Summary Table of Study Protocol

Title	Granulocyte Colony-Stimulating Factor ("G-CSF"): Patient profiles, Scheduling Patterns and Clinical Outcomes
Protocol version identifier	Original Protocol, Version 1.0
Date of last version of the protocol	*25 September 2020*
EU Post Authorization Study (PAS) Register No	EUPAS38906
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Medicinal Product	Neulasta Onpro® (pegfilgrastim)
Device	*NA*
Product Reference	*NA*
Procedure Number	*NA*
Joint PASS	Yes
Research Question and Objectives	The aim of this study is to understand the patient profiles, scheduling patterns and clinical outcomes among patients with breast cancer, colorectal cancer, lung cancer, ovarian cancer, or NHL treated with pegfilgrastim in the US community setting.
Country(ies) of Study	United States
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Marketing Authorization Holder

Marketing authorization holder(s)	NA
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Investigator's Agreement

I have read the attached protocol entitled Granulocyte Colony-Stimulating Factor ("G-CSF"): Patient profiles, Scheduling Patterns and Clinical Outcomes, dated 25 September 2020, and agree to abide by all provisions set forth therein.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my Sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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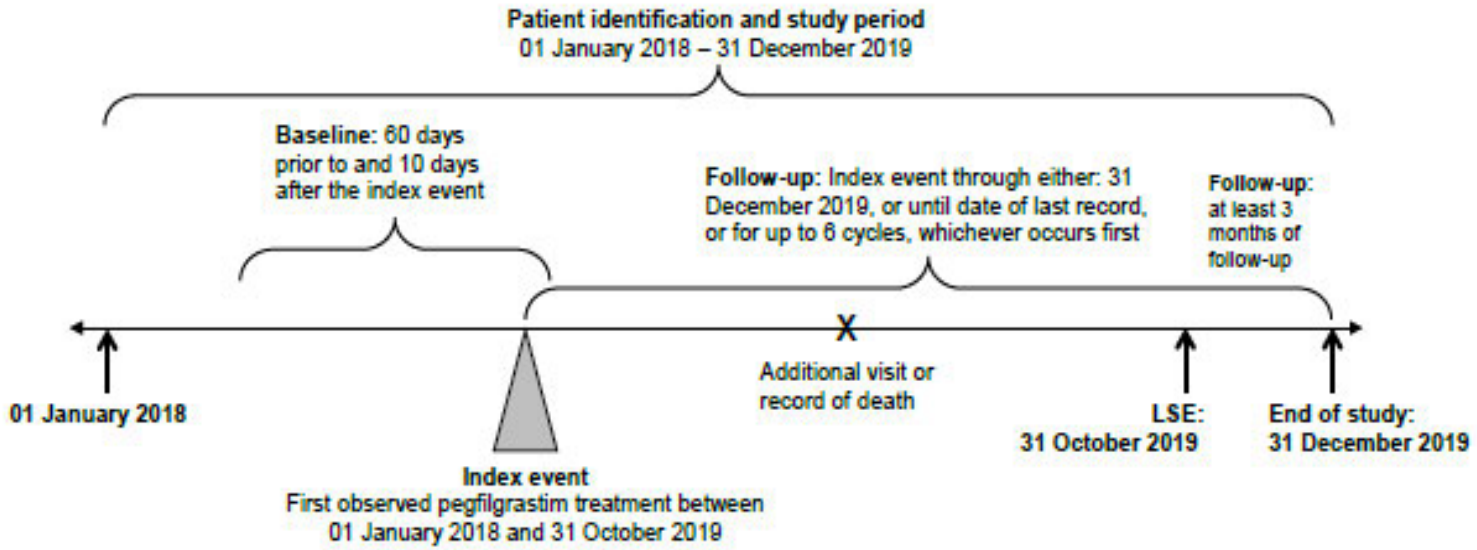
Signature

Name of Investigator: Date (DD Month YYYY)

PPD , MD, MPH

Study Design Schema



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2. List of Abbreviations

BMI	Body mass index
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic healthcare record
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
ICD	International Classification of Diseases
ICJME	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISS	International Staging System
iKM	iKnowMed
MSH	McKesson Specialty Health
NHL	Non-Hodgkin's Lymphoma
NSCLC	Non-Small Cell Lung Cancer
SSDI	Social Security Death Index
SSN	Social Security number
USON	US Oncology Network

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4. Abstract

- Study Title:
  - Granulocyte Colony-Stimulating Factor ("G-CSF"): Patient profiles, Scheduling Patterns and Clinical Outcomes
- Study Background and Rationale:
  - Treatment injections with long-acting (pegylated) G-CSFs (pegfilgrastim) at least 24 hours after administration of cytotoxic chemotherapy has been shown to be safe and effective in decreasing the incidence of chemotherapy-induced febrile neutropenia (FN). However, this 24-hour time frame also creates a challenge for administration of G-CSF as primary prophylaxis (PP) due to the need for a 'next-day' return visit to the clinic. The Neulasta® (pegfilgrastim) Onpro® on-body injector (OBI) was designed to eliminate the requirement for a patient to return to the clinic the day after chemotherapy to receive pegfilgrastim as primary prophylaxis. However, limited data is available on the treatment scheduling and clinical outcomes with traditional G-CSF treatment by pre-filled syringe (PFS) and with use of the Onpro OBI.
- Study Feasibility and Futility Considerations
  - A preliminary feasibility analysis of the iKM database identified 15,443 patients diagnosed with breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, receiving treatment with pegfilgrastim within the USON between January 1, 2018 and October 31, 2019. The final study population for analysis will be defined after identification and review of the patient population meeting the inclusion criteria in the iKM database. A specific power calculation will not be performed as this is a descriptive analysis. Any limitation of sample size will be taken into account when interpreting study results.

- Research Question and Objective(s):
  - This study proposes to describe real-world patient profiles, treatment patterns and clinical outcomes with use of the different G-CSF products in US Oncology Network (USON) clinics. All study data will originate from the electronic healthcare record (EHR) of the USON. Structured data fields within the EHR will be sufficient to provide the information needed to address most research questions. To supplement these discrete and mapped data elements, a targeted chart review will be performed to capture additional information recorded in the chart, such as that noted in free-text fields.

Primary Objectives	**Endpoints**
Phase 1 (structured EMR data)	

• To examine patient demographics and clinical disease characteristics of breast cancer, colorectal cancer, NSCLC, or ovarian cancer patients treated with pegfilgrastim in the adjuvant setting	• Patient demographics
	  • age at index, gender, race, BMI, practice location
	• Clinical disease characteristics
	  • stage at diagnosis, metastatic diagnosis, metastatic sites, ECOG status, laboratory results – white blood cell count, body temperature

• To examine patient demographics and clinical disease characteristics of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer patients treated with pegfilgrastim in the metastatic setting - 1L and 2L+	• Patient demographics
	  • age at index, gender, race, BMI, practice location
	• Clinical disease characteristics
	  • stage at diagnosis, metastatic diagnosis, metastatic sites, ECOG status, laboratory results - white blood cell count, body temperature

• To describe scheduling patterns with pegfilgrastim:
  • Patient timing of actual administration of pegfilgrastim relative to completion of chemotherapy - defined as chemotherapy end date, or day 0 (eg. day 6+ administrations/appointments, same day, next day)
	• The timing of actual administration of pegfilgrastim treatment relative to completion of chemotherapy - defined as chemotherapy end date, or day 0, will be categorized as:
	  • PFS: recommended (day 1), non-recommended (day 0, 2-5), day 6+
	  • Onpro OBI: recommended (day 0), non-recommended (day 1-5), day 6+.

Primary Objectives	Endpoints
Phase 2 (Structured and Unstructured EMR data)	
• To describe scheduling patterns with pegfilgrastim: • Patient scheduling patterns and concordance to guidelines	• Order date and prophylactic use of pegfilgrastim based on FN-risk (as recommended by NCCN guidelines)

• To examine clinical outcomes among patients initiating pegfilgrastim:
  • Incidence of febrile neutropenia
  • Incidence and reason for dose delay in chemotherapy treatment
  • Frequency and reason for day 6+ visit, non-recommended pegfilgrastim
  • Onpro OBI device failure
	• Occurrences of FN (defined as either: 1) ANC of less than 500 neutrophils/μL and fever (≥ 38º C) during the anticancer treatment; or 2) documentation in the record (eg, physician notes, lab reports), identified by performing a keyword search of the problem list in the structured data) will be captured from day 6 for each cycle, up to first 6 cycles of treatment.
	• Incidence and reason for dose delay in chemotherapy treatment (reasons listed in Table 2)
	• Frequency and reason for day 6+ visit and non-recommended pegfilgrastim (reasons listed in Table 2)
	• Onpro OBI device failure

• To examine resource utilization (hospitalization and ER visits) among patients initiating pegfilgrastim	• Occurrence and reason for hospitalizations • Occurrence and reason for emergency department visits

– Hypothesis(es)/Estimation

As this is a descriptive analysis study, no formal sample size calculations will be performed. No specific hypotheses are being tested that require sample size estimates.

- Study Design/Type

  This study is a retrospective cohort study assessing patient characteristics, scheduling patterns and clinical outcomes among patients with a diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, treated with pegfilgrastim in the US Oncology network between January 1, 2018 and October 31, 2019, with follow-up until December 31, 2019.

- Study Population or Data Resource

  The study population will be adult patients with a diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, treated with pegfilgrastim within US Oncology Network (USON) clinics during the study identification period and who

meet all eligibility criteria. Structured data fields will primarily be extracted from the McKesson Specialty Health (MSH)/USON electronic healthcare record (EHR) database, iKnowMed (iKM), with supplemental vitality status from the Limited Access Death Master File (LADMF). These data will be supplemented by additional unstructured data collected through chart review for a subset of the study population.

- Summary of Patient Eligibility Criteria

  Inclusion criteria:

  - *Patients with a diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer*
  - *Patients ≥ 18 years of age at first diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer*
  - *Patients who received at least one dose of pegfilgrastim as either pegfilgrastim PFS (Neulasta PFS or biosimilar pegfilgrastim PFS) or Onpro OBI during the patient identification period (01 January 2018 to 31 October 2019)*
  - *During the study period, observed with either ≥ 1 visits within the USON in addition to the index event visit or a documented record of death*
    - *Visits are defined as physical encounters with the practice, detected by vital sign records. The second visit must be observed after the index date to demonstrate continuity of care. There is no required time span between the additional visit and the index date*

  Exclusion Criteria

  - *Patients enrolled in interventional clinical trials during the study observation period*
  - *Patients who received treatment indicated for another primary cancer or diagnosed with another primary cancer during the study observation period*

  Note: The number of patients who received short-acting G-CSF treatment (filgrastim and filgrastim biosimilars) in addition to pegfilgrastim during study observation period will be reported.

- Follow-up

  Patients will be identified from 01 January 2018 through 31 October 2019 and followed through 31 December 2019, or until date of last record, which is defined as the last visit with documented vital sign or recorded death. Index date will be the first date of the pegfilgrastim treatment (pegfilgrastim PFS or Neulasta Onpro OBI) during the study identification period. Depending on each patient's initiation date and the last documented contact date (or death) available, patients will have variable length

of follow-up. All study variables and outcomes will be assessed regardless of maximum follow-up using data available until the end of the study period, 31 December 2019.

- Variables
  - *Outcome Variable(s)*

    Incidence of febrile neutropenia:

    - Phase 2: Occurrences of FN during the anticancer treatment will be captured from day 6 for each cycle, up to first 6 cycles of treatment. FN for any particular cycle will be identified by the chart reviewer through either of the following methods: 1) visits with documented ANC of less than 500 neutrophils/mcL and fever (≥ 38º C); or 2) documentation in the record (eg, physician notes, lab reports), identified by performing a keyword search of the problem list in the structured data.
      - It is important to note that the operational definition of FN used for this study aligns with the clinical definition from the NCCN Guidelines Management of Neutropenia (NCCN 2021), namely "Febrile neutropenia is defined as single temperature: ≥ 38.3 ºC orally or ≥ 38.0 ºC over 1 h; neutropenia: < 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 h." Additionally, documentation in the record would constitute a clinical diagnosis of FN.
      - It should be noted that different definitions of FN used for other claims-based analyses exist, where either a specific clinical diagnosis or an ANC value and temperature are not available in the data. Those algorithms to identify FN were developed for claims data, as there is no single ICD-10 code for FN. This study, however, captures FN more directly: either through the use of an FN definition aligned with that from the NCCN Guidelines, or directly from a documented clinical diagnosis.
  - Reason for dose delay in chemotherapy treatment (on cycle basis)
    - Phase 2: Reasons for dose delay (treatment hold and/or delay of the anticancer therapy for 1 cycle) in chemotherapy treatment will be captured in chart review as described in Table 2. All chemotherapy cycle delays from index through December 31, 2019 will be captured.
  - Day 6+ appointments for pegfilgrastim
    - Phase 2: Among chemotherapy regimens with pegfilgrastim as part of regimen, day 6+ appointments will be captured within a chemotherapy course. Day 6+ cycles are defined as cycles which received pegfilgrastim between day 6 and the end of the chemotherapy cycle.
  - Reasons for day 6+ visit and non-recommended pegfilgrastim administration
    - Phase 2: Data for day 6+ appointments and non-recommended administration of pegfilgrastim reasons will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts.

- If available, reason patients received non-recommended or day 6+ administration will be abstracted:
    - Anemia
    - Thrombocytopenia
    - Fatigue
    - Anxiety
    - Flu season
    - Patient forgot appointment
    - Nausea
    - Drive time or distance (typically by car)
    - Travel burden (regardless of travel method [eg, car, bus, subway, train])
    - Burden on caregiver to travel
    - Difficulty arranging travel
    - Need to care for dependent(s)
    - Need to return to work
    - Weekend/holiday the day after chemo
    - Bad weather after chemo
    - Request for Onpro OBI device
    - Onpro OBI device failure
    - Other
    - No information

  Reviewers will specify other reasons; these will be reported if any represent > 5% of patients

- Occurrence and reason for hospitalizations
    - Phase 2: Observed record of hospitalization due to any cause during the study observation period (01 January 2018 – 31 December 2019), will be recorded during chart review. The start and stop dates of the hospitalizations as well as reasons for hospitalizations will be recorded.
- Occurrence and reason for emergency department (ED) visits
    - Phase 2: Observed record of ED visits due to any cause during the study observation period (01 January 2018 – 31 December 2019), will be recorded during chart review. The ED visit dates as well as reasons will be recorded.
- Patient timing of actual administration of pegfilgrastim
    - Phase 1 and Phase 2: The timing of actual administration of pegfilgrastim treatment relative to completion of chemotherapy - defined as chemotherapy end date, or day 0, will be categorized as:

- PFS: recommended (day 1), non-recommended (day 0, 2-5), Day 6+
- Onpro OBI: recommended (day 0), non-recommended (day 1-5), Day 6+.

Findings will be summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported.

- Onpro OBI device failure
  - Phase 2: Observed record of Onpro OBI device failure will be recorded during the study observation period.

– *Exposure Variable(s)*

Patients to be included in the analytical cohort were exposed to pegfilgrastim during the time frame of 01 January 2018 through 31 October 2019. Treatment patterns that will be evaluated for the study population include: Chemotherapy regimen (stratified by FN risk: high-risk, intermediate-risk and unclassified) (Phase 1 and 2), pegfilgrastim start/stop date (Phase 1 and 2), reasons for anti-cancer treatment discontinuation (Phase 2), actual number of cycles during follow-up (Phase 1 and 2), planned number of cycles (Phase 2), actual and planned average cycle length (Phase 2).

– *Other Covariate(s)*

Patient demographic and clinical characteristics at baseline will also be assessed (Phase 1 and 2). Demographic characteristics include age, sex, body mass index (BMI), race, clinic practice location. Clinical characteristics captured in Phase 1 and Phase 2 (unless otherwise specified) include: stage at diagnosis, adjuvant/neoadjuvant setting, metastatic site(s), Eastern Cooperative Oncology Group (ECOG) performance status, laboratory values (WBC), body temperature, and febrile neutropenia (Phase 2 only).

- Study Sample Size

A preliminary feasibility analysis of the iKM database identified 15,443 patients with breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, receiving treatment with pegfilgrastim within the USON between January 1, 2018 and October 31, 2019. Phase 2 objectives will be assessed in a sample of 500 patients through a targeted chart review. These patients will be identified into mutually exclusive groups of patients who received pegfilgrastim in at least 1 of the first 6 cycles as follows: 100 patients who received Neulasta Onpro OBI, 100 patients

with day 6+ pegfilgrastim PFS, 100 patients who received non-recommended pegfilgrastim PFS and a random sample of 200 patients from the remaining study population. See section 8.2.2 for details on chart review selection.

The final study population for analysis will be defined after identification and review of the patient population meeting the inclusion criteria in the iKM database. A specific power calculation will not be performed as this is a descriptive analysis. Any limitation of sample size will be taken into account when interpreting study results.

- Data Analysis

Descriptive analyses will be conducted to summarize the baseline patient characteristics for the study population (see list in Table 2 for a complete list of patient characteristics). Results will be reported in aggregate. Categorical variables (eg, gender, ECOG performance status) will be reported as frequency (%) with 95% CI. Continuous variables such as age will be reported as mean (±SD), median, range (maximum-minimum) and 95% CI. Descriptive statistics will be used to summarize chemotherapy regimens and patient scheduling patterns (day of administration), specifically the number and proportion of patients who received pegfilgrastim as part of their chemotherapy regimen and had a recommended, non-recommended, or day 6+ appointments for pegfilgrastim, within a chemotherapy course, will be reported (Phase 1 and 2). Reasons for day 6+ appointments, non-recommended, and delay in chemotherapy as described in Table 2, will be reported (Phase 2 only).

Counts and proportion of patients reporting a protocol-defined FN event, (as described in Section 8.3.2) will be reported (Phase 2 only). Counts and proportion of patients reporting an Onpro OBI device failure will also be reported (Phase 2 only).

Resource utilization (hospitalization and ER visit) will be assessed from the index date until end of the study period (31 December 2019), or the last record available in chart review, whichever comes first (Phase 2 only). Proportion of patients with a hospitalization or ER visit will be reported (Phase 2 only). Reasons for hospitalization or ER visit (as described in Table 2) will also be summarized (Phase 2 only).

All results will be reported at patient-level (stratified by recommended, non-recommended, or day 6+ appointments for pegfilgrastim) and cycle-level (stratified by chemotherapy cycle 1-6) (Phase 1 and 2).

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Neutropenia in the presence of fever (febrile neutropenia), characterized by a significant decrease in white blood cells, is a serious complication resulting from cancer chemotherapy treatment (Lyman et al. 2003). The risk of FN is the highest during the first cycle of chemotherapy (Lyman et al. 2003) and may result delays, reductions, and/or discontinuation of chemotherapy (Lalami et al. 2017). Patients who develop FN often require hospitalizations, published studies have found more than 80% of U.S. patients with febrile neutropenia require hospitalization. In addition to increased treatment costs, FN also been found to impact quality of life (Fortner et al. 2005).

Treatment injections with long-acting (pegylated) G-CSFs (pegfilgrastim) at least 24 hours after administration of cytotoxic chemotherapy has been shown to be safe and effective in decreasing the incidence of chemotherapy-induced febrile neutropenia (FN). The NCCN guidelines recommends prophylaxis for patients with a greater than 20% risk of febrile neutropenia; they also recommend taking therapy into consideration if the risk is 10% to 20% and note that G-CSF agents should be administered 24 to 72 hours after chemotherapy (NCNN 2020). However, this 24-hour time frame also creates a challenge for administration of G-CSF as primary prophylaxis (PP) due to the need for a 'next-day' return visit to the clinic. The Neulasta® (pegfilgrastim) Onpro® OBI was designed to eliminate the requirement for a patient to return to the clinic the day after chemotherapy to receive pegfilgrastim as primary prophylaxis.

Although pegfilgrastim pharmacokinetics and safety have been found to be comparable between the on-body injector and PFS (Yang et al. 2015), studies comparing treatment scheduling patterns and clinical outcomes between the Onpro OBI and the PFS delivery methods in a real-world setting are lacking.

6.2 Rationale

The Onpro OBI device provides a convenient dosage form of pegfilgrastim that eliminates the need for the patient to return to the clinic the day after receiving chemotherapy for [manual injection] of pegfilgrastim. This makes the medication more accessible for patients, especially for those who have difficulty returning to the clinic. However, device failure can also occur.

A study comparing grade 4 neutropenia associated with pegfilgrastim administered via the Onpro OBI device and PFS, did not find a significant difference between the two groups (Townley et al. 2018). Limited data exists to describe treatment scheduling and clinical outcomes with traditional G-CSF treatment and with use of the Onpro® OBI. For patients receiving Onpro® OBI, there is particularly little information regarding the scheduling patterns and clinical outcomes. This study proposes to describe real-world patient profiles, treatment patterns and clinical outcomes with use of the different G-CSF products in US Oncology Network (USON) clinics. The results of this study will provide insight into treatment scheduling patterns and clinical outcomes with pegfilgrastim across community oncology clinics.

6.3 Feasibility and Futility Considerations

A preliminary feasibility analysis of the iKM database identified 15,433 patients with breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, receiving treatment with pegfilgrastim within the USON between January 1, 2018 and October 31, 2019. The final study population for analysis will be defined after identification and review of the patient population meeting the inclusion criteria in the iKM database. A specific power calculation will not be performed as this is a descriptive analysis. Any limitation of sample size will be taken into account when interpreting study results.

6.4 Statistical Inference (Estimation or Hypothesis[es])

This study will describe the demographic, patient, treatment scheduling patterns, outcome characteristics and resource utilization among patients initiating pegfilgrastim treatment.

No specific hypotheses are being tested that require sample size estimates. No formal sample size calculations will be performed

7. Research Question and Objectives

The aim of this study is to describe real-world utilization of pegfilgrastim with particular focus on treatment scheduling patterns. Clinical outcomes and resource utilization will also be assessed.

All study data will originate from the electronic healthcare record (EHR) of the USON. Structured data fields within the EHR will be sufficient to provide the information needed to address most research questions. To supplement these discrete and mapped data elements, a targeted chart review will be performed for 500 patients (100 patients from the who received Neulasta Onpro OBI, 100 patients with day 6+ pegfilgrastim PFS,

100 patients who received non-recommended pegfilgrastim PFS and a random sample of 200 patients from the remaining population) to capture additional information recorded in the chart. It is necessary to conduct a chart review to assess this data element because this information will not be recorded in the structured EHR fields and instead in other sections of the chart, such as the providers' notes.

7.1 Primary

Phase 1 (Structured EMR Data):

1. To examine patient demographics and clinical disease characteristics (including age at index, gender, race, BMI, stage at diagnosis, duration of therapy) of breast cancer, colorectal cancer, NSCLC, or ovarian cancer patients treated with pegfilgrastim in the adjuvant setting
2. To examine patient demographics and clinical disease characteristics (including age at index, gender, race, BMI, stage at diagnosis, duration of therapy) of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer patients treated with pegfilgrastim in the metastatic setting - 1L and 2L+
3. To describe scheduling patterns with pegfilgrastim:
    a. Patient timing of actual administration of pegfilgrastim relative to completion of chemotherapy - defined as chemotherapy end date, or day 0 (eg, recommended, non-recommended, day 6+)

Phase 2 (Structured and Unstructured EMR data)

4. To describe scheduling patterns with pegfilgrastim:
    a. Patient scheduling patterns (order date) and concordance to guidelines (prophylactic use of pegfilgrastim based on FN-risk)
5. To examine clinical outcomes among patients initiating pegfilgrastim:
    a. Incidence of febrile neutropenia
    b. Incidence and reason for dose delay in chemotherapy treatment
    c. Frequency and reason for day 6+ visit and non-recommended pegfilgrastim administration
    d. Onpro OBI device failure
6. To examine resource utilization (hospitalization and ER visits) among patients initiating pegfilgrastim

Within each cancer type, results will be stratified by adjuvant and metastatic status (1L and 2L+).

8. Research Methods

8.1 Study Design

This study is a retrospective cohort study evaluating treatment scheduling patterns, clinical outcomes, resource utilization and patient characteristics among patients with a diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, treated with pegfilgrastim.

Phase 1 objectives will be assessed among patients who meet study eligibility criteria as specified in Section 9.2.

Phase 2 objectives will be assessed in a sample of 500 patients, 100 patients who received Neulasta Onpro OBI, 100 patients with day 6+ pegfilgrastim PFS, 100 patients who received non-recommended pegfilgrastim PFS and a random sample of 200 patients from the remaining population, through a targeted chart review, as specified in Section 8.2.2.

8.2 Setting and Study Population

The study population will consist of adult patients with breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer who received pegfilgrastim treatment within the USON (EMR) and met the eligibility criteria described in section 8.2.2. below.

8.2.1 Study Period

This is a retrospective, observational study of patients initiating pegfilgrastim between 01 January 2018 and 31 October 2019 in USON community practices who meet all inclusion criteria and none of the exclusion criteria outlined in section 8.2.2. Index date will be defined as first date of pegfilgrastim during the study identification period, 01 January 2018 through 31 October 2019. Patients will be followed from index date until 31 December 2019 or date of last record, which is defined as the last visit with documented vital sign or recorded death. Patients will have variable follow-up time periods, depending on their index and last contact dates.

8.2.2 Subject/Patient/Healthcare Professional Eligibility

The study's population will be patients with breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer receiving pegfilgrastim between 01 January 2018 and 31 October 2019 in USON community practices who meet all inclusion criteria and none of the exclusion criteria outlined in below.

Chart review selection:

Among patients who meet the eligibility criteria defined by the inclusion/exclusion criteria in Section 8.2.2.1-8.2.2.2, a sample of 500 patients will be identified for chart review for assessing Phase 2 objectives. These patients will be identified into mutually exclusive groups of patients who received pegfilgrastim in at least 1 of the first 6 cycles as follows: 100 patients who received Neulasta Onpro OBI, 100 patients with day 6+ pegfilgrastim PFS, 100 patients who received non-recommended pegfilgrastim PFS and a random sample of 200 patients from the remaining study population. Patients will be identified in the following order of priority: day 6+ pegfilgrastim PFS, non-recommended pegfilgrastim PFS, Neulasta Onpro OBI, and random sample. In the event the number of eligible patients following structured data screening is lower than the planned number of charts for a particular category, the balance of that category will be added to (in order): 1) Day 6+ PFS; 2) Non-recommended PFS; 3) Neulasta Onpro OBI; 4) Random sample. In the event the number of eligible patients following structured data screening is greater than the planned number of charts for a particular category, a random sample will be selected to fill that category per the quantities stated previously (eg, 100 patients with day 6+ Neulasta PFS), and the balance of patients in that category will be returned to the pool for possible selection in the remaining categories. Once a patient is selected for chart review in a particular category, that patient cannot be selected for another category.

Some patients may be disqualified during chart review based on information in the chart that differed from what was available in iKM. Reasons for disqualification will be captured and reported. Up to 100 additional charts will be pulled to replace disqualified chart review patients.

8.2.2.1 Inclusion Criteria

1. Patients with a diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer
2. Patients ≥ 18 years of age at first diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer
3. Patients who received at least one dose of pegfilgrastim as either pegfilgrastim PFS (Neulasta PFS or biosimilar pegfilgrastim PFS) or Neulasta Onpro OBI during the patient identification period (01 January 2018 to 31 October 2019)
4. During the study period, observed with either ≥1 visits within the USON in addition to the index event visit or a documented record of death
    - Visits are defined as physical encounters with the practice, detected by vital sign records

- The second visit must be observed after the index date to demonstrate continuity of care
- There is no required time span between the additional visit and the index date

8.2.2.2 Exclusion Criteria

1. Patients enrolled in interventional clinical trials during the study observation period
2. Patients who received treatment indicated for another primary cancer (other than breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer) or diagnosed with another primary cancer (other than breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer) during baseline period (60 days prior and 10 days after index)

Note: The number of patients who received short-acting G-CSF treatment (filgrastim and filgrastim biosimilars) in addition to pegfilgrastim during study observation period will be reported.

8.2.3 Matching

There is no plan at the current time to generate a matched reference group for this study. If Amgen and MSH agree that matching would be appropriate, a scope amendment can be developed.

8.2.4 Baseline Period

The baseline period will consist of the 60 days prior to and 10 days following initiation of pegfilgrastim (index date) during the study identification period. The baseline period will be evaluated only if available as prior medical history may not be well-documented for all patients.

8.2.5 Study Follow-up

Patients will be identified from 01 January 2018 through 31 October 2019 and followed through 31 December 2019, or until date of last record, which is defined as the last visit with documented vital sign or recorded death. Index date will be the first date of the pegfilgrastim treatment (pegfilgrastim PFS or Neulasta Onpro OBI) during the study identification period. Depending on each patient's initiation date and the last documented contact date (or death) available, patients will have variable length of follow-up. All study variables and outcomes will be assessed regardless of maximum follow-up using data available until the end of the study period, 31 December 2019.

8.3 Variables

Patients will be identified from 01 January 2018 through 31 October 2019 and followed through 31 December 2019, or until date of last record, which is defined as the last visit with documented vital sign or recorded death. Index date will be the first date of the pegfilgrastim treatment (pegfilgrastim PFS or Neulasta Onpro OBI) during the study identification period. Depending on each patient's initiation date and the last documented contact date (or death) available, patients will have variable length of follow-up. All study variables and outcomes will be assessed regardless of maximum follow-up using data available until the end of the study period, 31 December 2019.

8.3.1 Exposure Assessment

Patients to be included in the analytical cohort were exposed to pegfilgrastim during the time frame of 01 January 2018 through 31 October 2019. Patients exposed to pegfilgrastim (pegfilgrastim PFS or Neulasta Onpro OBI) during the study identification period, will be followed until 31 December 2019 or until date of last record, whichever occurs first.

For the study population, the following treatment patterns will be assessed during the study period:

- Chemotherapy regimen (Phase 1 and 2):
  - The anticancer regimen for which pegfilgrastim was administered to prevent FN during the study identification period will be reported. Chemotherapy regimen will be stratified by FN-risk (high-risk, intermediate-risk and unclassified risk) as listed in Table 1.
- Pegfilgrastim start/stop date(s) (Phase 1 and 2):
  - Any pegfilgrastim treatment received by patients during the study identification period will be summarized and reported
- Reasons for treatment discontinuation (Phase 2)
  - Discontinuation data for anticancer treatment (for which pegfilgrastim was administered), including reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts.
  - If available, reason patients discontinued treatment will be abstracted:
    - Completion of therapy
    - Provider-documented disease progression
    - Death
    - Insurance/cost-related
    - Loss to follow-up
    - Patient preference

- Toxicity
- Anemia
- Febrile Neutropenia
- Thrombocytopenia
- Other
- No information

Reviewers will specify other reasons; these will be reported if any represent > 5% of patients

- Actual number of cycles (Phase 1 and 2) and planned number of cycles (Phase 2):
  - Actual and planned number of cycles of anticancer regimen for which pegfilgrastim was administered to prevent FN during the study identification period, per patient and across all patients, as we as difference in actual and planned number of cycles per patient and across all patients.
- Actual and planned average cycle length (Phase 2):
  - Actual and planned average cycle length, as well as the difference between actual and planned, reported in aggregate across cycles and patients.
  - The cycle length of anticancer regimens (for which pegfilgrastim was administered to prevent FN) is recorded as days in a standard field in iKM. It is defined as the course where the patient receives the administration and then briefly suspends treatment to allow the body to recover, if applicable.
  - Each patient's cycle lengths by regimen, will be calculated, then averaged. This average cycle length per person will then be summarized across patients.

To capture this exposure information, the iKM database will be used. Within iKM, there is a data table for physician-planned regimen of chemotherapy, which is completed prior to the start of chemotherapy. The data fields include planned chemotherapy agent(s) and planned cycle length (eg, two weeks/three weeks/four weeks) which will be used in this study if standard regimen information is not available.

Additionally, the drug administration table in iKM database includes records of the actual delivered chemotherapy cycles and cycle length. A chemotherapy course is assumed to be terminated after a chemotherapy administration if there was no evidence of receipt of any subsequent chemotherapy administration within 60 days after that administration, or if death, or disease progression or unplanned regimen change occurred. The termination date of a chemotherapy course is assumed to be the date of the last chemotherapy

administration plus the standard cycle length (according to the corresponding standard regimen as identified based on first cycle agent[s]), the death date, the date of disease progression or the date of unplanned regimen change, whichever occurred first.

Table 1. Chemotherapy Regimen and FN-risk

Cancer type	Regimen	Risk Level
Breast	AT (doxorubicin + docetaxel) Q3W	High
Breast	Docetaxel Q3W	High
Breast	Docetaxel + trastuzumab	High
Breast	TAC (cyclophosphamide + doxorubicin + docetaxel) Q3W	High
Breast	TC (docetaxel + cyclophosphamide) Q3W	High
Breast	TCH (docetaxel + carboplatin) Q3W	High
Breast	TCH + pertuzumab (docetaxel + carboplatin + trastuzumab) Q3W	High
Breast	Dose dense-Fluorouracil + epirubicin + cyclophosphamide followed by paclitaxel	High
Breast	Dose dense-doxorubicin + cyclophosphamide	High
Breast	Dose dense-epirubicin + cyclophosphamide	High
Breast	Dose dense-epirubicin + cyclophosphamide followed by docetaxel	High
Breast	Dose dense-fluorouracil + epirubicin + cyclophosphamide followed by docetaxel	High
Breast	Dose dense-docetaxel before doxorubicin + cyclophosphamide	High
Non-Hodgkin's Lymphoma	Dose dense-Rituximab+ cyclophosphamide + doxorubicin + vincristine + prednisone-14 (R-CHOP-14)	High
Non-Hodgkin's Lymphoma	Dose dense-Cyclophosphamide + doxorubicin + vincristine + prednisone-14 (CHOP-14)	High

Table 1. Chemotherapy Regimen and FN-risk

Cancer type	Regimen	Risk Level
Non-Hodgkin's Lymphoma	R-ESHAP (rituximab + etoposide + methylprednisolone + cisplatin + cytarabine)	High
Non-Hodgkin's Lymphoma	R-DHAP (rituximab + dexamethasone + cisplatin + cytarabine)	High
Non-Hodgkin's Lymphoma	R-MINE (rituximab + mesna + ifosfamide + mixotantrone + etoposide)	High
Non-Hodgkin's Lymphoma	R-EPOCH (rituximab + etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin)	High
Non-Hodgkin's Lymphoma	HyperCVAD (cyclophosphamide + vincristine + doxorubicin +dexamethasone	High
Non-Hodgkin's Lymphoma	Dose-adjusted EPOCH a (etoposide, prednisone, vincristine, cyclophosphamide,doxorubicin)	High
Non-Hodgkin's Lymphoma	BR (bendamustine + rituximab)	High
Non-Hodgkin's Lymphoma	CHOP ± R (cyclophosphamide + doxorubicin + vincristine + predniso[lo]ne with or without rituximab) Q3W	High
Non-Hodgkin's Lymphoma	DHAP (dexamethasone + cisplatin + cytarabine)	High
Non-Hodgkin's Lymphoma	ESHAP (etoposide + methylprednisolone + cisplatin + cytarabine)	High
Non-Hodgkin's Lymphoma	HyperCVAD + R (cyclophosphamide + vincristine + doxorubicin + dexamethasone + rituximab)	High
Non-Hodgkin's Lymphoma	ICE (ifosfamide + carboplatin + etoposide)	High
Non-Hodgkin's Lymphoma	R-ICE (rituximab + ifosfamide + carboplatin + etoposide)	High
Non-Hodgkin's Lymphoma	MINE (mesna + ifosfamide + novantrone + etoposide)	High
Non-Hodgkin's Lymphoma	EPOCH (etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin)	High
Ovarian	Docetaxel	High
Ovarian	Topotecan	High
Non-Small-Cell Lung	Carboplatin + paclitaxel Q3W	High
Breast	AC (doxorubicin + cyclophosphamide) + sequential docetaxel	Intermediate
Breast	AC (doxorubicin + cyclophosphamide) + sequential docetaxel + trastuzumab	Intermediate
Breast	FEC (fluorouracil + epirubicin + cyclophosphamide) + sequential docetaxel	Intermediate

Table 1. Chemotherapy Regimen and FN-risk

Cancer type	Regimen	Risk Level
Breast	Paclitaxel Q3W	Intermediate
Breast	Docetaxel	Intermediate
Non-Hodgkin's Lymphoma	GDP (gemcitabine + dexamethasone + cisplatin)	Intermediate
Non-Hodgkin's Lymphoma	GDP (gemcitabine + dexamethasone + cisplatin) + rituximab	Intermediate
Non-Hodgkin's Lymphoma	CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) including regimens with pegylated liposomal doxorubicin	Intermediate
Non-Small-Cell Lung	Cisplatin + etoposide	Intermediate
Non-Small-Cell Lung	Cisplatin + paclitaxel	Intermediate
Non-Small-Cell Lung	Cisplatin + vinorelbine	Intermediate
Non-Small-Cell Lung	Cisplatin + docetaxel	Intermediate
Non-Small-Cell Lung	DC (docetaxel + cisplatin)	Intermediate
Non-Small-Cell Lung	DCb (docetaxel + carboplatin)	Intermediate
Non-Small-Cell Lung	Paclitaxel + sequential cisplatin	Intermediate
Non-Small-Cell Lung	Carboplatin + paclitaxel + bevacizumab	Intermediate
Non-Small-Cell Lung	Docetaxel	Intermediate
Colorectal	FOLFOX-4 (leucovorin + 5-fluorouracil + oxaliplatin)	Intermediate
Colorectal	FOLFOX-4+ Bevacizumab	Intermediate
Colorectal	FOLFOX-4 + Cetuximab	Intermediate
Colorectal	FOLFOX-4 + Panitumomab	Intermediate
Colorectal	FOLFOXFIRI + Bevacizumab	Intermediate
Ovarian	DCb (docetaxel + carboplatin)	Intermediate

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8.3.2 Outcome Assessment

The outcomes of the study are:

- Incidence of febrile neutropenia (Phase 2 only):
  - Occurrences of FN during the anticancer treatment will be captured from day 6 for each cycle, up to first 6 cycles of treatment. FN for any particular cycle will be identified by the chart reviewer through either of the following methods: 1) visits with documented ANC of less than 500 neutrophils/mcL and fever (≥ 38º C); or 2) documentation in the record (eg, physician notes, lab reports), identified by performing a keyword search of the problem list in the structured data.
    - It is important to note that the operational definition of FN used for this study aligns with the clinical definition from the NCCN Guidelines Management of Neutropenia (NCCN 2021), namely "Febrile neutropenia is defined as single temperature: ≥ 38.3 ºC orally or ≥ 38.0 ºC over 1 h; neutropenia: < 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 h." Additionally, documentation in the record would constitute a clinical diagnosis of FN.
    - It should be noted that different definitions of FN used for other claims-based analyses exist, where either a specific clinical diagnosis or an ANC value and temperature are not available in the data. Those algorithms to identify FN were developed for claims data, as there is no single ICD-10 code for FN. This study, however, captures FN more directly: either through the use of an FN definition aligned with that from the NCCN Guidelines, or directly from a documented clinical diagnosis.
- Incidence and reason for dose delay in chemotherapy treatment (on cycle basis) (Phase 2)
  - Proportion of patients with a dose delay and reasons for dose delay (treatment hold and/or delay of the anticancer therapy for 1 cycle) in chemotherapy treatment will be captured in chart review as described in Table 2.
- Frequency of day 6+ appointments for pegfilgrastim (Phase 1 and 2)
  - Among chemotherapy regimens with pegfilgrastim as part of regimen, day 6+ appointments will be captured within a chemotherapy course. Day 6+ cycles are defined as cycles which received pegfilgrastim between day 6 and the end of the chemotherapy cycle.
- Reasons for day 6+ visit and non-recommended pegfilgrastim administration (Phase 2)
  - Data for day 6+ appointments and non-recommended pegfilgrastim PFS administration reasons will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts.

- If available, reason patients day 6+ treatment or received non-recommended pegfilgrastim will be abstracted:
    - Anemia
    - Thrombocytopenia
    - Fatigue
    - Anxiety
    - Flu season
    - Patient forgot appointment
    - Nausea
    - Drive time or distance (typically by car)
    - Travel burden (regardless of travel method [eg, car, bus, subway, train])
    - Burden on caregiver to travel
    - Difficulty arranging travel
    - Need to care for dependent(s)
    - Need to return to work
    - Weekend/holiday the day after chemo
    - Bad weather after chemo
    - Request for Onpro OBI device
    - Onpro OBI device failure
    - Other
    - No information

  Reviewers will specify other reasons; these will be reported if any represent > 5% of patients

- Occurrence and reason for hospitalizations (Phase 2)
    - Observed record of hospitalizations due to any cause during the study observation period (01 January 2018 – 31 December 2019), will be recorded during chart review. The hospitalization dates as well as reasons will be recorded.
- Occurrence and reason for emergency department visits (Phase 2)
    - Observed record of ED visits due to any cause during the study observation period (01 January 2018 – 31 December 2019), will be recorded during chart review. The ED visit dates as well as reasons will be recorded.
- Patient timing of actual administration of pegfilgrastim (Phase 1 and 2)
    - The timing of actual administration of pegfilgrastim treatment relative to completion of chemotherapy - defined as chemotherapy end date, or day 0, will be categorized as:

- PFS: recommended (day 1), non-recommended (day 0, 2-5), day 6+
- Onpro OBI: recommended (day 0), non-recommended (day 1-5), day 6+.

- Findings will be summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported.

- Onpro OBI device failure (Phase 2)
  - Observed record of Onpro OBI device failure will be recorded during the study observation period.

8.3.3 Covariate Assessment

Table 2. is a summary of the variables considered as potential covariates that will be used to meet the objectives of this study. Note that some variables are collected to support specific metric reporting and will not be reported separately (eg, height and weight are collected for body mass index [BMI] calculations).

Variables described as being captured “at index” will be captured at the date closest to initiation of pegfilgrastim (index date). Unless otherwise specified, baseline measurements will be assessed in the period 60 days prior to and 10 days after either index date, as defined in section 8.2.4. If multiple baseline values are available during this time frame, the one closest (in absolute value) to the index event will be used within the predefined time periods discussed above.

The majority of data elements are sourced from iKM. Death date is sourced from both iKM and SSDI, giving SSDI priority for conflicting information.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Demographic and patient characteristics				
PatID	iKM structured data	Data linkage	Study observation period	Unique patient identifier that will be used to link clinical records. This information will not be disclosed to the study sponsor.
Medical record number (MRN)	iKM structured data	Data linkage	Study observation period	Unique patient identifier that will be used to link clinical records. This information will not be disclosed to the study sponsor.
Clinical trial participation	iKM structured data + chart review	Eligibility criteria	Follow-up	Patients enrolled in interventional clinical trials (patients in only observational studies will be retained, if applicable) in the USON during the study observation period will be excluded.
Other cancer diagnosis	iKM structured data + chart review	Eligibility criteria	Prior medical history + study observation period	Patients will be confirmed as having no additional primary malignancies (other than breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer) during the study baseline period.
Additional visits	iKM structured data	Eligibility criteria	Follow-up	To capture a sample of patients with longitudinal records, patients will be required to have 2 records of either additional visits following the index date visit and/or a record of death prior to the end of the study follow-up period. Visits are defined as physical encounters with the practice, detected by vital sign records. There will be no distinction made, for purposes of inclusion, between patients that have an additional USON visit and those with a record of death. There is no minimum or maximum requirement on time from index date to these qualifying events.
Short-acting G-CSF treatment	iKM structured data	Eligibility criteria	Follow-up	The number of patients who received short-acting G-CSF treatment (filgrastim and filgrastim biosimilars) in addition to pegfilgrastim during study observation period will be reported.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Demographic and patient characteristics				
Gender	iKM structured data + chart review (Phase 1 & 2)	Baseline characteristic	**Prior** medical history	Patients will be categorized as: Male Female
Date of birth	iKM structured data	Eligibility; Data linkage; Baseline characteristic	Prior medical history	Patient's date of birth as recorded in iKM. This information will not be disclosed to the study sponsor.
Age	iKM structured data (derived) (Phase 1 & 2)	Eligibility; Baseline characteristic	Baseline	Patient's age (in years) at the date of diagnosis, which will be calculated as the integer of [(diagnosis date – date of birth + 1) / 365.25]. Patients aged less than 18 years at the initial recorded diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer will be excluded from the study.
Age groups	iKM structured data (derived) (Phase 1 & 2)	Baseline characteristic	Baseline	Multiple age categories will be created based on the continuous age data: < 65 years ≥ 65 years No information
Race	iKM structured data (Phase 1 & 2)	Baseline characteristic	Prior medical history	Categorized as: Caucasian African American Asian Native American Other No information The specific categories outside of Caucasian and African American will be confirmed after reviewing sample sizes and the added value to the study with McKesson's Privacy and Compliance team.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Demographic and patient characteristics				
Height	iKM structured data	Baseline characteristic	Baseline	Patient's height in meters.
Weight	iKM structured data	Baseline characteristic	Baseline	Patient's weight in kilograms.
Body mass index (BMI)	iKM structured data (derived) (Phase 1 & 2)	Baseline characteristic	Baseline	BMI = Weight (in kilograms)/(Height (in meters))^2 Based on the resulting BMI values, patients will then be categorized as underweight (BMI $<$ 18.5), normal (BMI 18.5 – 24.9), overweight (BMI 25 – 29.9), obese (BMI $\geq$ 30) or no information (missing height or weight data).
Healthcare setting and provider characteristics				
Practice location	iKM structured data (derived) (Phase 1 & 2)	Baseline characteristic	Baseline	The US census region of the USON clinic where the patient received care at the index visit: Midwest: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota and South Dakota Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Pennsylvania, New Jersey and New York South: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma and Texas West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, California, Oregon and Washington State Missing clinic values will be captured in a "no information" category. Some of the regions may need to be collapsed if there are small sample sizes (eg, South vs. non-South). This determination will be confirmed after reviewing sample sizes and the added value to the study with McKesson's Privacy and Compliance team.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Healthcare setting and provider characteristics				
Date of initial breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer diagnosis	iKM structured data + chart review	Eligibility criteria, Baseline characteristic	Medical history prior to index	To assess breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer diagnoses that occurred prior to index date, patients' available medical history in iKM will be searched. The completeness of this history will vary based on the length of disease and the time within the USON. Records may also be incomplete for patients with an initial cancer diagnosis that occurred outside of the USON. Diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care (International Classification of Diseases [ICD] codes will not be used). If no initial diagnosis date is documented, the first recorded diagnosis date in iKM will be used. This date will be used in calculations, not reported separately. Patients without a recorded diagnosis of breast cancer, colorectal cancer, NHL, NSCLC, or ovarian will be excluded from the study.
Stage at initial breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer diagnosis	iKM structured data	Baseline characteristic	Medical history prior to index	Categorized as: Stage 0 Stage IA Stage IB Stage IIA Stage IIB Stage IIIA Stage IIIB Stage IV No information

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Healthcare setting and provider characteristics				
Date of metastatic disease diagnosis	iKM structured data + chart review	Baseline characteristic	Medical history prior to index	Date of first recorded diagnosis of metastatic disease within the EHR. Patients will be qualified initially based on the date identified in the structured data; this will be confirmed during chart review among patients selected for chart review. Ultimately, the primary source will be the chart if available. Date of first recorded diagnosis of metastatic disease within the iKM database. Specifically, the earliest associated date of any of these criteria: 1. Stage IV disease 2. TNM with M value of 1 3. Record of location of metastatic disease 4. Current or prior disease status containing reference to metastatic disease 5. A numbered LOT 6. A LOT with a reference to "metastatic"
TNM staging	iKM structured data	Baseline characteristic	Medical history prior to index	Patients' stage will be characterized according to TNM criteria recorded in the EHR.
Metastatic site(s) at initial diagnosis and metastatic diagnosis	iKM structured data + Chart review	Baseline characteristic	Baseline	Baseline metastatic location(s) will be identified and categorized as: Bone Brain Liver Lung Lymph nodes Other No information Note, "no information" can indicates that metastases were not documented in the chart, not necessarily that patients did not have metastases.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Healthcare setting and provider characteristics				
Count of metastatic site(s)	iKM structured data + chart review (derived)	Baseline characteristic	Baseline	The total count of metastatic site(s) at index: No documentation 1 2 3 4+ Note, "no documentation" can indicates that metastases were not documented in the chart, not necessarily that patients did not have metastases.
Laboratory results - WBC	iKM structured data	Baseline characteristic	Baseline	Assessment will be done for data collected at the closest date prior to the index date within 30 days of treatment initiation. Data will be summarized as a continuous measure (ie, mean, standard deviation, median and range).
Body Temperature	iKM structured data	Baseline characteristic	Baseline	Assessment will be done for data collected at the closest date prior to the index date within 30 days of treatment initiation. Data will be summarized as a continuous measure (ie, mean, standard deviation, median and range).
Febrile Neutropenia	iKM structured data + Chart review (Phase 2 only)	Baseline characteristic	Baseline	Occurrences of FN during the anticancer treatment (for which pegfilgrastim was administered) will be captured from Day 6 for each cycle, up to first 6 cycles of treatment. FN for any particular cycle will be identified by the chart reviewer through either of the following methods: 1) visits with documented ANC of less than 500 neutrophils/mcL and fever (≥ 38° C); or 2) documentation in the record (eg, physician notes, lab reports), identified by performing a keyword search of the problem list in the structured data.

Table 2. Study Variables

<table>
<tr><th>Variable</th><th>Source(s)</th><th>Role(s) in study</th><th>Period of measurement</th><th>Operational definition</th></tr>
<tr><td colspan="5">Healthcare setting and provider characteristics</td></tr>
<tr><td>Eastern Cooperative Oncology Group (ECOG) performance status</td><td>iKM structured data (Phase 1 & 2)</td><td>Baseline characteristic</td><td>Baseline</td><td>The ECOG performance status score is a rating of a patient's disease status, daily living activities and quality of life, with low scores indicating greater functioning than high scores:
0
1
2
≥ 3
No information
Karnofsky performance status is a similar measure and will be converted to ECOG using the methodology outlined below (Santin et al. 2011).
<table>
<tr><th>Karnofsky Performance Status</th><th>ECOG Performance Status</th><th>ECOG Performance Status Description</th></tr>
<tr><td>100</td><td>0</td><td>Fully active</td></tr>
<tr><td>80, 90</td><td>1</td><td>Restricted in physically strenuous activity</td></tr>
<tr><td>60, 70</td><td>2</td><td>Ambulatory and capable of self-care but unable to work</td></tr>
<tr><td>40, 50</td><td>3</td><td>Capable only of limited self-care</td></tr>
<tr><td>10, 20, 30</td><td>4</td><td>Completely disabled</td></tr>
<tr><td>0</td><td>5</td><td>Dead</td></tr>
</table></td></tr>
<tr><td>Chemotherapy regimen start/stop date(s)</td><td>iKM structured data (Phase 1 & 2)</td><td>Treatment pattern</td><td>Study Observation period</td><td>The anticancer regimen for which pegfilgrastim was administered to prevent FN during the study identification period. Chemotherapy regimen will be stratified by FN-risk (high-risk, intermediate-risk and unclassified risk) as listed in Table 1</td></tr>
</table>

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Treatment characteristics				
Pegfilgrastim start/stop date(s)	iKM structured data	Treatment pattern	Study Observation period	Any pegfilgrastim treatment (pegfilgrastim PFS or Neulasta Onpro OBI) received by patients during the study identification period.
Reasons for treatment discontinuation (all therapies)	Chart Review (Phase 2 only)	Treatment characteristics	Study Observation period	Data for anticancer treatment (for which pegfilgrastim was administered) discontinuation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients discontinued anticancer treatment will be abstracted: • Completion of therapy • Provider-documented disease progression • Death • Insurance/cost-related • Loss to follow-up • Patient preference • Toxicity • Anemia • Febrile Neutropenia • Thrombocytopenia • Other • No information Reviewers will specify other reasons; these will be reported if any represent > 5% of patients

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Treatment characteristics				
Actual and planned number of treatment cycles	iKM structured data (actual) (Phase 1 & 2) + Chart review (planned) (Phase 2 only)	Treatment characteristics	Study observation period	Actual and planned number of cycles of anticancer regimen for which pegfilgrastim was administered to prevent FN during the study identification period, per patient and across all patients, as well as difference in actual and planned number of cycles per patient and across all patients. The number of patients with available data will be reported.
Actual and Planned cycle length	iKM structured data (actual) (Phase 1 & 2) + Chart review (planned) (Phase 2 only)	Treatment characteristics	Study observation period	• Actual and planned average cycle length, as well as the difference between actual and planned, reported in aggregate across cycles and patients. • The cycle length of anticancer regimens (for which pegfilgrastim was administered to prevent FN) is recorded as days in a standard field in iKM. It is defined as the course where the patient receives the administration and then briefly suspends treatment to allow the body to recover, if applicable. • Each patient's cycle lengths will be calculated, then averaged (by regimen). This average cycle length per person will then be summarized across patients.
Clinical outcomes				
Last USON visit date	iKM structured data + chart review	Clinical outcomes	Study observation period	Each patient's most recent visit date, prior to or on close of study observation period, in the structured data will be recorded. A visit is defined as a physician encounter with the practice where either treatment is given, or vital signs are recorded. For patients with a death date, this last visit date should occur prior to the death date. This will not be reported separately; it will be used in calculating the patient's available follow-up time as a descriptive measure. Available follow-up time = Integer (latest of last visit date or death date – index date +1).7

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Clinical outcomes				
Vital status	iKM structured data + LADMF + chart review (derived)	Clinical outcomes	Study observation period	Patients without a date of death in either the LADMF or iKM will be assumed to be alive at the end of the study. Those with a date of death in either LADMF or iKM will be flagged as deceased.
Death date	iKM structured data + LADMF + chart review	Clinical outcomes	Study observation period	Date of death will be captured from the LADMF as well as iKM. If dates conflict between the two sources, the LADMF date will be prioritized. If severe data discordance is observed (ie, death is reported to occur prior to the index date), then the iKM death date will be used.
Febrile Neutropenia during treatment and date(s)	Chart Review (Phase 2 only)	Clinical outcomes	Study observation period	Occurrences of FN during anticancer treatment will be captured from day 6 for each cycle, up to first 6 cycles of treatment. FN for any particular cycle will be identified by the chart reviewer through either of the following methods: 1) visits with documented ANC of less than 500 neutrophils/mcL and fever (≥ 38º C); or 2) documentation in the record (eg, physician notes, lab reports), identified by performing a keyword search of the problem list in the structured data.
ANC nadir	iKM structured data (derived)	Treatment characteristics	During anticancer treatment for which pegfilgrastim was administered	The ANC nadir will be defined as the lowest ANC value observed during the anticancer treatment for which pegfilgrastim was administered.
Chemotherapy cycle delay	iKM structured data (derived) + Chart review (Phase 2 only)	Treatment characteristics	During anticancer treatment for which pegfilgrastim was administered	Defined as a treatment hold and/or delay of the anticancer therapy for 1 cycle. All chemotherapy cycle delays from index through December 31, 2019 will be captured.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Clinical outcomes				
Reason for chemotherapy cycle dose delay	Chart Review (Phase 2 only)	Treatment characteristics	During anticancer treatment for which pegfilgrastim was administered	Data for chemotherapy cycle dose delay reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason for chemotherapy dose delay will be abstracted: Lack of response Patient preference Toxicity Other No information Reviewers will specify other reasons; these will be reported if any represent > 5% of patients.
Healthcare Resource Utilization (HCRU)				
Occurrence and reason for hospitalizations	Chart Review (Phase 2 only)	HRCU outcomes	Study observation period	Observed record of hospitalization due to any cause will be recorded during the study observation period. The start and stop dates of the hospitalizations as well as reasons for hospitalizations will be recorded.
Occurrence and reason for emergency department visits	Chart Review (Phase 2 only)	HRCU outcomes	Study observation period	Observed record of ED visits due to any cause will be recorded during the study observation period. The ED visit dates as well as reasons will be recorded.
Day 6+ appointments for pegfilgrastim	iKM structured data (Phase 1 & 2)	Treatment characteristics	Study observation period	• Among chemotherapy regimens with pegfilgrastim as part of regimen, day 6+ appointments will be captured within a chemotherapy course.

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Healthcare Resource Utilization (HCRU)				
Reason for day 6+ appointments and non-recommended pegfilgrastim	Chart Review (Phase 2 only)	Treatment characteristics	Study observation period	Data for day 6+ appointments and non-recommended administration of pegfilgrastim will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients had day 6+ appointments and received non-recommended administration of pegfilgrastim will be abstracted: Anemia Thrombocytopenia Fatigue Anxiety Flu season Patient forgot appointment Nausea Drive time or distance (typically by car) Travel burden (regardless of travel method [eg, car, bus, subway, train]) Burden on caregiver to travel Difficulty arranging travel Need to care for dependent(s) Need to return to work Weekend/holiday the day after chemo Bad weather after chemo Request for Onpro OBI device Onpro OBI device failure Other No information Reviewers will specify other reasons; these will be reported if any represent > 5% of patients

Table 2. Study Variables

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Healthcare Resource Utilization (HCRU)				
Patient timing of actual administration of pegfilgrastim	iKM structured data (Phase 1 and 2)	Treatment characteristics	Study observation period	The timing of actual administration of pegfilgrastim treatment relative to completion of chemotherapy - defined as chemotherapy end date, or day 0, will be categorized as: • PFS: recommended (day 1), non-recommended (day 0, 2-5), day 6+ • Onpro OBI: recommended (day 0), non-recommended (day 1-5), day 6+. Findings will be summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported.
Onpro OBI device failure	Chart review (Phase 2 only)	Treatment characteristics	Study observation period	Observed record of Onpro OBI device failure will be recorded during the study observation period.

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8.3.4 Validity and Reliability

The study will only use data from USON practices utilizing EHR capacities of iKM, which have already been extensively checked and validated through MSH's quality assurance procedures. Thus, the study team does not plan to conduct any additional studies to validate the accuracy of demographic, clinical, treatment and outcome information inhere iKM EHR database.

8.4 Data Sources

Data for this study will be primarily extracted from the USON's iKnowMed (iKM) electronic health record (EHR), with supplemental vitality status from the Limited Access Death Master File (LADMF). These data primarily capture data on outpatient medical oncology care for patients treated across 19 US states and includes over 400 sites of care. Overall, the iKM EHR database captures data on approximately 10% of newly diagnosed cancer patients in the United States.

iKnowMed™ is an integrated web-based database of oncology-specific EHR maintained by MSH. iKM captures outpatient practice encounter histories for patients under community-based care, including, but not limited to patient demographics such as age and gender; clinical information such as disease diagnosis, diagnosis stages, performance status information and laboratory testing results; and treatment information, such as dosages and treatment administration within the USON.

Structured data fields within the iKM EHR database will provide information needed to address most research questions. These data will be supplemented by additional unstructured data collected through chart review for a subset of the study population. Electronic chart review data will be collected by means of a secure, web-based electronic case report form (eCRF) by healthcare professionals with oncology experience.

The study will only use data from USON phertices utilizing full EHR capacities of iKM. Data management and administrative processing is supported by McKesson's quality assurance procedures. Thus, the study team does not plan to conduct any additional studies to validate the accuracy of demographic, clinical, treatment and outcome information in the iKM EHR database.

The LADMF of the Social Security Death Index (SSDI) will be an additional source of vital status (death), in addition the death dates recorded in the EHR. Common patient identifiers (patient identification, name, and birth date) will be used to link patients from

the iKM data warehouse and iKM chart review. The social security number (SSN) will be used to link patients from iKM and LADMF data sources. All patients within iKM are assigned a unique patient identifier by iKM version (eg, some large practices have separate installations by location). When linking to the LADMF, patient SSN is used. Some practices do not collect SSN and some patients may not report it. In all cases, reported deaths captured in iKM will supplement the SSDI data.

Data from all sources and any derived variables will be merged into one master dataset for analysis. Data will be handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH).

8.5 Study Size

A preliminary feasibility analysis of the iKM database identified 15,443 patients with breast cancer, colorectal cancer, NHL, NSCLC, or ovarian cancer, receiving treatment with pegfilgrastim within the USON between January 1, 2018 and October 31, 2019. Phase 2 objectives will be assessed in a sample of 500 patients, 100 patients who received Neulasta Onpro OBI, 100 patients with day 6+ pegfilgrastim PFS, 100 patients who received non-recommended pegfilgrastim PFS and a random sample of 200 patients from the remaining population, through a targeted chart review.

The final study population for analysis will be defined after identification and review of the patient population meeting the inclusion criteria in the iKM database. A specific power calculation will not be performed as this is a descriptive analysis. Any limitation of sample size will be taken into account when interpreting study results.

8.6 Data Management

8.6.1 Obtaining Data Files

The McKesson study team will collaborate with McKesson's Commercial Intelligence group to collect the structured iKM data that will be used for analysis. The Commercial Intelligence team will be provided with a Data Collections Variable List, which will detail the specific data elements that will need to be included in the study dataset. A Data Analyst will begin by generating high-level study sample counts that demonstrate attrition rates of the inclusion/exclusion criteria.

The study team will review the attrition count and the Data Analyst will proceed with collecting the remaining data elements on the Data Collections Variable List. The Data Analyst will perform an initial quality control check of the study dataset before providing

the file to the study team's Biostatistician on a secure server. Once received by the Biostatistician, data validation will continue and will consist of, but is not limited to, quality control checks for appropriate values, logical sequences and quantity of missing values.

A list of patients eligible for chart review will be generated by the Data Analyst and the Biostatistician will apply the agreed upon sampling technique to identify the specific patients that will undergo chart review. This list of patients will then be securely transmitted to the Chart Review Team Manager. The chart review team consists of experienced oncology healthcare providers.

The McKesson study team will lead a training session with chart abstractors to discuss study specific considerations. Reference materials will also be provided to abstractors at this time. If chart abstractors have questions during the abstraction process, these will first be raised to the Chart Review Team Manager. If needed, questions can be escalated to the Outcomes Researcher and Principal Investigator.

Chart review will be accomplished by use of a secure, web-based eCRF. The main purpose of the eCRF is to obtain data required by this non-interventional study protocol in a complete, accurate, legible and in a timely manner.

8.6.2 Linking Data Files

The unstructured data will be linked to structured data, which will be converted to structured form by a computer using automated/algorithmic methods, such as natural language processing. Common patient identifiers (patient ID, name and birth date) will be used to link patients from the iKM data warehouse and iKM chart review. The Social Security number (SSN) will be used to link patients from iKM and SSDI data sources. Analyses will be conducted using SAS® (SAS Institute Inc., Cary, NC, US) and/or R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) as appropriate.

8.6.3 Review and Verification of Data Quality

Descriptive analysis will be conducted for all the study variables. The data will be examined for outliers. Inconsistencies will be identified as any value that does not conform to the literature findings and the variables as outlined in the statistical analysis plan (SAP)/protocol.

If any data is inconsistent, the data is to be rechecked by the researcher. After this point, if data is still ambiguous it shall be referred to the Principal Investigator assigned to the

study. Data cleaning will occur during the analysis and again during the completion of preliminary and final report to check for inconsistencies/errors.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Interim Analysis/Analyses

No interim analysis is planned for this study.

8.7.1.2 Primary Analysis

The planned analysis will commence following acquisition of retrospective study data. The objective of Phase 1 analysis will be to describe treatment scheduling patterns with pegfilgrastim among the study population. The objective of Phase 2 will be to describe clinical outcomes and resource utilization by conducting a chart review. Details on the analysis plan are provided in the sections below.

8.7.1.3 Final Analysis

No separate final analysis is planned for this study.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

Descriptive analyses will be conducted to evaluate the demographic, clinical and treatment characteristics of the overall study population. Descriptive statistics will be used to summarize clinical outcomes and resource utilization among patients selected for chart review in Phase 2.

No multivariable statistical analyses will be conducted (eg, multivariable logistic regression). Results will be reported in aggregate using SAS® 9.4 (SAS Institute Inc., Cary, NC, US).

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data (ie, documented as an unknown value or not documented) will be identified and reported as percentages. Depending on the specific missing values, percentage of missing data, missing patterns or missing mechanisms, different strategies will be employed to address the issue. Approaches may include but are not limited to complete case analysis, mean substitution or multiple imputation. If missing data is minimal and at random, complete case analysis can be employed. If known values are randomly distributed and the sample size is small, mean substitution (with either sample mean or conditional mean from cases that are similar to the case with the missing values) may be employed. If the variable is used in any statistical analysis, and percentage of missing

data is not large (less than 30%), multiple imputation methods could be employed to substitute the missing values with what is drawn from an estimate of the distribution of this variable (Hardt et al. 2013). MSH and Amgen will agree on any imputation method(s), if this becomes necessary.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

To be included in the study population, patients must meet each of the inclusion criteria and none of the exclusion criteria listed in section 8.2.2. A sample of 500 patients, 100 patients who received Neulasta Onpro OBI, 100 patients with day 6+ pegfilgrastim PFS, 100 patients who received non-recommended pegfilgrastim PFS and a random sample of 200 patients from the remaining population, will be selected for a targeted chart review (details in section 8.2.2) .

Patient attrition will be reported and reviewed with Amgen prior to finalization of the study samples. Any modifications made to the selection criteria would need to be agreed between MSH and Amgen and could impact the timeline and/or study costs.

8.7.2.3.2 Description of Subject/Patient Characteristics

Descriptive analyses will be conducted to summarize the baseline patient characteristics for the study population. Results will be reported in aggregate. Categorical variables (eg, gender, ECOG performance status) will be reported as frequency (%) with 95% CI. Continuous variables such as age will be reported as mean (±SD), median, range (maximum-minimum) and 95% CI.

8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Descriptive statistics will be used to summarize chemotherapy regimens and patient scheduling patterns (day of administration) (Phase 1 and 2), specifically, the number and proportion of patients who received pegfilgrastim as part of their chemotherapy regimen and had a recommended, non-recommended, or day 6+ appointments for pegfilgrastim, within a chemotherapy course, will be reported (Phase 1 and 2). Reasons for non-recommended and day 6+ appointments, and delay in chemotherapy as described in Table 2, will be reported (Phase 2 only).

Counts and proportion of patients reporting a protocol-defined FN event (as described in Section 8.3.2) will be reported (Phase 2 only). Percentages will be calculated with the denominator being the total number of people in the study (patient count) at any point in

time and the numerator being number of patients reporting a FN event during anticancer treatment from day 5 through the first 6 cycles of treatment (Phase 2 only).

Counts and proportion of patients reporting a Onpro OBI device failure will be reported (Phase 2 only). Percentages will be calculated with the denominator being the total number of patients who were prescribed Neulasta Onpro OBI (patient count) at any point in time and the numerator being number of patients reporting Onpro OBI device failure (Phase 2 only).

Resource utilization (hospitalization and ER visit) will be assessed from the index date until end of the study period (31 December 2019), or the last record available in chart review, whichever comes first (Phase 2 only). Proportion of patients with a hospitalization or ER visit will be reported (Phase 2 only). Reasons for hospitalization or ER visit (as described in Table 2.) will also be summarized (Phase 2 only).

Continuous variables will be described by means, standard deviation, median and range (maximum and minimum). The continuous variables include variables such as age and time since diagnosis. Some may be defined into mutually exclusive groups as well and used as categorical variables.

Categorical variables will be defined by patient counts and percentage with a numerator and denominator, with the denominator being the number of people in the study (ie, patient counts) at any point in time and the numerator being some characteristic of these patients (eg, percent with a specific comorbidity), if dynamic, duration from index event.

All results will be reported at patient-level (stratified by recommended, non-recommended, or day 6+ appointments for pegfilgrastim) and cycle-level (stratified by chemotherapy cycle 1-6).

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

No subgroup analysis is planned at this time.

8.7.2.5.2 Stratified Analysis

All results will be reported at patient-level (stratified by recommended, non-recommended, or day 6+ appointments for pegfilgrastim) and cycle-level (stratified by chemotherapy cycle 1-6).

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

No sensitivity analysis is planned.

8.7.2.5.4 Other Sensitivity Analysis

No additional sensitivity analysis is planned.

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Safety data will not be collected or analyzed in this study.

8.8 Quality Control

MSH's Healthcare Informatics and Research Services team conducts quality assurance checks on all analytics projects. The process includes both technical and clinical quality checks.

The quality assurance process includes the following areas:

- Project scope and study rules
- Protocol/SAP development
- Data extraction and integrity
- Populated tables and Study Report development

As results of quality assurance and quality control, we confirm

- The source of the data and/or results will be documented and that results, and data will be verified against the source
- The internal consistency of the medical research data presented
- The conclusions are objective, balanced and consistent with the study results
- The format and content of the document are aligned with the agreed upon template and standards

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

This observational and retrospective study uses iKM EHR data. The iKM database is not collected for research purposes but for clinical practice reasons. This may impede the standardization of the data collection methods and instruments and the reporting practices of the physician. As with all administrative databases, iKM data are subject to coding errors of omission and commission. Problems with inadequate or inaccurate codes in the databases may introduce some level of misclassification bias of certain diagnoses, events, or procedures of interest.in the study. Likewise, some variables of interest may not be as complete across the entire population. The iKM EHR contains information on patients only when they are seen by USON physicians. Services and procedures provided outside of the USON are not captured by the database, as well as drugs received by patients from pharmacies not affiliated with USON practices.

A patient's treatment history prior to his/her first encounter at a USON practice may be only available in physician progress notes and is not well captured in the iKM EHR. We cannot rule out the possibility that some patients coded as receiving being treatment naïve for advanced disease in iKM EHR actually had previous chemotherapy or other treatment for advanced disease in healthcare facilities outside the USON.

8.9.1.2 Information Bias

Due to the nature of the study design, there is potential for bias to be introduced into the calculations of clinical outcomes. Specifically, patients who received treatment during the patient identification period may be meaningfully different from other patients who received therapy prior or after the study identification period.

8.9.1.3 Confounding

The iKM system is used for clinical practice reasons, not solely for research purposes. As such, associations but not causality can be detected, thus bias may be introduced by confounding factors. For example, data may be collected with an intent-to-treat approach, meaning based on when treatment is assigned rather than received. Likewise, patients who do and do not receive the treatment at one point in time may be fundamentally different than those who received treatment during the observation period. These confounding factors are most likely to affect the outcomes being considered for this estimation study.

8.9.2 External Validity of Study Design

Not all community oncology practices are included in the iKM dataset. Furthermore, not all of the USON utilize the full capabilities of the iKM EHR. The USON encourages use of evidence-based treatment guidelines. Therefore, practices that participate in the USON may be different from other community oncology practices in the patient population that is seen or the prescribing practices of the physicians.

It should be noted that the assessment of FN in Phase 2 (chart review) has limitations. First, the sample size for Phase 2 is relatively small, so any reporting on FN captured will need to be qualified as such. Second, since the data used in this study are from the iKM EHR, generally completed in the clinic, hospitalizations from FN may not be captured unless documented separately. Since FN hospitalizations are more likely than outpatient FN, the capture of FN overall in Phase 2 will likely be misleading, and will need to be qualified as such.

8.9.3 Analysis Limitations

As a retrospective observational study, data entry errors at the point of care cannot be detected or corrected during analysis.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

Although data quality checks are conducted, it is possible that some variables of interest may not be as complete across the entire population.

9. Protection of Human Subjects

9.1 Informed Consent

The MSH team will submit a request for exemption, waiver of informed consent and authorization to the Institutional Review Board (IRB). This project involves the study of existing data and records; study information will be analyzed by the MSH study team in such a manner that research participants will not be directly identified. Once exemption status and a waiver of informed consent are met, a waiver of authorization can be approved, allowing the retrospective study to occur.

9.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The retrospective research study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices. It will be necessary to obtain IRB and Compliance/Privacy approval prior to initiation of the retrospective research study data extraction and analysis. MSH will submit the appropriate documents, including but not limited to this protocol, to the MSH Compliance/Privacy department and the IRB for review. MSH will handle all correspondence with MSH Compliance/Privacy and the IRB; correspondence will be kept on file at MSH.

9.3 Patient Confidentiality

No patient level data transfer will occur between MSH and Amgen. The data will be reported to Amgen only in aggregate form and with attention to sample cell size.

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

This study is analyzing secondary data from USON's iKnowMed Electronic Health record database. The safety outcomes that are listed in section 8.3 will be documented on and analyzed in this study. These will be reported in aggregate in the final study report as incidences and rates. See section 8.3 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events

suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

11. Administrative and Legal Obligations

11.1 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 US Oncology, Inc. Institutional Review Board must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the US Oncology, Inc. Institutional Review Board 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 US Oncology, Inc. Institutional Review Board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

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.

12.1 Publication Policy

Results of this analysis will be submitted for publication.

MSH will collaborate with Amgen to determine the appropriate conference(s) and/or journal(s) for submission.

13. References

Fortner BV, Schwartzberg L, Tauer K, et al: Impact of chemotherapy-induced neutropenia on quality of life: a prospective pilot investigation. Support Care Cancer 13:522-8, 2005

Hardt J, Herke M, Brian T, et al: Multiple imputation of missing data: a simulation study on binary response. J Open Stats 3:370-378, 2013

Lalami Y, Klastersky J: Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: An overview about well-established and recently emerging clinical data. Crit Rev Oncol Hematol 120:163-179, 2017

Lyman GH, Kuderer NM: Epidemiology of febrile neutropenia. Support Cancer Ther 1:23-35, 2003

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Hematopoietic Growth Factors. Version 2.2020 - January 27 AJ, 2020

NCCN: NCCN Guidelines Version 1.2021 - Hematopoietic Growth Factors, National Comprehensive Cancer Network, 2021

Santin AD, Sill MW, McMeekin DS, et al: Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 122:495-500, 2011

Townley C., McMullen N, Porter C. Comparing Grade 4 Neutropenia Associated with Pegfilgrastim Administered via the Onpro Device versus Manual Injection with a Prefilled Syringe. JHOP - September 2018 Vol 8, No 3.

Yang BB, Morrow PK, Wu X, et al: Comparison of pharmacokinetics and safety of pegfilgrastim administered by two delivery methods: on-body injector and manual injection with a prefilled syringe. Cancer Chemother Pharmacol 75:1199-206, 2015

Annexes

Approval Signatures

Amgen Signatures

_____ _____

[Amgen Study Lead: PPD , PhD] Date (Day Month Year)

MLS/USON Signature(s)

_____ _____

[PI: PPD , MD, MPH] Date (Day Month Year)

_____ _____

[MLS Outcomes Researcher: PPD , MS] Date (Day Month Year)

Approval Signatures

Document Name: Protocol Original pegfilgrastim 20200230

Document Description: 20200230 Neulasta Original Protocol updated post ORRG Mtg for comp pub then final approval

Document Number: CLIN-000098199

Approval Date: 05 Apr 2022

Type of Study Protocol: Original

Protocol Amendment No.:

Document Approvals	
Reason for Signing: Functional Area	Name: PPD Date of Signature: 24-Mar-2022 12:26:11 GMT+0000
Reason for Signing: Management	Name: PPD Date of Signature: 05-Apr-2022 16:06:22 GMT+0000