Summary Table of Study Protocol

Title	An Observational Study to Assess the Effectiveness of the Neulasta® Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta® On-Body Injector
Protocol version identifier	**Amendment 1**
Date of last version of the protocol	**09 January 2019**
EU Post Authorisation Study (PAS) Register No	Not yet available
Active Substance	Pegfilgrastim
Medicinal Product	Neulasta® administered through the on-body injector (OBI)
Product Reference	EMEA/H/C/000420
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The study aims to address the following research questions: • Has the implementation of the Patient Alert Card (PAC) as an additional Risk Minimisation Measure (aRMM) been conducted as planned? • What is the level of respondent awareness and behavioural intent to act as recommended in the PAC? • What is the rate of medication errors observed in routine clinical practice? The primary objective of the study is: • To assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC. The secondary objectives of this study are: • To determine if the respondent received the PAC. • To estimate the proportion of OBI administrations associated with medication error.
Countries of Study	To be determined based on EU countries in which the OBI is approved and utilized**. A preliminary list includes Germany, Slovakia, Netherlands, and/or UK.**
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Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, The Netherlands.
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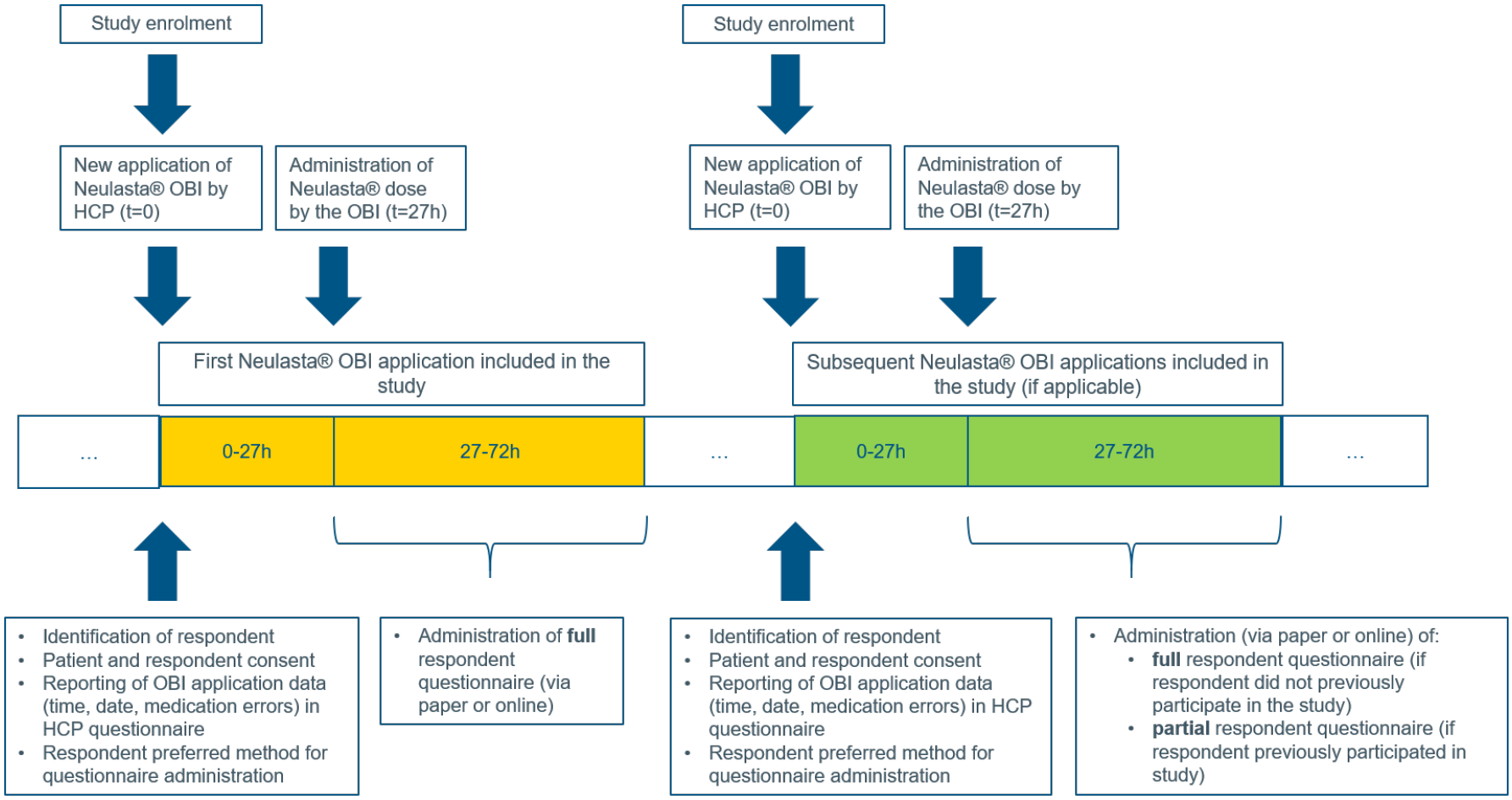
Investigator's Agreement

I have read the attached protocol entitled "An Observational Study to Assess the Effectiveness of the Neulasta® Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta® On-Body Injector", dated **10 April 2019**, and agree to abide by all provisions set forth therein.

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema



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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
aRMM	Additional Risk Minimisation Measure
BHLS	Brief Health Literacy Screen
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FMV	Fair Market Value
GVP	Good Pharmacovigilance Practices
HCP	HealthCare Provider
ICF	Informed Consent Form
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
OBI	On-body Injector
PAC	Patient Alert Card
PAS	Post Authorisation Study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
SAP	Statistical Analysis Plan
SDLC	System Development Life Cycle
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure

3. Responsible Parties

MAH	Amgen is the MAH which oversees MAH activities and facilitates Competent Authority submissions.
MAH Representative	The MAH representative for this study is IQVIA, a Clinical Research Organisation (CRO) delegated to serve as the study coordinating centre and conduct the study on behalf of Amgen. The MAH representative will be responsible for overall conduct, deliverables and timelines for the study and communication with Amgen.

4. Abstract

- **Study Title**

An Observational Study to Assess the Effectiveness of the Neulasta® Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta® On-Body Injector.

- **Study Background and Rationale**

Amgen received a positive opinion recommending a label variation for Neulasta® (pegfilgrastim) to include the Neulasta Onpro® Kit from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in February 2018. The Neulasta Onpro® Kit consists of one pre-filled syringe with Neulasta and an on-body injector (OBI) delivery system. While every OBI undergoes a thorough quality control process before being distributed into the market, issues such as leakage, the device coming loose from the skin, or other device issues, may occur. These device issues can result in medication errors which are defined as an 'unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient' (EMA, 2015). "Medication errors including underdose-On-body Injector, resulting in lack of efficacy" is an important identified risk in the Neulasta EU Risk Management Plan. An additional risk minimization measure (aRMM) in the form of a Patient Alert Card (PAC) has been developed to further support patients in the safe and appropriate use of the Neulasta OBI. The PAC is required to be distributed to all HCPs who place an order for Neulasta OBI as agreed with local health authorities according to local requirements. In line with regulatory guidance, aRMMs are required to be evaluated for their effectiveness. The proposed study is intended to evaluate the process of implementation and effectiveness of the aRMMs for the OBI by assessing the respondent awareness of key safety messages and their behavioural intent to implement recommended actions as described in the PAC.

- **Research Question and Objective(s)**
  - Primary Objective
    - To assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC.
  - Secondary Objectives
    - To determine if the respondent received the PAC.
    - To estimate the proportion of OBI administrations associated with medication error.
  - Hypothesis/Estimation
    - This is an estimation study. No formal hypothesis will be tested. Results will be presented as estimates with 95% confidence intervals as measures of precision.
- **Study Design/Type**

An observational cross-sectional study is planned in a number of EU countries after the introduction of the OBI for Neulasta in the EU market.

- **Study Population or Data Resource**

The source population will be the primary person responsible for monitoring the OBI after application, ie, patients or, if appropriate, their caregivers. This person will be defined as the "respondent". For every patient receiving OBI for Neulasta, the respondent will be defined at the time of study inclusion. Respondents can be included in the study multiple times at different chemotherapy cycles in which the OBI is being prescribed to the patient, if eligibility criteria including informed consent are met. In subsequent administrations of the questionnaire, data will only be collected to meet the secondary objective regarding medication errors (via a partial respondent questionnaire).

HCPs working at sites in which the OBI is being prescribed or expected to be prescribed will be approached for participation in the study.

- **Summary of Subject Eligibility Criteria**
  - Inclusion criteria
    - Respondent (ie, patients or caregivers primarily responsible for monitoring the OBI) who agrees to be contacted for the questionnaire.
    - Respondent aged 18 or more years.
    - Respondent with no cognitive impairment.
    - Respondent who can read and understand the language in which the study is being conducted and in which the PAC is provided.

  - Patient has been prescribed the OBI for Neulasta delivery for their current chemotherapy cycle.
  - Patient and respondent provide their written informed consent to participate in the study.
- Exclusion criteria
  - Respondent personally works, or works on a consultancy basis, for any pharmaceutical company or advertising/research agency.
  - Patient has participated or is participating in a clinical trial of Neulasta administered via OBI.

- **Follow-up**

No follow-up is conducted after the questionnaire administration in this cross-sectional study.

- **Variables**
  - Respondent demographics and characteristics, including age, sex, educational level, self-reported language skills, self-reported confidence to monitor the OBI, health literacy - using the questions from the Brief Health Literacy Screen (BHLS) questionnaire (Chew *et al.* 2004) -, respondent type (patient or caregiver)
  - Respondent prior use and/or monitorisation of the Neulasta OBI
  - Details of respondent receipt and use of the PAC
  - Respondent reported awareness of key safety messages in the PAC
  - Respondent reported behavioural intent to carry out recommended actions as described in the PAC
  - Device issues experienced by the patient (eg, whether the device came loose, red light came on, leakage, etc.) and any resulting actions
  - Symptoms of adverse events experienced by the patient (eg, fever, chills, sweating, etc.) and related consultations with HCPs
  - Details on dose delivery (eg, expected dose delivered on time, partial dose received, etc.)
  - Occurrence of a replacement granulocyte colony stimulating factor (G-CSF) dose (eg, type of replacement and timing)

In addition, the HCP will report the following variables through an electronic case report form (eCRF), to be completed at the time of respondent identification and consent:

  - HCP and site characteristics (only reported once per HCP)
  - HCP awareness of methods to obtain the PAC

- Date and time of OBI application
- Device issues observed by the HCP at the time of OBI application (eg, the device coming loose, problems filling the device, leakage, etc.)

- **Study Sample Size**

This study aims to include approximately 80 respondents, however, the final sample size will ultimately depend on the uptake of the OBI in participating countries and willingness of respondents to participate. Expected OBI use in Europe is <10,000 patients per year, therefore, a sample size of 80 respondents is considered feasible.

Assuming patients will use the OBI on average 3.5 times during a single chemotherapy course, 80 independent patients are estimated to receive a maximum of 280 OBI applications.

- **Data Analysis**

All the respondents participating in the study who meet the eligibility criteria will be included in the sample of respondents in which awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC will be assessed. These outcomes will be assessed for the first monitored OBI application only.

Distribution of the PAC, awareness of key messages in the PAC and behavioural intent to carry out recommended actions as described in the PAC will be described at respondent level, providing the percentage of correct responses. A success measure will be used to define the success of the PAC.

All OBI administrations reported by participant respondents will be included in the sample of treatments to estimate the proportion of OBI administrations associated with medication error. OBI administrations for Neulasta doses that have not been delivered (due to medication errors) will be also included in the full analysis set of OBI administrations. More than one OBI administration can be reported for the same respondent.

An interim analysis is planned to be performed at 1 year after the start of data collection.

5. Amendments and Updates

None.

6. Milestones

Milestone	Planned date
Start of data collection	Approximately **August** 2019*
End of data collection	Approximately July 2021*
Interim analysis	Approximately July 2020*
Registration in the EU PAS register	Approximately April 2019*
Final report of study results	Approximately July 2022*

* These timelines are subject to the timely launch of the OBI in participating countries and timely approvals from national competent authorities and ethics committees.

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Amgen received a positive opinion recommending a label variation for Neulasta® (pegfilgrastim) to include the Neulasta Onpro® Kit from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in February 2018. The Neulasta Onpro® Kit consists of one pre-filled syringe with Neulasta and an on-body injector (OBI) delivery system. Neulasta (pegfilgrastim) is approved for use in the European Union (EU) for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Neulasta® is to be administered at least 24 hours after cytotoxic chemotherapy (Neulasta EU SmPC), and often requires the patient to return to the healthcare facility for this purpose (Mahler *et al.* 2017). The Neulasta Onpro® Kit includes a specifically designed Neulasta pre-filled syringe along with a single use OBI. The small, lightweight OBI is applied to a patient's skin on the same day of chemotherapy. The OBI eliminates the burden to return to a healthcare setting for patients and physicians (Mahler *et al.* 2017), and is a preferred option for approximately 50% of the physicians when considering clinically compromised patients in the need of receiving Neulasta (Hauber *et al.* 2018).

The OBI is a device that must be filled with Neulasta by an HCP using a pre-filled syringe and then applied to the patient's skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the OBI for Neulasta. The OBI has a timed mechanism to deliver a subcutaneous injection of Neulasta 27 hours after the device is applied to the patient's skin. The Neulasta dose will be delivered over approximately 45 minutes. The OBI can be applied on the same day as the administration of cytotoxic chemotherapy, if application is timed to ensure the

OBI delivers Neulasta at least 24 hours after administration of cytotoxic chemotherapy (Neulasta EU SmPC).

While every OBI undergoes a thorough quality control process before being distributed into the market, issues such as leakage, the device coming loose from the skin, or other device issues, may occur. These device issues can result in medication errors which are defined as an 'unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient' (EMA, 2015). Examples for medication errors that may occur as the result of an issue with the device are missed or partial doses of pegfilgrastim which put patients at increased risk of a serious infection if a replacement dose isn't administered.

"Medication errors including underdose-On-body Injector, resulting in lack of efficacy" is an important identified risk in the Neulasta EU Risk Management Plan. In the clinical trial setting, no adverse events within the MedDRA Medication errors Standardised MedDRA Query (SMQ) were reported in 262 subjects who received at least 1 dose of pegfilgrastim via the OBI and among 339 subjects administered placebo via the OBI, 1 subject (<1%) experienced a medication error. A recent study that specifically evaluated the performance of the OBI device in healthy subjects reported that 292 of 297 administrations (98.3%) were successful, while five were considered unsuccessful: two due to hazard alarms, and three due to substantial leakage (Joshi *et al.* 2017).

Cases of medication errors including underdose events have been reported in the US post-marketing setting after approval of OBI in December 2014. Cumulatively through 31 January 2018, the most frequently reported medication error events in the post marketing setting were events with the preferred terms "wrong technique in product usage process", "drug dose omission", and "underdose".

Risk minimisation activities to address medication errors involve routine measures (eg, product label, Instructions for Use and the Patient Leaflet), as well as an aRMM in the form of a PAC that further supports patients in the safe and appropriate use of the Neulasta OBI. The PAC is printed in color on a wallet sized tri-fold card, and is intended for patients to keep with them as a reference.

Specifically, the PAC highlights important messages which are also included in the Package Leaflet - Instructions for Use that are directly related to the following. These messages represent the 'core content' of the PAC that will be assessed as part of this evaluation study:

1. When to expect the dose delivery of Neulasta to begin;
2. That the OBI should not be removed until after dose delivery is complete;
3. How to recognise signs that there may have been a failure in the delivery of the intended dose of Neulasta;
4. What actions to take in a suspected case of failed delivery or incomplete delivery of the dose;
5. What actions to take if symptoms of serious infection present (ie, the need to immediately contact his/her HCP and how that HCP can be reached).

The PAC includes illustrations of 4 scenarios of possible failed or incomplete administration of Neulasta via the OBI which the patient should recognise:

- status light flashes red;
- adhesive is wet and/or device drips;
- device comes loose, and;
- fill indicator does not indicate empty after the expected time of dose delivery.

The PAC underwent an iterative process of design and piloting, with patient and carer assisting in the co-creation of the final version. The final pilot-tested version is presented in Appendix E.

The PAC is required to be distributed to all HCPs who place an order for Neulasta OBI as agreed with local health authorities according to local requirements. The goal of the PAC is to communicate to patients at each application of the on-body injector how to monitor the on-body injector and recognize signs of device failure that may result in incomplete or failed dose delivery and the appropriate action to be taken.

7.2 Rationale

In line with regulatory guidance (EMA, 2014), aRMMs are required to be evaluated for their effectiveness. Additionally, following recommendations from the Committee for Medicinal Products for Human Use and the Pharmacovigilance Risk Assessment Committee (PRAC) review of the marketing authorisation application for the OBI, this study was developed to measure the rate of medication errors.

Amgen has developed the protocol for this study in accordance with the requirements of Good Pharmacovigilance Practice (GVP) Modules V (EMA, 2017), VIII (EMA, 2016) and XVI (EMA, 2014), the recommendations provided by the Council for International Organisations of Medical Sciences (CIOMS, 2014) Working Group IX, and an established public health model, the Theory of Reasoned Action (Fishbein 2008), which posits that the antecedents of individual behaviour change are knowledge and behavioural intent.

The proposed study is intended to evaluate the process of implementation and effectiveness of the aRMMs for the OBI by assessing the respondent awareness of key safety messages and their behavioural intent to implement recommended actions as described in the PAC.

7.3 Statistical Inference (Estimation or Hypothesis)

This is an estimation study. Due to sample size limitations, no formal hypothesis will be tested. Results will be presented as estimates with 95% confidence intervals as measures of precision.

8. Research Question and Objectives

The study aims to address the following research questions:

- Has the implementation of the PAC as an aRMM been conducted as planned?
- What is the level of respondent awareness and behavioural intent to act as recommended in the PAC?
- What is the rate of medication errors observed in routine clinical practice?

8.1 Primary

The primary objective of the study is to assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC.

8.2 Secondary

The secondary objectives of this study are:

- To determine if the respondent received the PAC.
- To estimate the proportion of OBI administrations associated with medication error.

8.3 Exploratory

The exploratory objective of this study is to describe the proportion of device issues at the time of OBI application.

9. Research Methods

9.1 Study Design

An observational cross-sectional study based on primary data collection is planned in a number of EU countries after the introduction of the OBI for Neulasta in the EU market.

The source population will be the primary person responsible for monitoring the OBI after application by the HCP, ie, patients or, if appropriate, their caregivers. This person will be defined as the "respondent". For every patient receiving OBI for Neulasta, the respondent will be defined at the time of study inclusion. In case the caregiver is identified as the respondent, the caregiver will need to be present at the time of OBI application and study inclusion.

Participating HCPs will assess the eligibility of respondents in a consecutive manner according to the date of OBI application. This approach is designed to minimise selection bias and to allow for the study results to be generalizable to the wider population of OBI treated patients. Upon patient and respondent consent to participate in the study, the HCP will immediately record in the study electronic case report form (eCRF) the information of the time and day of OBI application. Respondents will be contacted from approximately 27 to 72 hours after the OBI application (ie, approximately 0 to 45 hours after the Neulasta dose is expected to be delivered through the OBI) and asked to respond to a questionnaire. The questionnaire will be administered either by **paper** or online. Additionally, HCPs will be requested to provide data on their observations (eg, time and date of OBI administration, medication errors at the time OBI application, etc.) at each application of OBI for a participating patient in the eCRF.

Respondents can be included in the study multiple times at different chemotherapy cycles in which the OBI is being prescribed to the patient, if eligibility criteria including informed consent are met (Section 9.2.3). In subsequent administrations of the questionnaire, data will only be collected to meet the primary objective regarding medication errors (via a partial respondent questionnaire).

In case that for a unique patient, the respondent is different in subsequent administrations of the questionnaire (ie, from patient to caregiver, from caregiver to patient, or from caregiver to another caregiver), the new respondent would still be eligible if all eligibility criteria are met, but a full questionnaire would need to be filled in and he/she will be treated as a new respondent. The HCP will check at the time of study inclusion if the respondent identified has been included in a previous OBI administration, to avoid double counting of respondents.

The number of potential respondents screened but not enrolled into the study will be recorded.

9.2 Setting and Study Population

The study is planned to be conducted in a number of EU countries in which the OBI is approved and utilized. A selection of EU countries are planning launching the OBI over the period of 2018 and 2019. Based on the current forecasted launch timetable, a preliminary selection of countries for this study is likely to include Germany, **Netherlands,** Slovakia **and/or UK**. The final selection of countries will be informed by a country level feasibility assessment and will correspond to a combination of expected product uptake, adequate timing of the product launch and logistical barriers foreseen to allow for the completion of the study within the required timeframe, with a minimum of 2 different EU countries represented.

This rationale is based on factors that may change as the study progresses (ie, initial usage forecasts and planned launch schedule). Therefore, if recruitment of respondents is slower than anticipated other countries and/or sites may be added to meet sample size goals within the study timeline.

9.2.1 Study Period

The planned period for data collection will be approximately 2 years. However, as the timing of product launch and the time needed for regulatory/ethics approval will vary between countries, the exact length of this period is expected to differ between countries. The study will commence at an appropriate time post-launch in each participating country to allow for reasonable uptake of the product and familiarisation and use of the materials by HCPs.

9.2.2 Selection and Number of Sites

HCPs working at sites in which the OBI is being prescribed or expected to be prescribed will be approached for participation in the study. In order to rapidly recruit respondents, sites are likely to be selected based on volume of historical Neulasta and observed OBI use (ie, sales data) from six months after product launch in the country. To facilitate the representativeness of the sample, up to three HCPs per site will be participating in the study, and up to 9 patients will be allowed to be included per site.

Based on expected average site level use of the OBI, it is estimated that approximately 20 sites will need to be included in the study to recruit 80 new respondents into the study in 2 years. Assuming a site participation rate ranging 10-15%, to include 20 sites, would

require contacting approximately 133 – 200 sites for participation. If the site participation rate is < 10% after 50 sites have been asked to participate, Amgen will re-assess study methods for the probability of achieving study objectives successfully.

The number of HCPs contacted but not participating in the study will be recorded and their characteristics (ie, gender, age, years of practice and size/type of practice) will be gathered where possible to assess potential selection bias.

9.2.3 Subject Eligibility

9.2.3.1 Inclusion Criteria

- Respondent (ie, patients or caregivers primarily responsible for monitoring the OBI) who agrees to be contacted for the questionnaire.
- Respondent aged 18 or more years.
- Respondent with no cognitive impairment.
- Respondent who can read and understand the language in which the study is being conducted and in which the PAC is provided.
- Patient has been prescribed the OBI for Neulasta delivery for their current chemotherapy cycle.
- Patient and respondent provide their written informed consent to participate in the study.

Respondents can be included in the study regardless of the number of times they have monitored the OBI previously

9.2.3.2 Exclusion Criteria

- Respondent personally works, or works on a consultancy basis, for any pharmaceutical company or advertising/research agency.
- Patient has participated or is participating in a clinical trial of Neulasta administered via OBI.

9.2.4 Matching

Not Applicable.

9.2.5 Baseline Period

This is a cross-sectional study that does not involve any follow-up of respondents. Eligibility criteria will be assessed on the date of OBI administration and the respondent questionnaire will be administered approximately 27 to 72 hours after the OBI application (ie, approximately 0 to 45 hours after the Neulasta dose is expected to be delivered through the OBI). Respondents can be included in the study multiple times at different chemotherapy cycles in which the OBI is being prescribed to the patient, if eligibility criteria including informed consent are met (Section 9.2.3). In subsequent applications

of the questionnaire, data will only be collected to meet the primary objective regarding medication errors. This administration of the questionnaire will be considered independent from the previous one and no follow-up period will be considered.

9.2.6 Study Follow-up

No follow-up is conducted after the questionnaire administration in this cross-sectional study.

9.3 Variables

Variables collected in the respondent questionnaire, to be administered approximately 27 to 72 hours after OBI application, will include:

- Respondent demographics and characteristics, including age, sex, educational level, self-reported language skills, self-reported confidence to monitor the OBI, health literacy - using the questions from the Brief Health Literacy Screen (BHLS) questionnaire (Chew *et al.* 2004) -, respondent type (patient or caregiver)
- Respondent prior use and/or monitorisation of the Neulasta OBI
- Details of respondent receipt and use of the PAC
- Respondent reported awareness of key safety messages in the PAC (eg, OBI alerts for Neulasta dose delivery or issues, time of removal of OBI, etc.)
- Respondent reported behavioural intent to carry out recommended actions as described in the PAC (eg, symptoms related to infection, issues with Neulasta dose delivery via the OBI, etc.)
- Device issues experienced by the patient (eg, whether the device came loose, red light came on, leakage, etc.) and any resulting actions*
- Symptoms of adverse events potentially related to medication errors experienced by the patient (eg, fever, chills, sweating, etc.) and related consultations with HCPs*
- Details on dose delivery (eg, expected dose delivered on time, partial dose received, etc.)*
- Occurrence of a replacement G-CSF dose (eg, type of replacement and timing)*

* Indicates variables to be collected in the partial respondent questionnaire

In addition, the HCP will report the following variables through an eCRF, to be completed at the time of respondent identification and consent:

- HCP and site characteristics (only reported once per HCP)
- HCP awareness of methods to obtain the PAC
- Date and time of OBI application
- Device issues observed by the HCP at the time of OBI application (eg, the device coming loose, problems filling the device, leakage, etc.)

9.3.1 Exposure Assessment

Patients included in the study will have been administered the OBI as per routine clinical practice.

9.3.2 Outcome Assessment

The primary endpoint for the respondent questionnaire is:

- Awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC: will be evaluated using a set of multiple choice questions included in the questionnaire. A composite score for each individual will be calculated based on the proportion of all awareness and behavioural intent questions with correct responses.

The secondary endpoints for the respondent questionnaire are:

- Receipt of the PAC by the respondent: a categorical variable will describe if the respondent received the PAC.
- Medication errors with OBI administrations. The proportion of total OBI administrations with medication errors with respect to total OBI administrations, and the total number of patients will be calculated.

Measure of Success

The results of the study will be interpreted considering an acceptable level of patients and/or caregivers awareness and behavioural intent. The study estimates and associated 95% confidence intervals (CIs) will be evaluated in the context of a desired population-level threshold of at least 70%. The selection of a threshold for success is subjective and not based on a priori knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualised with other available information. The appropriateness of the minimum 70% threshold as a measure of success will be reviewed at the time of the 1-year interim analysis.

Table 1. Measures of Success

Description of measure	Assessment
Distribution of the PAC	The threshold of 70% is within the 95% CIs of the proportion of respondents who provide an affirmative response to the key question regarding receipt of the PAC.
Success of the PAC	For the respondents who have received the PAC, the threshold of 70% is within the 95% CIs of the composite score for awareness and behavioural intent

9.3.3 Covariate Assessment

The following sociodemographic characteristics will be collected and used to describe the respondent sample:

- Country
- PAC provided in a language respondent is fluent or proficient at (yes/no)
- Age group (<65 years; >65 years)
- Sex (male/female)
- Educational level (categories vary by country)
- Respondent type (patient/caregiver)
- Respondent health literacy (BHLS ≤ 9 points; BHLS > 9 points (Willens *et al.* 2013))
- Number of previous OBI administrations

9.3.4 Validity and Reliability

Qualitative techniques will be used to ensure that the respondent questionnaire is readable, understandable and easy-to-use.

The questionnaire will be developed in English language and conceptually reviewed by 5 patients who have received Neulasta (not through the OBI) or, if applicable, their caregivers in the UK. The questionnaire will be subsequently translated and linguistically validated with 3 patients/caregivers in each of the participating countries. Patients who have received the OBI or caregivers taking care of these patients will not be used to validate the questionnaire so that the recruitment for the study is not affected.

During the linguistic validation interviews, trained interviewers will ask participants to complete the questionnaire while 'thinking aloud' and to describe their thinking and thought processes as they answer each question, each section, and the questionnaire overall. The results will be used to optimize instructions, guidance, wording, response choices, as well as language.

A master version of the questionnaire will be generated following linguistic validation in the participating countries.

The eCRF will be developed and administered in English and we do not anticipate the need of validating it.

9.4 Data Sources

Data for this study will be collected through a questionnaire developed for the primary person responsible for monitoring the OBI after application (ie, patients or, if appropriate, their caregivers). Responses will be collected either by **paper** or online.

The questionnaire has been developed following standard questionnaire principles (Bowling, 2014). It will mainly include multiple choice questions with limited free text fields.

In addition, an eCRF for the HCP will be used to collect descriptive information about the HCP and site, information about the time and date of OBI administration, and of events related to medication errors.

9.5 Study Size

This study aims to include approximately 80 respondents, however, the final sample size will ultimately depend on the uptake of the OBI in participating countries and willingness of respondents to participate. Expected OBI use in Europe is <10,000 patients per year, therefore, a sample size of 80 respondents is considered feasible.

Table 2 gives the 95% confidence interval half-width around the proportion of respondents with correct answers to the questions around awareness and behavioural intent for a given sample size of questionnaire respondents.

Table 2. Half-width of 95% Confidence Intervals for Different Proportions of Correct Answers to Questions by Size of Questionnaire Respondents

Sample Size	Proportion	Half-width 95% CI
60	0.5	0.13
60	0.6	0.12
60	0.7	0.12
60	0.8	0.10
60	0.9	0.08
80	0.5	0.11
80	0.6	0.11
80	0.7	0.10
80	0.8	0.09
80	0.9	0.07
100	0.5	0.10
100	0.6	0.10
100	0.7	0.09
100	0.8	0.08
100	0.9	0.06

95% CI calculated using the normal approximation

Assuming patients will use the OBI on average 3.5 times during a single chemotherapy course, 80 independent patients are estimated to receive a maximum of 280 OBI applications.

9.6 Data Management

As specified in Section 9.4 above, study data will be collected through two different sources:

- A respondent questionnaire developed to collect information from the primary person responsible for monitoring the OBI after application (ie, patients or, if appropriate, their caregivers). Responses will be collected either by **paper** or online.
- An eCRF for the HCP will be used to collect descriptive information about the HCP and the site, information about the time and date of OBI administration, and of events related to medication errors.

Upon inclusion of a new respondent **in**to the study (and after obtaining patient and respondent consent), the **HCP** will be asked to immediately complete information requested in the eCRF (ie, identification if the respondent is the patient or the caregiver, inclusion and exclusion criteria, and information of the current OBI application - medication errors and time and date of administration). The eCRF will subsequently generate a unique patient and respondent code (eg, UK-01-01-01). This code will be manually added to the ICF of the respondent by the **HCP** for reference purposes.

The HCP will give the respondent an envelope containing the instructions about how to complete the questionnaire (two options will be provided in the same envelope):

a) **Option 1. A document with the link to complete the questionnaire online.**
b) **Option 2. Pre-paid and pre-filled envelope containing a paper copy of the respondent questionnaire and instructions for delivery to IQVIA to perform data entry.**

The HCP will be subsequently responsible for conducting **a telephone** follow-up with the respondents **to remind them about** respondent questionnaire completion, within the timeframe established by the study protocol (ie, 27-72h post OBI application). For both **options provided for questionnaire completion**, the respondent will be initially **requested** to **include** the information on the respondent code (as provided by the **HCP** in the copy of the ICF, eg, UK-01-01-01), then respondent will be able to complete the rest of the questionnaire.

In case respondent completes the electronic questionnaire online, IQVIA will ensure that no contact information (eg, IP address, email, etc.) is recorded or captured in the corresponding database.

IQVIA will therefore generate and maintain two independent databases (one generated from the eCRF and one generated from the respondent questionnaire), with a unique identifier, but IQVIA will **not** hold information that can be used to identify or contact the respondent and clinical data, thus ensuring data privacy. Only the **HCP** will be able to identify the patient, through a patient tracking sheet, which will link the patient identity and the unique identifier. This document will be strictly maintained at the site.

eCRF

An eCRF (web-based form) will be used for collection of data reported by the **HCP**.

The eCRF will include specific logic checks and filters for collected variables in an effort to minimize errors in data entry. The eCRF will also allow the study team to obtain 'real-time' statistics on recruitment and eCRF completion progression.

Site staff will be trained on data entry and patient data will be handled in compliance with all applicable confidentiality and privacy laws within participating countries.

The use of a private login and password will be necessary to access the website functionalities.

Daily, weekly and monthly backups of data entered in the eCRF will be performed to prevent any data loss or damage.

The study database will be locked once validated. At database lock, edit access rights will be removed, in order to prevent any data modification. Read-only access will remain active.

The data collected through the eCRF will be stored for a minimum of 5 years on an IQVIA secure server.

Electronic respondent questionnaire

Data on the respondent questionnaire will be collected using an electronic data capture system (different to the eCRF) developed following a full validation process. A rigorous System Development Life Cycle (SDLC) is used for validation that complies with internal IT Standard Operating Procedures (SOPs) of the Primary Intelligence team of IQVIA. Unit testing and formal validation occur on all appropriate systems and components during the build stage. The SDLC is fortified with SOPs addressing validation for all

clinical and risk management-related applications. The internet-based repository will be used to store survey data and other relevant program information.

Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomized to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

Collected data will be entered and stored in a database specific to the survey.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required),
- Data labelling and data formatting,
- Range and consistency checks for each variable to identify potential non admissible values,
- Cross-check the consistency of data for related variables (if feasible).

The study database will be locked once validated.

Participating respondents will access the website (https secured site) via a secure link unique to each respondent.

The data collected will be stored on a secure IQVIA server, and will be stored for a minimum of 5 years after the end of the study.

A data management plan (DMP) will be written to guide of all aspects of data handling. It will include all data forms and annotations, testing documentation and summaries, database documentation, merging of datasets and transfer of files into SAS for statistical analysis. All data collected during the study will be held confidentially.

As discussed in Section 10.3, the identities of patients and respondents taking part in the study will be controlled using unique identification codes. These source ID numbers will be held securely, and these data will be used solely for the purpose of identifying whether the respondent has completed the questionnaire.

9.6.1 Obtaining Data Files

Completed paper forms will be forwarded to IQVIA by respondents for data entry.

IQVIA data entry staff will enter the paper questionnaire into a database for analysis.

A database will be created and tested before data entry, two copies of the same database will be prepared for double data entry to be performed. Databases will be compared until no discrepancies are found. The final database will be merged with the online questionnaire results and transferred to SAS for analysis.

9.6.2 Linking Data Files

The only linkage required for the study will be between the data reported in the eCRF and that reported in the respondent questionnaire. Linkage will be performed using a unique code assigned to each patient and respondent (see Section 10.3). The same code will be used to collect all data related to OBI applications monitored by the same respondent, and each application will also be identified. The code corresponding to patient, respondent and administration will be electronically assigned at completion of the eCRF.

9.6.3 Review and Verification of Data Quality

This study is collecting data from patients or, if applicable, from caregivers through a questionnaire as the primary data source, and complementary data from the HCP through an eCRF. It is not planned to generate queries in the study and closed questions will limit the need for data checks.

9.7 Data Analysis

9.7.1 Planned Analyses

The statistical analysis will be conducted with SAS® statistical software or R. A detailed statistical analysis plan (SAP) will be prepared and accepted before the data analysis initiation.

All the respondents participating in the study who meet the eligibility criteria will be included in the sample of respondents in which reception of the PAC, awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC will be assessed. Respondents monitoring more than one OBI application in the context of the study will complete reception of PAC, awareness of key safety messages and behavioural intent sections only for the first OBI application

All OBI applications reported by participant respondents will be included in the sample of treatments to estimate the proportion of OBI applications associated with medication error. OBI applications for Neulasta doses that have not been delivered (due to medication error) will be also included in the full analysis set of OBI applications. More than one OBI application can be reported for the same respondent.

9.7.1.1 Interim Analysis/Analyses

An interim analysis is planned to be implemented at 1 year after start of data collection. All respondents and OBI applications available at time of analysis will be included. All descriptive tables planned for the final analysis will be also performed in the interim analysis. The appropriateness of the minimum 70% population-level threshold established as the measure of success for the distribution of the PAC and for the awarereness and behavioural intent to carry out recommended actions in the PAC will be reviewed at the time of the 1-year interim analysis, and addressed if required.

9.7.1.2 Primary Analysis

The primary analysis will be performed at the end of data collection including all respondents and OBI administrations fulfilling selection criteria. All statistical analyses planned in the SAP approved prior to initiation of the statistical analysis will be performed.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

All analyses will be descriptive. Continuous variables will be summarised by mean, median, standard deviation, Q1, Q3, minimum, maximum, 95% confidence intervals and number of valid and missing values for outcome variables. Categorical variables will be summarised by number and percentage of responses per category and 95% confidence intervals for outcome variables. The number of valid and missing values will be reported for each variable. Missing values will not be included in the denominator to calculate the percentage of responses per response category. Additional details about management of missing values per study variable will be described in the SAP.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Given the real-world nature of the data and the descriptive purpose of the study imputation methods for missing or incomplete data will be not used.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

A description of the number and percentage of respondents and OBI applications will be reported:

- Study population: All respondents invited to participate in the study.
- Eligible set: All respondents included in the study population who fulfill all selection criteria. Detailed information about eligible criteria not fulfilled will be also reported.
- Enrolled set: All respondents included in the eligible set who accept to participate in the study or who sign the informed consent.
- Full analysis set of respondents: Will include all respondents enrolled in the study who complete the questionnaire corresponding to at least one OBI administration and have valid responses to allow for the assessment of the primary objective.
- Full analysis set of OBI administrations: Will include all OBI administrations monitored by respondents included in the full analysis set of respondents and for which the corresponding questionnaire is completed and allows for the assessment of the primary objective.

9.7.2.3.2 Description of Subject Characteristics

HCP and/or respondent representativeness will be assessed by describing the characteristics of HCPs/respondents participating in the study and HCPs/respondents not participating in the study, where the collection of characteristics for those not included in the study is feasible. Number and percentage of respondents included in study population, eligible set, enrolled set and full analysis set of respondents will be described.

A description of respondent demographics and health literacy will be reported.

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

Primary

Awareness of key safety messages and behavioural intent to carry out recommended actions will be analysed considering individual questions, as well as calculating a composite score. The composite score will be calculated based on the proportion of all awareness and behavioural intent questions with correct responses. Composite scores will be described using descriptive measures for continuous variables, as well as categorical variables using a cut-off point of 70% of correct responses. The composite score will also be presented by whether the respondent received the PAC or not (if occurred), by prior OBI administrations and by the level of health literacy. Awareness and behavioural intent of respondents (composite score) will be also described at

HCP/site level and analysed according to site and HCP professional characteristics and prior experience with Neulasta OBI. The primary objective will be analysed in the full sample of respondents who fulfill selection criteria (full analysis set of respondents).

Secondary

In order to assess if the respondent received the PAC, the unique specific question included in the questionnaire will be used. The number and percentage of respondents who have received the PAC will be reported.

This study will help indicate if the PAC is effective as an aRMM based on the assessment described in Section 9.3.2. For the respondents who have received the PAC, the composite score and associated 95% CIs for awareness and behavioural intent will be reported. The selection of a threshold for success is subjective and not based on a priori knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualised with other available information.

Device issues identified during OBI administration and subsequent events will be used to identify medication errors. Medication errors will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20 or later and analysed using the medication error Standardised MedDRA Query (SMQ). Subject incidence proportions of medication errors will be summarised. Medication errors will also be presented with respect to the total number of OBI administrations. The subgroups of initial and subsequent OBI applications will be analysed separately to assess the potential impact of subsequent administrations. If differences are not observed, the incidence of medication errors will be reported at overall level. If differences are observed, both subgroups will be separately reported.

Exploratory

The proportion of device issues at the time of OBI application (as reported by the HCP) will be reported at OBI administration and patient level.

9.7.2.5 Sensitivity Analysis

Sensitivity analysis is not planned for this study.

9.7.2.5.1 Subgroup Analysis

The awareness and behavioural intent endpoints will also be presented by whether the respondent received the PAC or not, by prior use and monitoring of OBI administrations and by the level of health literacy.

9.7.2.5.2 Stratified Analysis

Not applicable

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

9.7.2.5.4 Other Sensitivity Analysis

Not applicable.

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

The Medical Dictionary for Regulatory Activities (MedDRA) version 20 or later will be used to code all adverse events reported in the respondent questionnaire. Subject incidence proportions will be presented by system organ class (SOC) and preferred term (PT).

9.8 Quality Control

Standard operating procedures will be applied to ensure quality to all aspects of the study conduct, data management and statistical analysis.

Prior to the study initiation, investigators and all study collaborators will receive specific training on the protocol and on the use of the eCRF. The participant investigators will also be provided personal secure access credentials for the eCRF. Respondents that opt to respond the questionnaire online will be provided with **a unique generic link** for the respondent questionnaire. In case respondents opt to respond the questionnaire by **paper, respondent will send the completed questionnaire to IQVIA in a pre-paid and pre-filled envelope, and** data will be directly **entered** by **IQVIA** into a specific study database.

Investigators, patients, and their corresponding respondents will have a unique code. The unique code will consist of a combination of the country code, investigator code, and a sequential number of the patient and respondent (this will be detailed in a separate Data Management Plan) (see Section 10.3). This unique code will be generated automatically by the eCRF.

A confidential tracking sheet, listing patient and respondent codes together with patient name and date of birth and respondent name, will be kept by investigators at the study

site for identification purposes, if required. Only the investigator and their delegated site team members will have access to the confidential tracking sheet.

All information entered in the eCRF must be traceable to the source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient and the respondent (a signed copy is given to the patient and to the respondent).

In addition, data generated by this study must be available for inspection upon request by representatives of national and/or local health authorities, sponsor monitors, representatives, and collaborators, as appropriate. The investigator must notify Amgen promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Amgen.

All study documentation generated in the study, including the final study database and the statistical programming will be kept in a secure server.

The quality control for validating the results will be conducted at five levels:

1. At data management level, every efforts will be undertaken to collect complete and valid data:
    - The respondent questionnaire will be developed in English, conceptually reviewed by patients or their caregivers in the UK and will be subsequently translated and linguistically validated with patients/caregivers in each of the participating countries,
    - Verification of the reliability and security of the web questionnaire interface by a qualified web-master for each country,
    - Monitoring of the quality and datasets definition by a qualified data manager. In the background of the web questionnaire, real-time checks of the answers provided by the respondents will be developed. Non admissible answers (ie, incorrect or unusual values, outlying values) will be detected.
    - **A database will be created and tested before data entry, two copies of the same database will be prepared to ensure a double data entry. Both databases will be compared until no discrepancies are found.**
2. At the study database level, final data quality checks will be applied (beyond data management process):
    - Distribution of each variable in order to count the number of missing values and estimate the associated relative percentage,
    - Identification and count of non-analysable questionnaires
    - Any changes in the database will be tracked and documented. The datasets will be stored in a dedicated database. Once data validated and quality checked, the database will be locked.

3. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA.

The study documents have been approved by qualified professionals in medical and safety areas of IQVIA.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

The collection of patient symptoms potentially related to adverse events of interest in the study is very limited due to the time-window since OBI application for infection to develop (27 to 72 hours after OBI application). This fact will limit the validity of these health outcomes measured after OBI application, which will need to be interpreted with caution.

9.9.1.2 Information Bias

Self-reporting of actions and behavior intent may be biased, eg, towards a more positive effect. The development of a questionnaire carefully pre-tested before actual study start aims to minimize such a bias. Recall bias is an inherent limitation of questions asking about the past. However, the questionnaire will be administered within 72 hours post-application of Neulasta via the OBI, which will help to reduce potential recall bias.

9.9.1.3 Selection Bias

The study population is likely to be a convenience sample given that the approach is aimed to enhance speed of recruitment. Participation rates by potential sites/HCPs and eligible respondents may be low creating uncertainty on the level of selection bias. This is being mitigated by integrating the administration of the questionnaire into standard of care practice as much as possible. The consecutive selection of eligible respondents at

each site and the allowance of a maximum number of patients per site are also designed to minimise selection bias of respondents.

It might be discussed that the exclusion of respondents that do not read and understand the language of the questionnaire can bring a selection bias, but as the objective of the study is to evaluate the effectiveness of the PAC, the understanding of the language is needed.

The need that caregivers who will monitor the OBI administration are present at the time of application of the OBI for them to be eligible to participate as a respondent is a limitation of the study design. It cannot be discarded that this fact leads to a certain selection bias, although impact is expected to be low, as it is unlikely that caregivers not formally trained by an HCP will monitor the OBI administration.

9.9.1.4 Confounding

A potential confounder would be the level of literacy of the respondents and/or their level of understanding of the language, which may have an impact on results. If the respondent does not understand the language (and therefore the PAC) properly, the effectiveness of the PAC will decrease, but the reason for this will be the lack of language understanding.

In order to further recognise the level of understanding of the language of the respondents, a brief health literacy questionnaire will be used to classify the patients depending on their health literacy.

9.9.2 External Validity of Study Design

Low participation rates by potential sites/HCPs and eligible respondents may compromise representativeness to generalise the results to the general population of persons responsible for monitoring the OBI after application.

It cannot be discarded that by participating in the study, some HCPs alter their standard practice on the distribution of the PAC. This could translate into results for study endpoints that may not be generalizable to the general population, thus impacting external validity of the study. This limitation is inherent to study design. To partially mitigate this, HCPs will be asked to follow their regular clinical practices during the conduct of the study.

9.9.3 Analysis Limitations

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Given the short time window in which the respondent needs to answer the questionnaire (27 to 72 hours after OBI application) there is an increased risk of non-response to the questionnaire, due to respondent lack of availability.

10. Protection of Human Subjects

10.1 Informed Consent

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, respondents should provide written consent before enrollment into the study. Investigators must ensure that patients or, if applicable, their caregivers, are clearly and fully informed about the purpose of the study, potential risks, the patient/caregiver's rights and responsibilities when participating in this study. If local regulations do not require an informed consent form (ICF) to be signed by the patient/caregiver, the site staff should document key elements of the informed consent process in the patient's medical record.

Informed consent for the study participation will be sought. By signing the ICF, the patient/caregiver consents to participate in the study **and to be contacted by phone by the HCP for a follow up on questionnaire completion.**

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

This type of study requires review and approval by a central ethics committee (EC) in the participating countries. Thus, the study will be conducted under the auspices of an independent EC (and any local EC as applicable) in each country, as defined in local regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Patient/Caregiver Confidentiality

For the purposes of protecting the patient and the respondent's identity, a unique code will be assigned to each patient and their correspondent respondent(s), such as a series of numbers and/or letters (for example, UK-01-01-01). The data that is recorded with the patient and respondent's assigned codes is called "key-coded data". Key-coded study data will be managed by the sponsor and/or its delegates in a study-specific electronic database (the "study database"). Only the investigator and the site staff have access to the link between patient and respondent's assigned codes and the patient and respondent's identity. However, in case of an audit or inspection, subject to local laws

and regulations, government officials, IRB/EC representatives and sponsor representatives may access this information at the study site. Data that could directly identify the patient will not be collected in the "study database".

The investigator's personal data and the patient/caregiver's key-coded data, which may be included in the study database, shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the investigator and the patient/caregiver's key-coded data, all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact Amgen prior to destroying any records associated with the study.

The study documentation will be stored in the study master file.

All documentation pertaining to the study held by IQVIA will be transferred to Amgen throughout the duration of the study, and will be retained per Amgen retention policy.

Location of database and supporting documentation will be outlined in the final study report.

10.4 Subjects Decision to Withdraw

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

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

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

11.1 Definition of Safety Events

11.1.1 Adverse Events

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

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

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

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

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

11.1.2 Serious Adverse Events

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

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

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

"Other significant medical hazards" refer to important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

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

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

11.1.4 Product Complaints

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

Product complaints of Neulasta and Neulasta Onpro® will be reported

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients (or their corresponding caregivers) and from HCPs at the time of Neulasta OBI application and at a point in time following Neulasta OBI administration. All safety events (adverse events, product complaints and other safety findings) considered to have occurred following subject exposure to the Neulasta OBI will be collected from Neulasta OBI application and within the following 72h with the exception of the protocol exempted events **listed below**. **IQVIA** is responsible for recording safety events that they become aware of during study period in the patient's appropriate study documentation. **IQVIA** will be responsible for reporting to Amgen any available preliminary information on a suspected safety event **that is considered serious**, within 1 business day of vendor awareness. **Non-serious Adverse events (AEs) must be reported in an expeditious manner, not to exceed 15 calendar days of** vendor awareness.

Protocol Exempted Events

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

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of vendor awareness unless the event is due to disease progression.

All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.

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

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

11.2.1 Safety Reporting Requirement to Regulatory Bodies

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

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be

informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical 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 IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The protocol, study status updates and report(s) will be included in regulatory communications according to the risk minimisation plan, periodic benefit-risk evaluation reports and other regulatory milestones and requirements.

This study will be registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website before the start of data collection, and the study summary results will be posted on this public website no later than 12 months after study termination (defined as 'database lock').

A final study report will be developed and submitted to PRAC, and will serve as a basis for the development of publications and presentations in scientific journals, and press releases.

Abstracts, summaries, presentations and manuscripts will be prepared in line with dissemination guidelines of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors) and Guidelines for Good Pharmacoepidemiology Practice (International Society for Pharmacoepidemiology 2008) to help ensure the quality and integrity of pharmacoepidemiological research and to provide adequate documentation of research methods and results.

13.1 Publication Policy

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

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

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

14. Compensation

Patients/caregivers will not receive any incentives for their participation in the study. Investigators will receive a compensation for the recruitment of participants into the study if permitted under applicable regional laws or regulatory guidelines. This compensation will be based on a Fair Market Value (FMV) assessment (eg, time and effort) in each participating country

15. References

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16. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number.	Date	Title
1	*Number*	*22 March 2018*	*Respondent questionnaire*
2	*Number*	*22 March 2018*	*Electronic Case Report Form*

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Observational Study to Assess the Effectiveness of the Neulasta® Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta® On-Body Injector

Study reference number: 20170701

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☒	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.3

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.2 Age and sex?	☒	☐	☐	9.2.3.1
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.6
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.9.1.4
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9.1
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9.1
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.4

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.5.1

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9..4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates?	☐	☐	☒	

Section 9: Data sources	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.2

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.2.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.2.3
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2.5.1
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	13

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: _____

Date: 03/April/2018

Signature: _____

Appendix C. Sample Safety Reporting Form(s)

Project ID: 20170701	A	Observational Research Safety Reporting Form	Date of Reporter Awareness:
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Initial: ☐ Follow-up: ☐
2. Site Number: Subject Number:
3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator)

Name	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

5. Reporter ID

Name or ID	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	*State/Province*	*Postal Code*
Phone	*Fax*	

7. Patient

Initials (optional)	*Sex*	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?*
	☐ F ☐ M		☐ Yes ☐ No

Weight	*Height*	*Race*	*Is patient also reporter?*
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx _____; Date Admitted (day month year)	Hospitalization: Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	Severity: 1=mild 2=moderate 3=severe	Relationship to Product/Device: Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

Reporter Signature: _____ Page 3 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year											
	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Reporter Signature: _____ **Page 4 of ____**

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Appendix D. Additional Safety Reporting Form

Adverse Event Severity Scoring System

For oncology studies, the CTCAE is to be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ____/ dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm_____/ dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____/ dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix F. Patient Alert Card

How to monitor the on-body injector

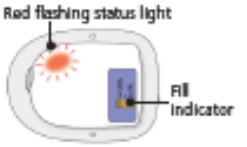
- For the first 27 hours you are wearing the on-body injector, you should see a slow flashing green light.
- Two minutes before dose delivery begins, you will hear a series of beeps.
- When dose delivery begins, you will see a fast green light.
- The dose will take 45 minutes to deliver.
- When the delivery is done, you will hear a long beeping sound and the status light will be solid green.
- Now, slowly pull off the on-body injector. Check to see if it is empty.

- **Call your healthcare professional immediately if you have any issues with the on-body injector, or symptoms of infection such as fever, chills or sweating.**
- **Do not try to secure the on-body injector if it becomes loose or try to reapply it.**

5

Call your healthcare professional immediately if any of the following happens - you may not have received your full dose:

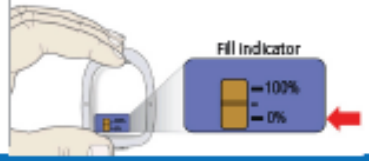
- The status light flashes red.



- The adhesive comes loose from the skin at any time before the end of dose delivery.

- The adhesive (the part touching your skin) is clearly wet and/or there are drips.

- If there is no line in the fill indicator next to 0% after the 45-minute dose delivery period is over.



DO NOT try to secure the on-body injector if it becomes loose or reapply it under any circumstances.

6 7

Neulasta® (pegfilgrastim)

On-body Injector Patient Alert Card

- Please open this card and read both sides.
- Keep it with you.
- This card contains important safety information that you need when receiving treatment with the pegfilgrastim on-body injector.
- Show this card to your healthcare professional if you need to seek urgent medical advice for the on-body injector.

Dated December 2017

Important information

The purpose of this card is to help prevent medication errors - mainly, drug underdose.

- A drug underdose may happen if the on-body injector comes loose from your skin, leaks, or otherwise malfunctions.
- If that happens, you may be at increased risk of a serious infection.

For more information:

- Read the Package Leaflet that comes with your on-body injector.
- Visit the European Medicines Agency (EMA) website (http:bit.ly/2kt26wk) and/or local equivalent websites.

1

The following activities may interfere with the on-body injector's performance:

- **Do not** knock or pull the on-body injector.
- **Do not** get lotions, creams, oils or cleaning agents near the on-body injector.
- **Do not** sleep on the on-body injector or apply pressure during wear.
- **Do not** expose the on-body injector to CT scan, MRI, x-ray, ultrasound, radiation treatment, or hyperbaric chambers.
- **Do** wear loose clothing and be careful when changing clothes.
- **Do** keep the on-body injector at least 10 cm (4 inches) away from electrical equipment (such as mobile phones or microwaves).

2

Please read this card and keep it with you

This information should be completed by your healthcare professional

Your on-body injector was applied to your skin:

_____
Day *Time* *AM / PM*

Your dose delivery will start around:

_____
Day *Time* *AM / PM*

On-body injector lot number:

_____

3

Emergency contact information

Name and contact number of healthcare professional:

_____
Surname, Given Name

_____
Contact Number

Out-of-hours urgent care contact details:

_____

_____

_____

PegFilgrastim_EU_Patient Alert Card_EU RMP V5.0
Dated December 2017

4

Appendix G. Protocol Exempted Events

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

Event	MedDRA PT(s)
Dysgeusia	Dysgeusia
Inability to taste food	Ageusia
Anorexia	Decreased appetite
Headache	Headache
Na	Blood sodium abnormal, blood sodium increased, blood sodium decreased, hypernatremia, hyponatremia
K	Blood potassium abnormal, blood potassium increased, blood potassium decreased, hyperkalemia, hypokalemia
Chloride	Blood chloride abnormal, blood chloride decreased, blood chloride increased, hypochloremia, hyperchloremia
CO2	Carbon dioxide abnormal, carbon dioxide increased, carbon dioxide decreased
Bicarbonate	Blood bicarbonate abnormal, blood bicarbonate increased, blood bicarbonate decreased,
BUN	Blood urea abnormal, blood urea decreased, blood urea increased
Creatinine	Blood creatinine abnormal, blood creatinine increased, blood creatinine decreased, creatinine renal clearance abnormal, creatinine renal clearance decreased, creatinine renal clearance increased, hypercreatininemia, hypocreatininemia
AST	Aspartate aminotransferase abnormal, aspartate aminotransferase decreased, aspartate aminotransferase increased,
ALT	Alanine aminotransferase abnormal, alanine aminotransferase increased, alanine aminotransferase decreased
Alkaline phosphatase	Blood alkaline phosphatase abnormal, blood alkaline phosphatase increased, blood alkaline phosphatase decreased
Bilirubin	Blood bilirubin abnormal, blood bilirubin decreased, blood bilirubin increased, blood bilirubin unconjugated abnormal, blood bilirubin unconjugated increased, blood bilirubin unconjugated decreased, blood bilirubin conjugated abnormal, blood bilirubin conjugated increased, blood bilirubin conjugated decreased
Albumin	Blood albumin abnormal, blood albumin decreased, blood albumin decreased, hyperalbuminaemia, hypoalbuminaemia
Total protein	Hyperproteinaemia, hypoproteinaemia,

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

Amendment 1

Protocol Title: An Observational Study to Assess the Effectiveness of the Neulasta® Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta® On-Body Injector

Amgen Protocol Number Pegfilgrastim 20170701

Amendment Date: 10 April 2019

Rationale:

This protocol is being amended to:

- To remove the option of delivering the questionnaire by telephone due to the use of a third-party vendor and replace with the administration a paper questionnaire.
- Updates to Section 11.2 Safety Collection, Recording and Submission to Amgen Requirements have been implemented to align with the current template.
- The start of data collection was updated to the latest known status.
- The list of countries for consideration were updated to the latest known status.
- Limited administration, typographical and formatting changes were made throughout the protocol.

Description of Changes

Section: Global

Change:

Version updated throughout document from 03 April 2018 to **10 April 2019**

Section: Global

Change:

Editorial changes (ie, typographic, grammatical, and formatting errors) were made throughout the protocol in accordance with Amgen Inc. Style

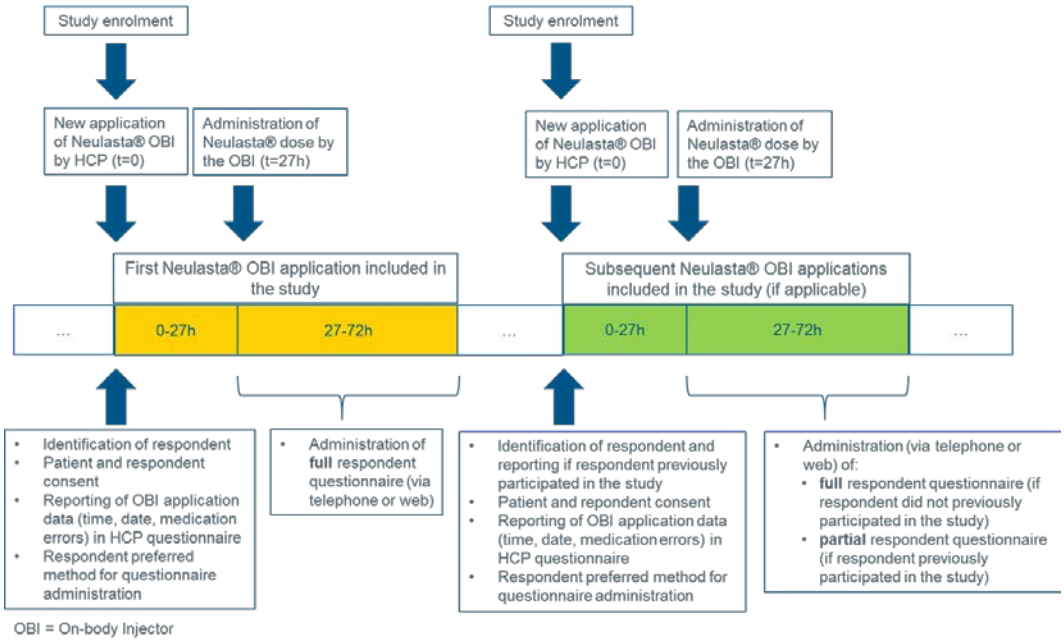
Section: Summary Table of Study Protocol

Add:

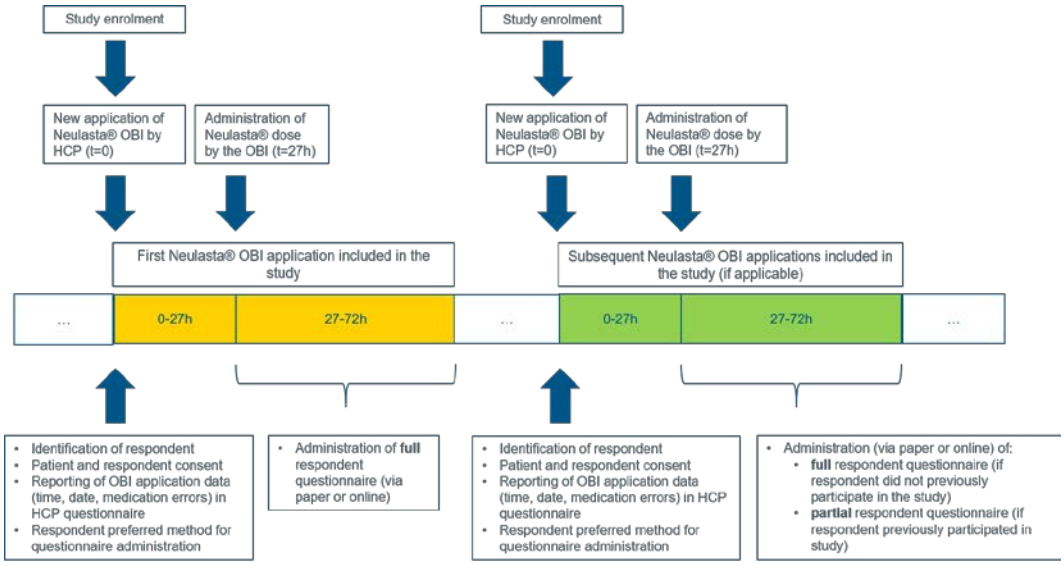
A preliminary list includes Germany, Slovakia, Netherlands, and/or UK.

Section: Study Design Schema

Replace:



With:



Section: Section 6, Milestones

Replace:

Approximately July 2019*

With:

Approximately **August** 2019*

Section: Section 9.1, Study Design

Replace:

The questionnaire will be administered either by telephone or online.

With:

The questionnaire will be administered either by **paper** or online.

Section: Section 9.2, Setting and Study Population

Add:

Based on the current forecasted launch timetable, a preliminary selection of countries for this study is likely to include Germany, **Netherlands**, Slovakia **and/or UK**.

Section: Section 9.4, Data Sources

Replace:

Responses will be collected either by telephone or online.

With:

Responses will be collected either by **paper** or online.

Section: Section 9.6, Data Management

Delete:

A~~**n electronic**~~ respondent questionnaire developed to collect information from the primary person responsible for monitoring the OBI after application (ie, patients or, if appropriate, their caregivers)

Section: Section 9.6, Data Management

Replace:

Responses will be collected either by telephone or online.

With:

Responses will be collected either by **paper** or online.

Section: Section 9.6, Data Management

Delete:

~~**In addition, one additional electronic external data capture platform will be developed to capture patient/caregiver contact information only, to be completed by the physician at patient/respondent inclusion**~~

Section: Section 9.6, Data Management

Replace:

Upon inclusion of a new respondent to the study (and after obtaining patient and respondent consent), the physician will be asked to immediately complete information

With:

Upon inclusion of a new respondent **in**to the study (and after obtaining patient and respondent consent), the **HCP** will be asked to immediately complete information

Section: Section 9.6, Data Management

Replace:

This code will be manually added to the ICF of the respondent by the physician for reference purposes.

With:

This code will be manually added to the ICF of the respondent by the **HCP** for reference purposes.

Section: Section 9.6, Data Management

Add:

The HCP will give the respondent an envelope containing the instructions about how to complete the questionnaire (two options will be provided in the same envelope):

a) **Option 1. A document with the link to complete the questionnaire online.**
b) **Option 2. Pre-paid and pre-filled envelope containing a paper copy of the respondent questionnaire and instructions for delivery to IQVIA to perform data entry.**

Section: Section 9.6, Data Management

Delete:

~~**In addition, the physician will be requested to input respondent contact details and preferred method for respondent questionnaire administration (by telephone or online) in the electronic external data capture platform, which will be developed and maintained by an external party to IQVIA and Amgen. The unique patient and respondent code generated by the eCRF will not be registered in this platform.**~~

~~**The external party**~~

Section: Section 9.6, Data Management

Replace:

The external party will be subsequently responsible for conducting a telephone follow-up with the respondents to remind them about respondent questionnaire completion, within the timeframe established by the study protocol (ie, 27-72h post OBI application).

With:

The HCP will be subsequently responsible for conducting a **telephone** follow-up with the respondents **to remind them about** respondent questionnaire completion, within the timeframe established by the study protocol (ie, 27-72h post OBI application).

Section: Section 9.6, Data Management

Delete:

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- ~~**If the respondent opted for completing the questionnaire online, the external party will be providing the respondent with a secure link generated by the IQVIA electronic questionnaire software.**~~
- ~~**If the respondent opted for completing the questionnaire by telephone, the external party will be responsible for calling the respondent at the pre-agreed time and complete the secure link generated by the IQVIA electronic questionnaire software, as per respondent's input.**~~

Section: Section 9.6, Data Management

Replace:

For both alternatives, the respondent will be initially asked to provide the information on the respondent code (as provided by the physician in the copy of the ICF, eg, UK-01-01-01), then respondent will be able to complete the rest of the questionnaire.

With:

For both **options provided for questionnaire completion**, the respondent will be initially **requested** to **include** the information on the respondent code (as provided by the **HCP** in the copy of the ICF, eg, UK-01-01-01), then respondent will be able to complete the rest of the questionnaire.

Section: Section 9.6, Data Management

Replace:

IQVIA will therefore generate and maintain two independent databases (one generated from the eCRF and one generated from the respondent questionnaire), with a unique identifier, but none of the parties involved (IQVIA or external party) will hold information that can be used to identify or contact the respondent and clinical data, thus ensuring data privacy.

With:

IQVIA will therefore generate and maintain two independent databases (one generated from the eCRF and one generated from the respondent questionnaire), with a unique identifier, but IQVIA will **not** hold information that can be used to identify or contact the respondent and clinical data, thus ensuring data privacy.

Section: Section 9.6, Data Management, Electronic respondent questionnaire

Delete:

~~**Electronic external data capture platform**~~

~~The electronic external data capture platform will be developed and maintained by an external party to IQVIA and Amgen, in order to ensure that respondent contact details and any clinical data collected as part of the study are not maintained in the same database or the same entity.~~

~~Respondent contact details will only be maintained by the external party for a limited time period aligned with the study characteristics (ie, up to after 1 week following OBI administration).~~

~~IQVIA and Amgen will ensure that the characteristics of the external data capture platform and of the database generated by the external party are compliant with protocol specifications and with all the relevant regulations.~~

Section: Section 9.6.1, Obtaining Data Files

Replace:

Not applicable, the study will be not conducted based on existing databases.

With:

Completed paper forms will be forwarded to IQVIA by respondents for data entry. IQVIA data entry staff will enter the paper questionnaire into a database for analysis.
A database will be created and tested before data entry, two copies of the same database will be prepared for double data entry to be performed. Databases will be compared until no discrepancies are found. The final database will be merged with the online questionnaire results and transferred to SAS for analysis.

Section: Section 9.8, Quality Control

Replace:

Respondents that opt to respond the questionnaire online will be provided with personal secure access credentials for the respondent questionnaire. In case respondents opt to respond the questionnaire by telephone, and data will be directly inputted by the interviewer into a specific study database.

With:

Respondents that opt to respond the questionnaire online will be provided with **a unique generic link** for the respondent questionnaire. In case respondents opt to respond the questionnaire by **paper, respondent will send the completed questionnaire to IQVIA**

in a pre-paid and pre-filled envelope, and data will be directly **entered** by **IQVIA** into a specific study database.

Section: Section 9.8, Quality Control

Add:

- **A database will be created and tested before data entry, two copies of the same database will be prepared to ensure a double data entry. Both databases will be compared until no discrepancies are found.**

Section: Section 10.1, Informed Consent

Add:

Informed consent for the study participation will be sought. By signing the ICF, the patient/caregiver consents to participate in the study **and to be contacted by phone by the HCP for a follow up on questionnaire completion.**

Section: Section 11.2, Safety Collection, Recording and submission to Amgen Requirements

Replace:

All safety events (adverse events, product complaints and other safety findings) considered to have occurred following subject exposure to the Neulasta OBI will be collected from Neulasta OBI application and within the following 72h with the exception of the protocol exempted events. The vendor is responsible for recording safety events that they become aware of during study period in the patient's appropriate study documentation. The vendor will be responsible for reporting to Amgen any available preliminary information on a suspected safety event that is considered serious, within 1 business day of the vendor awareness. Collected safety events must be submitted as individual safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper) within 1 business day of vendor awareness.

With:

All safety events (adverse events, product complaints and other safety findings) considered to have occurred following subject exposure to the Neulasta OBI will be collected from Neulasta OBI application and within the following 72h with the exception of the protocol exempted events **listed below**. **IQVIA** is responsible for recording safety events that they become aware of during study period in the patient's appropriate study documentation. **IQVIA** will be responsible for reporting to Amgen any available preliminary information on a suspected safety event that is considered serious, within

1 business day of vendor awareness. **Non-serious Adverse events (AEs) must be reported in an expeditious manner, not to exceed 15 calendar days of** vendor awareness.

Section: Section 11.2, Safety Collection, Recording and Submission to Amgen Requirements – Protocol Exempted Events

Replace:

See Appendix C for sample Safety Report Form(s), and Appendix E for sample Pregnancy and Lactation Notification Worksheets

With:

See Appendix C for sample Safety Report Form(s), **Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study**, and Appendix E for sample Pregnancy and Lactation Notification Worksheets.