% - 8.65%]
Other physician choice options:	10.0%, 95% CI [8.69% - 11.31%]

With fewer than 2000 subjects in each group, the 95% CIs are wider and hence overlap cannot be ruled out. Therefore, the target sample size is 2000 subjects receiving Neulasta Onpro kit and 2000 subjects receiving other physician choice options for FN prophylaxis, for a total of 4000 subjects. Due to the requirement to capture adequate data in subjects receiving chemotherapy with palliative as well as curative intent, 4000 subjects are required in each chemotherapy cohort, for a total of 8000 subjects.

It is possible that some subjects may discontinue Neulasta Onpro kit (switch to receive another G-CSF or receive no G-CSF) while still receiving chemotherapy during the first 4 cycles. The rate of discontinuation will be monitored throughout the enrollment period. It is anticipated that the proportion of subjects who discontinue will be low (< 10%), yet it is a prudent consideration for sample size planning and as such it may be required to increase the enrollment of subjects receiving Neulasta Onpro kit to account for this. In addition, across both Neulasta Onpro kit and other physician choice groups, a dropout rate of ~11% is expected to occur during the study. Given this dropout rate, a final overall sample size of 8 880 subjects is anticipated. Therefore, 4 440 subjects will be enrolled in the curative intent cohort and 4 440 subjects in the palliative intent cohort and within each cohort, 2 220 subjects will be enrolled to each of the Neulasta Onpro kit and other physician choice option groups.

9.6 Data Management

All subject data relating to the study will be recorded into the eCRF. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation that support the information entered into the eCRF.

Clinical monitors will perform source data verification at regular intervals to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from medical records; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and local laws and regulations per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of the monitoring visits, including delays in completing eCRFs, are resolved.

The Amgen representative(s) are responsible for contacting and visiting investigator for the purpose of inspecting the facilities and, upon request, inspecting various records of the study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

9.6.1 Obtaining Data Files

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's audit trail.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

Upon entry of the data by the study site staff, Amgen will check the data for potential errors and inconsistencies. The data will be evaluated for potential outliers, missing information, and logical consistency with the study variables. Sites will be queried for clarification if unlikely values, potential errors, or inconsistencies are identified. The investigator and study staff should verify the data against medical records, and investigator will confirm and guarantee, by signing, the accuracy and integrity of the data corresponding to the information contained in the medical records.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the study database. Self-Evident Corrections will be documented in the eCRF standard instructions and the eCRF Specific Instructions, both of these will be available

through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data, (ie, the same results sent twice with the same date with different visit [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analysis/Analyses

The baseline FN rate in the other physician choice options group is estimated to be 10% and approximately 450 subjects are expected to enroll per month. The results of the interim analyses will be used to consider provide adaptive design modifications if the key baseline assumptions are not met and to assess the extent of missing data. The first interim analysis will be performed after 1000 subjects have been enrolled and the second interim analysis will be performed after 2000 subjects have been enrolled. Data on baseline subject characteristics, chemotherapy treatment, G-CSF prophylaxis use (including discontinuation within the Neulasta Onpro kit subjects), and incidence of FN and extent of missing covariate in the overall subject population will be summarized. No formal comparison of FN outcomes between Neulasta Onpro kit and other physician choice options subjects will be performed at either of the interim analyses. However, compliance and persistence will be described at each of the 2 interim analyses. G-CSF support, utilization and access data will also be described at the 2 interim analyses. Adaptive design modifications will be considered if baseline assumptions, level of missing covariate data, and subject enrollment are not meeting expectations. These modifications will be based on advice from the proposed steering committee.

A steering committee will be formed to monitor study conduct and data (refer to Section 9.4 for further details).

9.7.1.2 Primary Analysis

The primary analysis will be conducted once enrollment is complete and the last subject has ended study follow-up, as described in Section 9.1.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The incidence of FN in subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered cycle, and other physician choice options will be estimated using a standardized log binomial model (Richardson et al, 2015).

For descriptive analyses, categorical data will be summarized by the number and percentage of subjects in each category, and continuous data will be summarized by mean, standard deviation (SD), median, lower and upper quartiles, and minimum and maximum values.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The eCRFs will be designed to minimize missing data and to optimize the integrity of collected data. Subjects' records will not be excluded because of missing data and missing data will not be imputed. For categorical variables, missing responses will be shown as a separate category in the analysis. For numeric variables, the number of nonmissing observations will be presented.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

Subject enrollment by site and investigator will be summarized. Subjects that were not enrolled but who met the eligibility criteria will be listed in a nonparticipant log, along with reason for nonenrollment.

9.7.2.3.2 Description of Subject Characteristics

Baseline demographic and clinical characteristics will be summarized descriptively as outlined in Section 9.7.2.1.

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoints

The primary objective of the study is to estimate FN incidence in subjects who received Neulasta Onpro kit, Neulasta Onpro kit with every administered chemotherapy cycle, and subjects who received other physician choice options for FN prophylaxis. The sub-cohort of subjects who received Neulasta Onpro kit with every administered chemotherapy cycle will be easily identified from the overall Neulasta Onpro kit cohort. There is no requirement that subjects have to complete all 4 cycles of chemotherapy to be in the Neulasta Onpro kit with every administered chemotherapy cycle sub-cohort. Subjects must receive Neulasta Onpro kit with each chemotherapy cycle administered to be in this sub-cohort. For example, if a subject had chemotherapy discontinued after 2 cycles but if both of those chemotherapy cycles were administered with Neulasta Onpro kit support, the subject will be in the Neulasta Onpro kit with every cycle sub-cohort. In another example, a subject received all 4 cycles of chemotherapy but only received Neulasta Onpro kit for 3 of the chemotherapy cycles will not be included in the Neulasta Onpro kit with every cycle sub-cohort. However, this subject will be included in the Neulasta Onpro kit sub-cohort. This is an estimation study design with

sufficient sample size that will allow non-overlapping 95% confidence intervals for expected FN incidence among the subjects receiving Neulasta Onpro kit (ie, 7.5%) and subjects who received other physician choice options (ie, 10%) for FN prophylaxis.

The crude incidence of FN will be calculated as the crude proportion of subjects who experience FN, for the Neulasta Onpro kit, Neulasta Onpro kit in every administered chemotherapy cycle, and other physician choice options groups separately. Associated 95% CIs for the true incidence will be calculated by group. This analysis will be performed for overall study population, for subjects receiving chemotherapy with curative intent and for subjects receiving chemotherapy with palliative intent.

The adjusted incidence of FN will be calculated for the three sub-cohorts of subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered chemotherapy cycle, and other physician choice options for FN prophylaxis separately. The adjusted incidence will be calculated using standardized log binomial regression (Richardson et al 2015) where weight is assigned to each person that is equal to the inverse probability of receiving their own exposure conditional on their confounder information (Robins et al, 2000). The observed data will be weighted to the confounder distribution in overall population so that the sub-cohorts have same distribution of confounding factors. Associated 95% CIs for adjusted incidences will be calculated using boot-strap methods because the standardized binomial regression model is a weighted m-estimator (Stefanski and Boos, 2002). This analysis will be performed for the overall study population, for subjects receiving chemotherapy with curative intent and for subjects receiving chemotherapy with palliative intent.

If adequate sample size is accrued and the missing data is non-significant and missing at random, a standardized log binomial regression will be used to provide an estimate of the adjusted relative risk as a measure of the relative effect of a) Neulasta Onpro kit versus other physician choice options and b) Neulasta Onpro kit in every administered chemotherapy cycle versus other physician choice options on the incidence of FN. Associated 95% CIs for adjusted relative risk will be calculated using boot-strap methods. This analysis will be performed for the overall study population, for subjects receiving chemotherapy with curative intent and for subjects receiving chemotherapy with palliative intent.

Effect modification will be evaluated for variables that are biologically plausible to influence the effectiveness of Neulasta Onpro kit, Neulasta Onpro kit in every administered chemotherapy cycle, and other physician choice options at reducing FN

risk including age (< 65 versus ≥ 65 years), diabetes (yes versus no), cardiovascular dysfunction (yes versus no), COPD, previous surgery, and serum albumin (< 3.5 versus ≥ 3.5). Effect modification will be evaluated by presenting adjusted incidences and 95% CI for each stratum of exposure and effect modifier with a single reference category (Knoll MJ and VanderWeele 2012). This analysis will be performed for the overall study population, for subjects receiving chemotherapy with curative intent and for subjects receiving chemotherapy with palliative intent.

Chemotherapy delivery endpoints will be described and compared for Neulasta Onpro kit versus other physician choice options subjects using the standardized log binomial regression methodology above. G-CSF support will be summarized descriptively as outlined in Section 9.7.2.1.

For G-CSF access and utilization objective Neulasta Onpro kit payer denials, health insurance status and health plan information will be summarized descriptively as described in Section 9.7.2.1.

G-CSF persistence is defined as persistence G-CSF support for all chemotherapy cycles (persistence G-CSF support is defined as 1 Neulasta Onpro kit per cycle, 1 Neulasta PFS per cycle, 1 pegfilgrastim biosimilar PFS per cycle, or 10 short acting G-CSF injections per cycle) regardless of timing G-CSF administration. Persistence will be descriptively compared between Neulasta Onpro kit group with other physician choice options group as described in Section 9.7.2.1.

G-CSF compliance is defined as pegfilgrastim administered on the day after the last day of chemotherapy administration. Compliance will be compared between Neulasta Onpro kit group with subjects who received Neulasta PFS or pegfilgrastim biosimilar PFS in the other physician choice options group as described in Section 9.7.2.1.

For analysis of safety outcomes refer to Section 9.7.3 for further details.

HRQoL is an exploratory endpoint. HRQoL scores will be calculated using the SF-12 and respective scoring algorithm for this instrument and described using summary statistics at each time point. Mean and 95% CIs will be used to plot score change over time graphically. Scores will be compared between Neulasta Onpro kit and other physician choice options subjects using a similar methodology to that described for the analysis of FN.

9.7.2.4.1 Standardized Binomial Models

Confounding will be controlled using standardized binomial models. The adjusted incidence of FN will be calculated for the 3 sub-cohorts of subjects receiving Neulasta Onpro kit, Neulasta Onpro kit in every administered chemotherapy cycle, and other physician choice options for FN prophylaxis separately using standardized binomial models. The adjusted incidence will be calculated using standardized log binomial regression (Richardson et al 2015) where weight is assigned to each person that is equal to the inverse probability of receiving their own exposure conditional on their confounder information (Robins et al, 2000). The observed data will be weighted to the confounder distribution in overall population so that the sub-cohorts have same distribution of confounding factors. Treatment status will be standardized on a set of independent confounding variables which will include those specified in Section 9.3.3.

Confounding factors were identified a priori using existing empirical evidence and clinical knowledge about G-CSF use and risk of FN (Lyman et al, 2014; Lyman et al, 2011; Lyman et al, 2006). A causal diagram (Appendix J) was developed to help identify confounders in the analytic models for primary objective (Greenland et al, 1999; Shrier and Platt, 2008). This minimally sufficient adjustment set will be used for standardization and includes age, sex, health plan information, tobacco use, performance status, prior chemotherapy and radiation within 6 months prior to enrollment, cardiovascular dysfunction, diabetes, COPD, baseline antibiotic use, bone marrow involvement, tumor type, albumin, LDH, and study site size. A similar approach will be used to identify confounders for secondary objectives.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

Where relevant and appropriate, analyses will be presented by subgroups of interest including but not limited to, chemotherapy intent (palliative and curative), tumour type (breast cancer, lung cancer, prostate cancer, and NHL), and chemotherapy regimen.

9.7.3 Analysis of Safety Outcomes

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or later will be used to code all reported adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all, serious, and fatal events. Adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

9.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen standard operating procedures (SOPs).

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections in to the eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Documents to be maintained for the study are as follows:

- subject files containing the completed eCRF, informed consent forms, as applicable, and subject identification list
- study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the Institutional Review Board (IRB) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs, and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

The assessment of Neulasta Onpro kit and Neulasta PFS, pegfilgrastim biosimilar PFS, filgrastim, other short-acting G-CSFs, and no G-CSF use will be collected and recorded into the eCRFs at the clinic. Although efforts will be made to gather accurate information, there is a possibility of missing/incorrect entry of G-CSF type or use in the

site electronic medical record (EMR). Since the entry of G-CSF type or use in EMR is unrelated to the occurrence of FN (ie, non-differential across outcome groups), it is expected this misclassification to bias the effect estimate of FN incidence towards the null. It is anticipated that there will be some missing/incorrect information on components of FN including fever, neutrophil count, selected antibiotics, and any IV antibiotics in the EMRs as well as some missing/incorrect data for FN events occurring outside the site. However, the completeness of this information in an EMR is unrelated to the use of Neulasta Onpro kit or other physician choice options. If this bias exists, it would only result in a weaker effect estimate of FN incidence than what actually exists. It is anticipated that from vacation delays or planned breaks for subject convenience would create an error in calculating relative dose intensity (RDI). Since the RDI calculation is independent of the G-CSF use, the result of this misclassification would bias the effect estimates of FN incidence towards the null. Errors in identifying G-CSF use, FN, and RDI are expected to be small and therefore the resulting bias would be minimal.

The information on baseline covariates such as demographics, comorbidities, medications, and laboratory parameters is collected during the first visit along with information on G-CSF type and use. Since the research study personnel are likely unaware of the study question, it is not anticipated that there will be any exposure dependent misclassification of baseline covariates. However, independent misclassification of baseline covariates would result in increased residual confounding.

9.9.1.2 Selection Bias

Selection bias in this prospective cohort may occur as a result of subjects being lost to follow-up after study enrollment. It is not possible to identify the risk of FN among these subjects or to evaluate how different the risk of FN would be across the exposed and unexposed groups. Subjects who were lost to follow-up will be identified and their characteristics will be compared with subjects who were never lost to follow-up during the study period, overall and by sub-cohorts.

9.9.1.3 Confounding

Confounding by indication in this study of intended effect is of some concern. It is likely that subjects perceived to be at higher risk by the investigator are more likely to receive G-CSF for primary prophylaxis. In this scenario, the other physician choice options group could potentially have lower incidence of FN than the Neulasta Onpro kit group because of physicians not providing G-CSF prophylaxis to relatively healthier subjects.

It is planned to identify factors that are associated with possible sources of confounding by indication and include them in the standardized log binomial regression to address any imbalance between the exposed and unexposed arm of the study (Richardson et al 2015). While a standardized log binomial regression analysis controlling for known confounders would account for systematic differences between subgroups, in terms of unobserved confounders, study results may be confounded.

9.9.2 External Validity of Study Design

The study will enroll subjects from approximately 150 sites in the US. However, most or all of these sites are likely community oncology clinics and not representative of the entire US population. The study results therefore may not be applicable to subjects being treated in a different setting (eg, large academic center). It is possible that the sites participating in this study could alter their practices merely by being in this study which could impact the generalizability of study results.

9.9.3 Analysis Limitations

One of the limitations of standardized log binomial regression is that it does not account for censoring events that occur during study follow-up period. It is possible that subjects in one arm of the study may have shorter overall at-risk period for developing FN compared to another arm of the study because of censoring events. Cox proportional hazard model was not considered for the analysis because censoring events would likely be related to the outcome thus violating the non-informative censoring assumption.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Refer to Section 9.9.

9.10 Other Aspects

9.10.1 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.10.1.1 Demographics

Demographics data collection including sex, age, and race will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.10.1.2 Medical History

The Investigator or designee will collect a complete medical and surgical history that started within 30 days prior to enrollment through the start of the adverse event reporting period. Medical history will include information on the subject's medical conditions,

malignancy for which subject is receiving chemotherapy, malignancy characteristics (eg, malignancy histology, date of initial malignancy diagnosis, stage at diagnosis, current malignancy stage, any previous cancer therapy [radiation, surgery or chemotherapy]), concurrent chronic medical conditions, and history of other malignancies except for non-melanoma skin cancer. Record all findings on the medical history eCRF. In addition, the history must date back to the original diagnosis for the current diagnosis for which subject is receiving chemotherapy.

9.10.1.3 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate eCRF (eg, medical history, event). Clinically significant abnormal physical examination findings identified prior to signing the informed consent form should be reported as part of medical history, not as an adverse event.

9.10.1.4 Physical Measurements

Height in centimeters should be measured. Weight in kilograms should be measured.

9.10.1.5 Health Plan Information

Obtain the following health plan information at study enrollment: no insurance, Medicare, Medicaid, dual eligible, and commercial insurance (eg, Aetna, Anthem, Blue Cross Blue Shield).

9.10.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

9.10.1.7 Vital Signs

The following measurements will be collected: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Record all measurements on the vital signs eCRF.

The investigator is to collect all fever episodes from the subject since the last office visit.

9.10.1.8 Clinical Laboratory

During the subject's chart review, the tests detailed in Table 3 will be collected if available.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. All hematology laboratory assessments are to be collected and captured on the appropriate eCRF whether it was done at a physician's office, hospital, emergency room, or per Table 1.

Table 3. Analyte Listing

Local Laboratory: Chemistry	**Local Laboratory: Hematology**
Sodium	RBC
Potassium	Hemoglobin
Chloride	Hematocrit
Bicarbonate/CO_2	MCV
Total protein	MCH
Albumin	MCHC
Calcium	RDW
Glucose	Platelets
BUN/Urea	WBC
Creatinine	Differential
Total bilirubin	• Neutrophils (ANC and segmented)
ALP	• Bands
LDH (if available)	• Eosinophils
AST (SGOT)	• Basophils
ALT (SGPT)	• Lymphocytes
GFR	• Monocytes
Phosphorus/phosphate	

ALP = alkaline phosphatase; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO2 = carbon dioxide; GFR = glomerular filtration rate; LDH = lactic dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell

9.10.1.9 Prior and Concomitant Medications

Concomitant medications will be collected up to 30 days prior to the initial visit through the EOS. History of prior chemotherapy use (including specific chemotherapy drugs used) within 6 months prior to study enrollment, history of prior use of non-chemotherapy targeted therapy (eg, kinase inhibitors and checkpoint inhibitors) within 6 months prior to study enrollment, and history of prior radiation therapy within 6 months prior to study enrollment.

The following will be collected during the study;

- Screening/Enrollment/day 1: targeted therapies (eg, checkpoint inhibitors, kinase inhibitors, and monoclonal antibodies [record name(s), dose (s), and date(s) administered]), chemotherapy intent (curative or palliative), and chemotherapy agents (name(s), dose (s), and date(s) administered) G-CSF administered (eg, Neulasta Onpro, pegfilgrastim, pegfilgrastim biosimilar, filgrastim, filgrastim-sndz, tbo-filgrastim, other filgrastim biosimilar [dose and date(s) administered).
- observation and EOS periods collect the drug name, dose, and dates given for the following:
    - chemotherapy (any dose change if applicable)
    - antibiotic use

- G-CSF (eg, Neulasta Onpro, pegfilgrastim, pegfilgrastim biosimilar, filgrastim, filgrastim-sndz, tbo-filgrastim, other filgrastim biosimilar [if applicable, dose changes and/or reason for discontinuation]).
- Other medications (eg, corticosteroids, anti-emetics)

9.10.1.10 Patient Reported Outcomes

The SF-12 instrument will be used by the clinical research staff to collect HRQoL data from subjects.

- The SF-12 is a 12-item questionnaire used to assess functional health and well-being from the subject's point of view. The SF-12 includes 8 domains of health outcomes, including physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH) scored to produce individual domain scores as well as a physical component summary score and a mental component summary score. Amgen's internal statistical group will manage the scoring of the SF-12. The reliability and validity of the SF-12v2 has been demonstrated in various conditions including adults with cancer (Ware et al, 1996; Bhandari et al, 2018).

9.10.1.11 ECOG Performance Status

The subject's performance status will be assessed using ECOG (refer to Appendix I).

10. Protection of Human Subjects

This study will comply will all applicable ethical, legal and regulatory requirements, and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen policies and procedures regarding adverse event reporting and product complaints. This study and data collection will be conducted in accordance with all applicable laws.

The responsible physician is responsible for forwarding the following documents to Amgen or its representative for review before study initiation occurs:

- signed and dated protocol signature page (Responsible Physician's Agreement)
- copy of the IRB approval of the protocol
- subject or subject's legally acceptable representative has provided informed consent (for countries where required per local regulations)
- up-to-date curriculum vitae of responsible physician and all co/sub-physicians
- signed confidentiality agreement
- signed study contract

The responsible physician will be charged with maintaining correct and comprehensive documentation, while the Amgen monitor/designee is tasked to ensure that the responsible physician is following the correct study protocol.

10.1 Informed Consent

An initial sample informed consent form will be provided by Amgen for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language of the potential subject population.

Before a subject can participate in the study, the investigator is responsible for obtaining written informed consent, using an IRB approved informed consent form, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent on behalf the subject, to the subject's participation in the clinical study.

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed informed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

10.2 Institutional Review Board (IRB)

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed subject recruitment material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before study can be executed. The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The Investigator is to notify the IRB of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. The Investigator is responsible for obtaining annual IRB approval and IRB

renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB continuance of approval must be sent to Amgen.

Any protocol amendments will be submitted to the IRB for their review and approval. Annual IRB approval/renewal throughout the duration of the study will be obtained and copies of the IRB continuance of approval will be sent to Amgen.

10.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- subjects are to be identified by a unique subject identification number.
- on the eCRFs demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.
- for serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number
- documents that are not for submission to Amgen (eg, signed informed consent form, as applicable) are to be kept in confidence by the Investigator, except as described below.

In compliance with applicable law and regulations, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Subjects Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording and Reporting of Safety Information and Product Complaints

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

An adverse device effect is any adverse event related to the use of a medical device (eg, Neulasta Onpro kit). Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least 1 of the following serious criteria:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistence or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the

subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes the Neulasta PFS and OBI Onpro, as well as the Neupogen PFS.

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from subjects prospectively. All safety events (adverse events, product complaints and other safety findings) considered to have occurred following subject exposure to Neulasta PFS or Onpro and/or Neupogen PFS will be collected from enrollment to 30 days after administration of Neulasta or Neupogen, with the exception of the protocol exempted events listed in Appendix G. The Investigator is responsible for ensuring that all safety events they become aware of during the study period, are recorded in the subject's appropriate study documentation. These safety events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness. Non-serious Adverse Events (AEs) must be

reported in an expeditious manner, not to exceed 15 calendars days of Investigator awareness.

If the EDC system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper an Adverse Event Contingency Report Form within 1 business day of Investigator awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

Protocol Exempted Events

Adverse events that are anticipated to occur in this study population because they are known adverse reactions to chemotherapy or are known to occur in the context of the underlying disease are not planned to be collected in this study. A list of all events and corresponding MedDRA preferred terms that are not to be collected in the study is provided in Appendix G.

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of investigator awareness.

Protocol exempted events and safety events that are suspected to be related to any medicinal product other than Neulasta and Neupogen should be reported to the local authority in line with the local country requirements.

See Appendix B for sample Safety Report Form(s), Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy and Lactation Notification Worksheets. The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may be recorded.

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

Amgen will submit the results of this study for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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15. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. Sample of Safety Reporting Forms

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for Observational Research Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

What to report on this form:

- **All adverse events associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol**
- **The following safety findings are to be reported on this form as events regardless of association with an adverse event**
  - **Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **Transmission of infectious agents**
  - **Reports of uses outside the terms for authorized use of the product including off label use**
  - **Occupational exposure**
  - **Any lack or loss of intended effect of the product(s)**
  - **Product complaint ONLY IF ASSOCIATED WITH AN ADVERSE EVENT**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **Pregnancy and lactation reports**
- **Product complaints without association with an AE**

1. **Site Information**
   Site Number* – Enter your assigned site number for this study
   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested
2. **Subject Information**
   Subject ID Number* – Enter the entire number assigned to the subject
   Age at event onset, Sex, and Race – Enter the subject's demographic information
   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. **Adverse Event**
   Provide the date the Investigator became aware of this Information
   Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalizion. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**
   Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.
   Is event serious?* – Indicate Yes or No. This is a mandatory field.
   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   Immediately life-threatening: Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

4. **IP Administration including Lot # and Serial # when known / available.**
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported. **This is a mandatory field.**

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

Outcome of Event – Enter the code for the outcome of the event at the time the form is completed if outcome is known.
Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

5. **Hospitalization**
If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

6. **Amgen drug Under Study Administration including Lot # and Serial # when known / available.**
Initial Start Date – Enter date the product was first administered, regardless of dose.
Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
Action Taken with Product – Enter the status of the product administration.

7. **Concomitant Medications**
Indicate if there are any medications.
Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
Co-suspect – Indicate if the medication is co-suspect in the event
Continuing – Indicate if the subject is still taking the medication
Event Treatment – Indicate if the medication was used to treat the event

8. **Relevant Medical History**
Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

9. **Relevant Laboratory Tests**
Indicate if there are any relevant laboratory values.
For each test type, enter the test name, units, date the test was run and the results.

10. **Other Relevant Tests**
Indicate if there are any tests, including any diagnostics or procedures.
For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

11. **Case Description**
Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20170758 Neulasta / Neupogen	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of drug under study	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study?						**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						Neulasta		Neupogen		Device			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No									
				☐Yes ☐No									
				☐Yes ☐No									

Serious Criteria:	01 Fatal	03 Required/prolonged hospitalization	05 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	**Date Discharged** Day Month Year

AMGEN Study # 20170758 Neulasta / Neupogen	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<< Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20170758 Neulasta / Neupogen	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix C. Additional Safety Reporting Information

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

When an adverse event cannot be graded by CTCAE Version 4.0, the following severity grade should be used:

Adverse Event Grading Scale

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING: Refers to an event in which the subject was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe).
5	FATAL

Appendix D. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20170758

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name ____________________ **Site #** ____________________

Phone (_____)____________________ **Fax** (_____)____________________ **Email** ____________________

Institution ____________________

Address ____________________

3. Subject Information

Subject ID # ____________________ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm /dd /yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy______ ☐ Unknown

Estimated date of delivery mm_______ / dd_______/ yyyy ___ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy_______

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ________/ dd________/ yyyy________

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:____________________

____

____

Form Completed by:

Print Name: ____________________ **Title:** ____________________

Signature: ____________________ **Date:** ____________________

****

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20170758

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

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Appendix E. Dosing Guidelines for High (> 20% risk) and Intermediate Risk Febrile Neutropenia (10% to 20%)

Subjects must satisfy the inclusion criteria if initiated at the first cycle following a chemotherapy regimen and minimum dosing for each drug

High Risk for FN (> 20% risk)

Regimen	Schedule	Dosing	Allowed variations of dosing
TAC	every 3 weeks for 6 cycles	docetaxel (75 mg/m^2 day 1) + doxorubicin (50 mg/m^2 day 1) + cyclophosphamide (500 mg/m^2 day 1)	-
TC	every 3 weeks for 4 cycles	docetaxel (75 mg/m^2) + cyclophosphamide (600 mg/m^2)	-
TCH	every 3 weeks for 6 cycles	docetaxel (75 mg/m^2), carboplatin (AUC 6), and trastuzumab given on day 1	-
TCHP	every 3 weeks for 6 cycles	docetaxel (75 mg/m^2), carboplatin (AUC 6), trastuzumab on day 1, pertuzumab on day 1	-
MINE	every 3 or 4 weeks	etoposide 65 mg/m^2 days 1 to 3 + ifosfamide 1.33 gm/m^2 days 1 to 3 + mesna 1.33 g/m^2 IV days 1 to 3 + Mesna 500 mg PO days 1 to 3 + Mitoxantrone 8 mg/m^2 day 1	-
DHAP	6 cycles every 3 or 4 weeks	cisplatin (100 mg/m^2 IV continuous infusion over 24 hours) + cytarabine (2 pulses each at a dose of 2 g/m^2 given 12 hours apart) + dexamethasone (40 mg orally or IV was given on days 1 to 4)	-
R-DHAP	6 cycles every 3 or 4 weeks	dexamethasone 40 mg on days 1 to 4 + cytarabine 2 g/m^2 every 12 hours for 2 doses on day 2 + cisplatin 100 mg/m^2 on day 3 + rituximab 375 mg/m^2 weekly for 4 weeks starting on day 1 of first cycle	-
ESHAP	6 cycles every 3 or 4 weeks	cisplatin (25 mg/m^2, total 100 mg/m^2, days 1 to-4) +cytarabine (2 g/m^2 day 5) +etoposide (40 mg/m2 days 1 to 4) +methylprednisolone (250 to 500 mg days 1 to 5)	-
R-ESHAP	6 cycles every 3 or 4 weeks	cisplatin (25 mg/m^2, total 100 mg/m^2, days 1 to 4) + cytarabine (2 g/m^2 day 5) + etoposide (40 mg/m^2 days 1 to 4) +methylprednisolone (250 to 500 mg days 1 or 5) + Rituxan 375 mg/m^2 day 1 or 5	-
Dose-adjusted EPOCH	6 cycles every 3 weeks	cyclophosphamide (750 mg/m^{2}IV, day 5) +doxorubicin (10 mg/m^2, CIV, days 1 to 4) + etoposide (50 mg/m^2, CIV days 1 to 4) +vincristine (0.4 mg/m^2, CIV, days 1 to 4) + prednisone (60 mg, by mouth, days 1 to 5)	Etoposide 60 mg/m^2/day is allowed
Topotecan	every 3 weeks for 4 cycles	topotecan (1.5 mg/m^2 as a 30-minute infusion daily for 5 days every 21 days)	-

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Footnotes are on final page of this table.

Intermediate Risk for FN (10% to 20%)

Regimen	Schedule	Dosing	Allowed Variations of Dosing
TH	every 3 weeks for 4 cycles	docetaxel (6 cycles at 100 mg/m^2 IV every 3 weeks) + trastuzumab (4 mg/kg IV loading dose followed by 2 mg/kg weekly)	Every 3 weeks, dosing of trastuzumab is allowed
Docetaxel	every 3 weeks for 4 cycles	docetaxel (100 mg/m^2 as a 1 hour infusion, day 1)	Dose reduction to 75 mg/m^2 is allowed
Paclitaxel	every 3 weeks	paclitaxel 175 mg/m^2 3-hour infusion, day 1)	Dose escalation to 225 mg/m^2 is allowed
AC→T	4 cycles of AC every 3 weeks followed by 4 cycles of T every 3 week	doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2) →docetaxel (100 mg/m^2 every 3 weeks for 4 cycles cycles)	-
AC	every 3 weeks	doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles	-
CMF classic	every 4 weeks	cyclophosphamide (600 mg/m^2) + methotrexate (40 mg/m2) fluorouracil (600 mg/m^2)	-
FEC→T	3 cycles of FEC every 3 weeks followed by 3 cycles of T every 3 weeks	fluorouracil (500 mg/m^2 day 1) + epirubicin (100 mg/m^2, day 1) + cyclophosphamide (500 mg/m^2, day 1) →docetaxel (100 mg/m^2 IV on day 1)	-
R-CHOP	every 3 weeks	cyclophosphamide (750 mg/m^2 on day 1) + doxorubicin (50 mg/m^2 on day 1) + vincristine (1.4 mg/m^2 up to 2 mg) + prednisone (40 mg/m^2/day for 5 days) + rituximab (375 mg/m^2, on day 1 of each 8 CHOP cycles)	-
CHOP	every 3 weeks	cyclophosphamide (750 mg/m^2 on day 1) + doxorubicin (50 mg/m^2 on day 1) + vincristine (1.4 mg/m^2 up to 2 mg) + prednisone (40 mg/m^2/day for 5 days)	-
Etoposide/carboplatin	every 3 weeks	carboplatin (AUC=5, day 1) + etoposide (100mg/m^2 IV days 1 to 3)	-
Cisplatin/docetaxel	every 3 weeks	cisplatin (75mg/m^2) +docetaxel (75 mg/m^2) on day 1	-
Cisplatin/paclitaxel	every 3 weeks	cisplatin (75 mg/m^2, day 2) + paclitaxel (135 mg/m^2, over 24 hours, day 1)	-
Cisplatin/etoposide	6 cycles every 3 weeks	cisplatin (100 mg/m^2 IV day 1) + etoposide (100 mg/m^2 IV days 1 to 3)	-

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Footnotes defined on the next page of the table.

Regimen	Schedule	Dosing	Allowed Variations of Dosing
Carboplatin/paclitaxel	every 3 weeks for 4 cycles	carboplatin (AUC 5.0 to 6.0 min x mg/mL on day 1) + paclitaxel (175 to 225 mg/m^2 on day 1)	Dose reduction of paclitaxel to 175 mg/m^2 and carboplatin AUC = 5 is allowed
Docetaxel	every 3 weeks	docetaxel (75 mg/m^2 on day 1)	-
Cabazitaxel	every 3 weeks	cabazitaxel (20 to 25 mg/m^2 IV every 3 weeks)	-
Bendmaustine/ rituxan	every 3 or 4 weeks	Bendamustine (100 m/mg^2 on day 1 and 2) + Rituxan (375 mg/m^2 on day 1)	Bendamustine dosing 80-120 mg/m^2 is allowed
R-EPOCH	every 3 weeks	Rituxan (375 mg/m^2, IV, day 1), cyclophosphamide (750 mg/m^2, IV, day 5) +doxorubicin (10 mg/m^2, CIV, days 1 to 4) + etoposide (50 mg/m^2, CIV days 1 to 4) +vincristine (0.4 mg/m^2, CIV, days 1 to 4) + prednisone (60 mg/m^2, by mouth, days 1 to 5)	--

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"--" = not available; AC->T = adriamycin, cyclophosphamide followed by taxotere; AC = adriamycin, cyclophosphamide; AUC = area under the curve; CIV = continuous intravenous; DHAP = cisplatin, cytarabine, dexamethasone; EPOCH = etoposide, cyclophosphamide, adriamycin, vincristine, prednisone; ESHAP = cisplatin, etoposide, methylprednisolone, cytarabine; FEC->T = 5 fluorouracil, epirubicin, cyclophosphamide followed by taxotere; IV = intravenous; MINE = mesna, ifosfamide, novantrone, etoposide; PO = by mouth; R-CHOP = rituxan, cyclophosphamide, adriamycin, vincristine, prednisone; R-DHAP = rituxan, cisplatin, cytarabine, dexamethasone; R-ESHAP = rituxan, cisplatin, etoposide, methylprednisolone, cytarabine; R-EPOCH = Rituxan, Etoposide, Cyclophosphamide, Adriamycin, Vincristine, Prednisone; TAC = taxotere, adriamycin, cyclophosphamide; TC = taxotere, cyclophosphamide; TCH = taxotere, carboplatin, herceptin; TCHP = taxotere, carboplatin, herceptin, perjata; TH = taxotere, herceptin

Cerchione et al 2017; Dunleavy et al, 2013; NCCN guidelines 2017; Hurvitz et al, 2018; Fisher et al 1990; Witzig et al. 2008; Martin et al, 2008.

Appendix F. Subject Risk Factors for Febrile Neutropenia

- age > 65
- metastatic disease
- bone marrow involvement with tumor
- open wound
- poor nutritional status
- low baseline hemoglobin
- elevated serum LDH
- serum albumin < 3.5
- diabetes mellitus
- cardiovascular disease
- Chronic Obstructive Pulmonary Disease
- previous radiation therapy
- recent surgery

(Aapro et al, 2011; Crawford et al, 2008; Lyman et al, 2003; Smith et al, 2015.)

Appendix G. Non-collectable Adverse Events MedDRA Preferred Terms

Event	MedDRA Preferred Term(s)
Nausea	Nausea
Vomiting	Vomiting
Diarrhea	Diarrhoea
Jaundice	Jaundice, jaundice cholestatic, jaundice extrahepatic obstructive, jaundice hepatocellular
Numbness/tingling	Hypoaesthesia, paraesthesia
Neuropathy	Neuropathy peripheral
Fatigue	Fatigue
Depression	Depression, major depression, agitated depression, depression postoperative, menopausal depression
Manic symptoms	Mania, hypomania
Hallucinations	Hallucination, hallucination, auditory, hallucination, gustatory, hallucination, olfactory, hallucination, synaesthetic, hallucination, tactile, hallucination, visual, hallucinations, mixed, somatic hallucination
Insomnia	Insomnia
Asthenia/weakness of the limbs	Asthenia
Shortness of breath	Dyspnoea
Cough	Cough, productive cough
Sputum production	Sputum increased
Rhinorrhea	Rhinorrhoea, rhinitis
Dysuria	Dysuria
Polyuria	Polyuria
Hematuria	Haematuria, post procedural haematuria
Difficulty swallowing	Dysphagia
Mouth sores	Stomatitis
Painful swallowing	Odynophagia
Constipation	Constipation
Rectal bleeding	Rectal haemorrhage
Bloody stools	Haematochezia
Nail changes	Nail disorder
Alopecia	Alopecia
Dry skin	Dry skin
Mucositis	Mucosal inflammation
Dysgeusia	Dysgeusia
Inability to taste food	Ageusia
Anorexia	Decreased appetite
Headache	Headache

Event	MedDRA Preferred Term(s)
Na	Blood sodium abnormal, blood sodium increased, blood sodium decreased, hypernatremia, hyponatremia
K	Blood potassium abnormal, blood potassium increased, blood potassium decreased, hyperkalemia, hypokalemia
Chloride	Blood chloride abnormal, blood chloride decreased, blood chloride increased, hypochloremia, hyperchloremia
CO2	Carbon dioxide abnormal, carbon dioxide increased, carbon dioxide decreased
Bicarbonate	Blood bicarbonate abnormal, blood bicarbonate increased, blood bicarbonate decreased,
BUN	Blood urea abnormal, blood urea decreased, blood urea increased
Creatinine	Blood creatinine abnormal, blood creatinine increased, blood creatinine decreased, creatinine renal clearance abnormal, creatinine renal clearance decreased, creatinine renal clearance increased, hypercreatininemia, hypocreatininemia
AST	Aspartate aminotransferase abnormal, aspartate aminotransferase decreased, aspartate aminotransferase increased,
ALT	Alanine aminotransferase abnormal, alanine aminotransferase increased, alanine aminotransferase decreased
Alkaline phosphatase	Blood alkaline phosphatase abnormal, blood alkaline phosphatase increased, blood alkaline phosphatase decreased
Bilirubin	Blood bilirubin abnormal, blood bilirubin decreased, blood bilirubin increased, blood bilirubin unconjugated abnormal, blood bilirubin unconjugated increased, blood bilirubin unconjugated decreased, blood bilirubin conjugated abnormal, blood bilirubin conjugated increased, blood bilirubin conjugated decreased
Albumin	Blood albumin abnormal, blood albumin decreased, blood albumin decreased, hyperalbuminaemia, hypoalbuminaemia
Total protein	Hyperproteinaemia, hypoproteinaemia,
Magnesium	Blood magnesium abnormal, blood magnesium decreased, blood magnesium increased, protein total abnormal, protein total decreased, protein total increased
Phosphorus	Blood phosphorus abnormal, blood phosphorus decreased, blood phosphorus increased, hyperphosphataemia, hypophosphataemia

Event	MedDRA Preferred Term(s)
LDH	Blood lactate dehydrogenase abnormal, blood lactate dehydrogenase increased, blood lactate dehydrogenase decreased
Uric acid	Blood uric acid abnormal, blood uric acid decreased, blood uric acid increased, hyperuricaemia
CEA	Carcinoembryonic antigen abnormal, carcinoembryonic antigen increased, carcinoembryonic antigen high, carcinoembryonic antigen decreased
CA 19-9	Carbohydrate antigen 19-9 increased
CA 27-29	Carbohydrate antigen 27.29 increased
CA 15-3	Carbohydrate antigen 15-3 increased
Blood culture	Blood culture negative, blood culture positive
Urine culture	Urine culture negative, urine culture positive
Sputum culture	Sputum culture positive
Stool culture	Stool culture negative, stool culture positive
Seizures	Seizure
Epilepsy	Epilepsy
Hearing loss	Hypoacusis, deafness
Loss of vision	Visual impairment, blindness
Diplopia	Diplopia
Conjunctivitis	Conjunctivitis, adenoviral conjunctivitis, conjunctivitis bacterial, conjunctivitis viral
Excessive tearing	Lacrimation increased
Hand foot syndrome (Palmar-plantar dysesthesia)	Palmar-plantar erythrodysaesthesia syndrome
Lower/upper extremity swelling	Limbal swelling, oedema
Acid reflux	Gastrooesophageal reflux disease

Appendix H. Co-morbidity

Comorbidity conditions of interest (Chia et al, 2013) include;

- diabetes
- diabetes with end organ damage
- anemia
- hypertension
- cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease)
- cerebrovascular disease
- thromboembolic events
- Chronic Obstructive Pulmonary Disease/emphysema
- previous cancer
- moderate to severe liver disease (hepatitis, cirrhosis)
- moderate to severe renal failure
- autoimmune conditions (Rheumatoid Arthritis [RA])
- Systemic Lupus Erythematosus (SLE)
- Multiple Sclerosis (MS)
- thyroid disorders (including autoimmune thyroiditis)
- peptic ulcer disease
- dementia
- osteoarthritis
- connective tissue disease
- previous history of infections (eg, pneumonia, sepsis, etc.)

Appendix I. Eastern Cooperative Oncology Group Performance Status Scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken et al, 1982.

Appendix J. Directed Acyclic Graph Depicting the Causal Pathway Between Neulasta Onpro kit and Risk of Febrile Neutropenia