CLINICAL STUDY PROTOCOL

ZIN-130-1504

A Phase 1-2 ascending dose study to assess the pharmacodynamics, pharmacokinetics, and safety of HSP-130 in subjects with non-metastatic breast cancer following single-dose and multiple-dose administration by subcutaneous injection

IND Number	124793
EudraCT Number	2015-002057-35
Sponsor	Hospira, Inc. (Hospira)
	Hospira, Inc. 275 North Field Drive Lake Forest, IL 60045
Original Protocol v 2.0	31 July 2015
Amendment#2, Protocol v 3.0	22 December 2015

[redacted]

[redacted]

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SIGNATURE PAGE

PPD _____ Date: PPD

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INVESTIGATOR SIGNATURE PAGE

The signature below constitutes approval of this protocol and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements of confidentiality and in accordance with ICH GCP and local regulatory requirements.

Address of Institution/Site:	_____ _____ _____
Telephone Number:	
Signed:	
Print Name and Title:	
Date:	

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LIST OF IN-TEXT TABLES

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

The main reasons for this amendment are as follows (a complete listing of changes [except minor typographical errors] can be found in Appendix G.

- The Protocol version and the Protocol Date have been updated for accuracy
- Updated the Signature Page to provide information on the new Global Medical Director, Pharmacovigilance and Safety
- Removed the docetaxel and cyclophosphamide (TC) regimen in the following sections: Synopsis (Study Design) and Section-1.5.1 (Design Features)
- Modified the study population in the following sections: Synopsis (Study Design); Section-1.5.1 (Design Features); Section-1.5.2 (Study Population), Section-1.6 (Risk/Benefit) and Section-3.1 (Study Design)
- Removed TC regimen in the following sections: Synopsis (Study Design, Key Inclusion Criteria for all study subjects, Key Exclusion Criteria), Section-4.2 (Inclusion Criteria) and Section-4.3 (Exclusion Criteria)
- Modified the chemotherapy cycle duration in the following sections: Synopsis (Duration of Treatment, Safety Assessments), Section-1.5.3 (Dosing Regimen and Treatment Duration), Section-2.3 (Safety Variables) and Section-3.3 (Estimated Study Duration)
- Changes were made to the total blood volume collected and their breakdown during the study in the following sections: Synopsis (Pharmacodynamics and Pharmacokinetics of HSP-130; Pharmacodynamic Sampling/Collection); Section-6.2.12 (Total blood volume to be collected during the study) and Section-6.4.1 (Collection of samples for analysis)
- Modified the safety assessments in the following sections: Synopsis (Safety Assessments) and Section-2.3 (Safety Variables)
- Modified the Principal contacts information for reporting of Serious Adverse Events (SAEs) and in Section-8.5 (Serious Adverse Event Reporting)
- Inserted a footnote in Study Design Schematic (Figure 1)
- Modified Table 1 and Table 2 and Section-6.2.8 (Clinical Laboratory Tests) to reflect Table 1 and Table 2 modifications
- Added a footnote in Table 3
- Updated the Glossary of Abbreviations

- Corrected the definition of severe neutropenia in Section-1.5.4 (Pharmacodynamic Endpoints) and 10.2.3 (Assessment of Pharmacodynamics and Pharmacokinetics)

- Modified the Physical Examination in Section-6.2.4

- Inserted the grading of laboratory abnormalities in the following sections: Synopsis (Safety analysis); Sections-6.2.8 (Clinical Laboratory Tests) and Section-10.2.5 (Assessment of Safety)

- Modified the Adverse Events of Special Interest Section-8.1.2 (Adverse Events of Special Interest) and Section-10.2.5.1 (Adverse Events)

- Removed the preferred term tables Section-10.2.5.1 (Definitions of Adverse Events of Special Interest)

- Updated the References Section-13.0

- Updated the Appendix E Adverse events - categorized as SAEs to current version

- Updated the Appendix F Neulasta® (pegfilgrastim, Amgen) Summary of Product Characteristics

- Updated the Appendix H Neulasta® (pegfilgrastim, Amgen) Package Insert

PROTOCOL SYNOPSIS

Sponsor: Hospira, Inc. (Hospira)

Name of Finished Product: HSP-130

Name of Active Ingredient: HSP-130

Study Title: A Phase 1-2 ascending dose study to assess the pharmacodynamics, pharmacokinetics, and safety of HSP-130 in subjects with non-metastatic breast cancer following single-dose and multiple-dose administration by subcutaneous injection.

Study Number: ZIN-130-1504

OBJECTIVES

Cycle 0:

Primary Objective:

- To characterize the pharmacodynamic (PD) response of absolute neutrophil count (ANC) and $CD34^+$ count to HSP-130 at doses of 3 mg and 6 mg when administered as a single subcutaneous (SC) dose without chemotherapy to determine whether it is appropriate to study multiple doses of 3 mg with the context of background chemotherapy.

Secondary Objective(s):

- To characterize the pharmacokinetics (PK) of HSP-130 at doses of 3 mg and 6 mg when administered as a single SC injection without background chemotherapy.
- To characterize the safety of HSP-130 at doses of 3 mg and 6 mg when administered as a single SC dose without background chemotherapy.

Cycles 1-4:

Primary Objective:

- To characterize the PD response of duration of severe neutropenia (DSN) in Cycle 1 to HSP-130 over a range of doses when administered as single and multiple SC doses.

Secondary Objective(s):

- To characterize the PD response of ANC to HSP-130 in Cycles 1 and 4 over a range of doses when administered as single and multiple SC doses.
- To characterize the PK of HSP-130 in Cycles 1 and 4 over a range of doses when

administered as single and multiple SC doses.

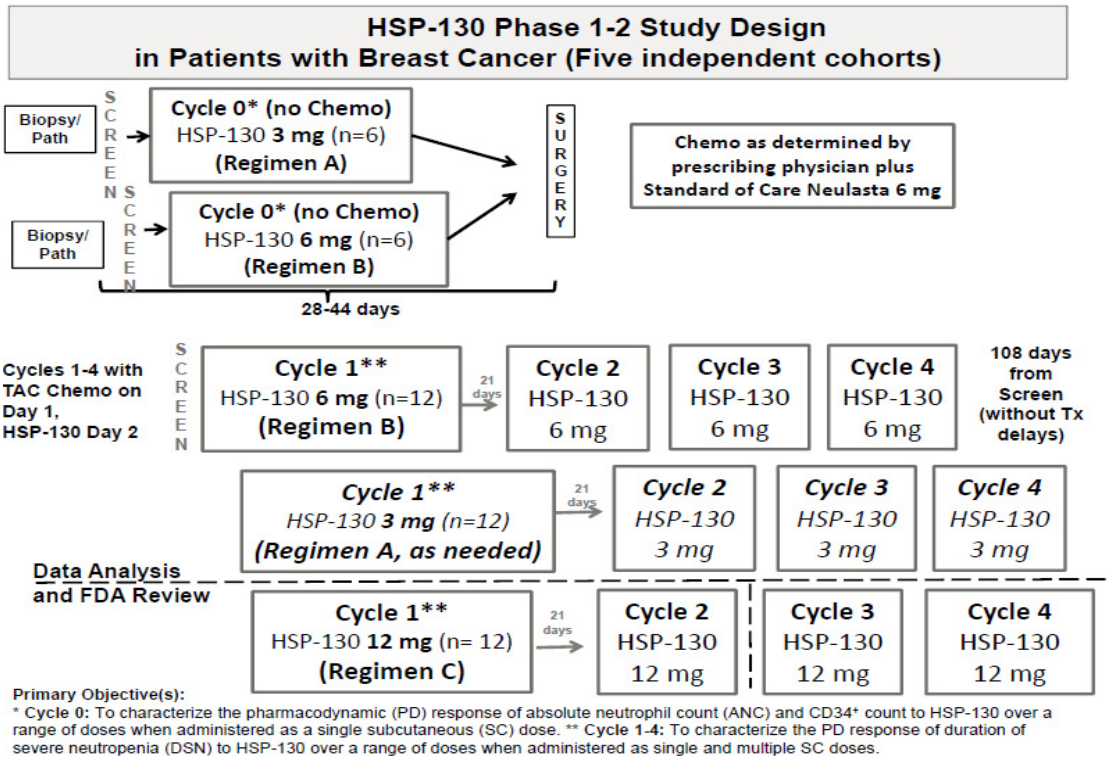
- To characterize the safety of HSP-130 over a range of doses when administered as single and multiple SC doses.

Study Design: An open-label, parallel group study characterizing the PD, PK, and safety of HSP-130 in subjects with non-distantly metastatic (non-Stage IV) breast cancer who have not previously received chemotherapy at any point prior to enrollment in this study (ZIN-130-1504).

There are two aspects of the study. In the initial part of the study, 6 subjects will be sequentially enrolled to receive HSP-130 treatment (3 mg or 6 mg by SC injection) without concomitant or background chemotherapy. This treatment setting will, therefore be referred to as Cycle 0. Patients in Cycle 0 will receive HSP-130 during the period between biopsy and definitive surgery.

The second group of subjects will receive up to 4 cycles of HSP-130, with concomitant background chemotherapy. Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Chemotherapy will consist of every 3 week taxane/cyclophosphamide-based regimen, i.e., docetaxel, doxorubicin and cyclophosphamide (TAC).

Specifics of these two groups are addressed below. Note that the 12 mg cohort will not be initiated until after discussion with the FDA as defined in Section 6.3.2.



Subjects in Cycle 0:

Subject eligibility will be determined during a 14-day Screening Period. Eligible subjects will be enrolled sequentially to each of the HSP-130 dose groups as follows:

Regimen A: HSP-130, 3 mg, single SC injection in the deltoid region (n = 6)

Regimen B: HSP-130, 6 mg, single SC injection in the deltoid region (n = 6)

Initiation of Regimen B will be based on safety assessments in the first 5 evaluable subjects receiving Regimen A. This will include assessment of vital signs, concomitant medications, laboratory assessments including chemistry and hematology (complete blood count [CBC] and platelets), electrocardiogram (ECG), physical exam, and any adverse events (AEs) occurring post-dose administration through Day 30. The specific safety criteria for assessment for dose escalation are listed in Section 6.3.2 of the protocol. If, based on these assessments, there is no contraindication for dose escalation, screening for the subsequent dose level (Regimen B) can be initiated.

In Cycle 0, Day 1 is the day that the subject receives HSP-130. Subjects obtain a baseline assessment of ANC and $CD34^+$ count on Day 1 prior to receipt of HSP-130. Subjects will return for ANC, $CD34^+$ measurement, and PK assessment for up to a maximum of 7 visits after HSP-130 dosing.

After completion of Cycle 0, each of the subjects in these dosing groups will have completed their participation in assessment of HSP-130. The site will be offered reimbursement for treatment with EU-approved Neulasta in accordance with local standard of care by the Investigator with subsequent non-study chemotherapy regimen.

Assessment of Regimen A (3 mg) for Cycles 1-4 will be conducted as follows:

Based on the dose-response curve published by B. Yang and A. Kido (1), the average concentration (C_{av}) of pegfilgrastim (calculated from the time of pegfilgrastim administration to the time of ANC nadir) for the 6 mg dose was 72 ng/mL, which corresponds to 90% of maximum response (EC_{90}).

For a 3 mg dose, the estimated C_{av} was about 21 ng/mL, which corresponds approximately 70% of maximum response (EC_{70}). The expected response for a 3 mg dose (EC_{70}) is 77.8% of that from a 6 mg dose (EC_{90}).

It is expected that approximately 30% of subjects receiving 3 mg of pegfilgrastim would have a C_{av} value below the EC_{50} value. Because the dose of 3 mg of HSP-130 is potentially sub-therapeutic in breast cancer patients, this dose will be tested in Cycle 0 without chemotherapy first.

If the PD response (ANC and/or $CD34^+$) of 3 mg HSP-130 and 6 mg HSP-130 in Cycle 0 indicate that the 3 mg dose level is sub-therapeutic, the 3 mg dose level will not be included in Cycle 1-4 assessment. This design feature will ensure that no subject with

chemotherapy will be treated with sub-therapeutic dose of HSP-130.

If, however, the individual PD measurement (ANC and/or $CD34^+$) of the treatment with HSP-130 3 mg and 6 mg in Cycle 0 are commensurate, as defined above, then treatment with Regimen A with background chemotherapy will be initiated.

Subjects in Cycles 1-4:

When enrollment of the 6 subjects receiving Regimen B in Cycle 0 is completed, an additional 12 subjects will be enrolled on Regimen B and entered in Cycle 1-4 as defined below. Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Eligible subjects will be enrolled sequentially to each of the HSP-130 dose groups as follows:

Regimen B: HSP-130, 6 mg, single SC injection in the deltoid region, at least 24 hours after administration of chemotherapy in Cycle 1, Cycle 2, Cycle 3, and Cycle 4 (n = 12).

Potential Regimen A (3 mg) with background chemotherapy: Inclusion of this cohort will be based on assessment of comparability between Regimens A and B in Cycle 0 for ANC and $CD34^+$ as defined above. If performed, this regimen will be HSP-130, 3 mg, single SC injection in the deltoid region, at least 24 hours after administration of chemotherapy in Cycle 1, Cycle 2, Cycle 3, and Cycle 4 (n = 12), as appropriate.

While noted in the protocol schema which is included as Figure 1, the 12 mg cohort will not be initiated until Hospira has analyzed the data from the Cycle 0 for 3 mg and 6 mg cohorts and the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and reviewed the results with the FDA. Escalation to 12 mg will only proceed if the exposure pattern of the PK/PD responses suggests that higher doses are required. Please see section 6.3.2 for additional details.

During Cycles 1-4 for each of the regimens, subjects will receive treatment with HSP-130 at 24 hours after administration of chemotherapy (Day 2). Subjects will return for ANC measurement and PK assessment for up to an additional 7 visits after dosing.

Subjects will return for a Follow-up Visit 30 (±2) days after the dose of HSP-130 in Cycle 4.

Number of Centers: Approximately 10 sites in Europe.

Study Population:

A total of 24-36 patients will be enrolled initially; a further 12 patients totaling approximately 36-48 patients will be treated if the 12 mg cohort is enrolled, as defined in Section 6.3.2.

- The number of 24 patients includes 12 patients in Cycle 0 and 12 patients in the

Cycles 1-4 6 mg cohort.

- The number of 36 patients includes the additional 12 patients if the second 3 mg cohort is included in the Cycles 1-4 part of the study.
- The number of 48 patients includes the potential for 12 patients in the 12 mg cohort if, after review of the data in the up to 36 patients with the FDA, a decision is jointly made based on the exposure pattern of the PK/PD responses that higher doses are required.

Approximately 12 subjects will be enrolled into two cohorts to receive ascending doses of HSP-130 (6 subjects on Regimen A [3 mg] and 6 subjects on Regimen B [6 mg] without background chemotherapy.

Twelve subjects will be enrolled in the 6 mg cohort in the setting of background chemotherapy. As mentioned, enrollment in a 12 mg cohort will not be initiated until criteria addressed in section 6.3.2 are met.

An additional 12 subjects will be enrolled into Regimen A (3 mg) as defined by the protocol in Section 1.5.1.

It is recommended that rescue management for subjects who develop febrile neutropenia (FN) during the study be consistent with several recent publications (2), (3), (4) and recent Cochrane review (5). Management of FN should also include consideration of locale-driven susceptibility patterns.

Key Inclusion Criteria for all study subjects (See Section 4.2 for full Inclusion Criteria)

A subject will be eligible for study participation if all of the following criteria are met at Screening:

1. Is informed, has been given ample time and opportunity to read about participation in the study and has signed and dated the written informed consent form approved by an Independent Ethics Committee (IEC) prior to any study related activities
2. Females ≥ 18 years
3. Histologically confirmed and documented invasive breast cancer
4. Breast cancer without evidence of distant metastases (non-Stage IV) based on staging work-up
5. Chemotherapy naïve, who have not received chemotherapy in the neoadjuvant setting and who are candidates for chemotherapy in the adjuvant setting of taxane/cyclophosphamide-based regimen, i.e., TAC as background chemotherapy
6. Zubrod/WHO/ECOG performance status ≤ 2

7. Adequate bone marrow, hepatic, and renal function reserve as evidenced by:
    a. Hemoglobin ≥ 10 mg/dL
    b. ANC ≥ 1.5 x 10^9/L
    c. Platelet count of ≥ 100 x 10^9/L
    d. Total bilirubin ≤ 2 mg/dL
    e. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 3 x the upper limit of normal (ULN) of the reference lab
    f. Serum creatinine of ≤ 1.5 x ULN for reference lab or estimated glomerular filtration rate (eGFR) of ≥ 60 mg/min
8. Subjects of childbearing potential, and their partners, agree to pregnancy prevention throughout the duration of the study (through the Follow-up Visit). Specific type of pregnancy prevention should be discussed with, and acceptable to, the treating oncologist in the context of the tumoral hormone receptor status and is summarized in Section 4.2
9. Able to understand verbal or written instructions and comply with all study requirements, to communicate effectively with study personnel and is available for the planned duration of the study

Key Exclusion Criteria (See Section 4.3 for full Exclusion Criteria)

A subject will NOT be eligible for study participation if any of the following criteria are met at Screening:

1. Previous granulocyte colony-stimulating factor (G-CSF) exposure, including filgrastim, lenograstim, pegfilgrastim, lipegfilgrastim, granulocyte/macrophage colony stimulating growth factor (GM-CSF), or any other branded or biosimilar G-CSF
2. Prior autologous stem cell harvest of any type
3. Drug sensitivity, allergic reaction, or known hypersensitivity or idiosyncratic reaction to *Escherichia coli (E. coli)*-derived proteins, filgrastim, other G-CSFs, or pegylated agents
4. Known hypersensitivity to docetaxel, polysorbate 80, or doxorubicin
5. Chemotherapy other than that included in this study (i.e., taxane/cyclophosphamide-based regimen, i.e., TAC) or neoadjuvant chemotherapy; or known immunosuppressive agents including chronic oral corticosteroid use, or radiation therapy within 4 weeks of first dose of HSP-130, prior bone marrow or stem

cell transplantation, or malignancy within 5 years

6. Known $HER2^{+}$ (overexpressing breast cancer)

7. Known triple negative (estrogen receptor-negative, progesterone receptor-negative and HER2-negative) breast cancer

8. Medical conditions including but not limited to: Known sickle cell disease, known severe persistent drug-induced myelosuppression; severe uncontrolled cardiac disease as defined in Section 4.3; any malignancy other than breast with the exception of adequately treated squamous or basal cell carcinoma or the skin or cervical carcinoma in situ within 5 years; pregnancy or lactation; received live, live-attenuated, or non-live vaccine within 4 weeks

9. Current or recent treatment (within 30 days before the first administration of the HSP-130) with any other Investigational Medicinal Product

10. Patient has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding or clinical lab finding giving reasonable suspicion of a disease or condition that contraindicated the use of an HSP-130, or patient is high risk for treatment complication

Investigational medicinal products, dosage and route of administration:

Test product: HSP-130, 3 mg, 6 mg or 12 mg administered as a SC injection
(Note: 12 mg will be administered as 2 concurrent injections and only if the decision is made with the FDA to pursue a 12 mg dose. See Section 6.3.2 for details.)

In Cycle 0, subjects will receive treatment with HSP-130 only, without concomitant background chemotherapy.

In Cycles 1-4, subjects will receive treatment with HSP-130 concomitantly with chemotherapy.

Duration of Treatment:

Subjects on Regimen A or Regimen B during Cycle 0 will receive a single dose of HSP-130 (3 mg or 6 mg) and be in the study for approximately 30 (±2) days and will not receive concomitant background chemotherapy.

Subjects receiving Regimen B (6 mg), and, if performed, multiple dose Regimen A (3 mg) [and Regimen C (12 mg) if the decision is made with the FDA to pursue a 12 mg dose. See Section 6.3.2 for details], will receive up to 4 doses of HSP-130 in the context of 4 cycles of chemotherapy (≥ 21 days per cycle). Exclusive of chemotherapy-related treatment delays, these subjects will participate in the study, for approximately 94 days (including Follow-up Visit).

Pharmacodynamics and Pharmacokinetics of HSP-130

Cycle 0:

Pharmacodynamic Sampling/Collection:

Blood samples for ANC (2.7 mL) and $CD34^+$ count (2.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 48, 96, 144, 192, 240, and 312 hours post-dose.

Pharmacokinetic Sampling/Collection:

Blood samples (7.0 mL) for HSP-130 assay will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose.

Pharmacodynamic and Pharmacokinetic Assessments:

Pharmacodynamic Variables:

Primary Variable: Area under the effect curve for ANC ($AUEC_{ANC}$)

Secondary Variables: Maximum effect for ANC (ANC_E_{max}), time of maximum effect for ANC ($ANC\ T_{max}$), Area under the effect curve for $CD34^+$ ($AUEC_{CD34+}$), maximum effect for CD34+ count ($CD34^+\_E_{max}$), time of maximum effect for $CD34^+$ count ($CD34^+\ T_{max}$)

The PD variables will be calculated using non-compartmental methods.

Pharmacokinetic Variables:

Primary Variables: Area under the serum HSP-130 versus time curve from the time of dose administration to time infinity ($AUC_{0-\infty}$) and the maximum observed serum HSP-130 concentration (C_{max})

Secondary Variables: Area under the serum HSP-130 versus time curve from the time of dose administration to the time of last measurable concentration (AUC_{0-t}), the time of maximum serum HSP-130 concentration (T_{max}), elimination half-life ($t_{1/2}$), elimination rate constant (λz), and apparent clearance (CL)

The PK variables will be calculated using non-compartmental methods.

Cycles 1-4:

Pharmacodynamic Sampling/Collection:

Blood samples for ANC (2.7 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy

cycle and at 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be applied to Cycles 1 and 4 with HSP-130 treatment groups.

Pharmacokinetic Sampling/Collection:

Blood samples (7.0 mL) for HSP-130 assay will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be applied to Cycles 1 and 4 with HSP-130 treatment groups.

Pharmacodynamic and Pharmacokinetic Assessments:

Pharmacodynamic Variables:

Primary Variable: Duration of severe neutropenia (DSN). DSN is defined as days with grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) in Cycle 1.

Secondary Variables: Duration of severe neutropenia (DSN) in Cycle 4. ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of FN, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour with ANC $< 1.0 \times 10^9$/L, incidence of severe neutropenia (grade 4, ANC $< 0.5 \times 10^9$/L) and time to ANC recovery (the first day with ANC $\geq 2.0 \times 10^9$/L after any day with ANC $< 2.0 \times 10^9$/L) in Cycle 1 and Cycle 4.

The PD variables will be calculated using non-compartmental methods.

Pharmacokinetic Variables:

Primary Variables: AUC_{0-t} and C_{max}

Secondary Variables: $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λz, and CL

The PK variables will be calculated using non-compartmental methods.

Safety Assessments:

The safety variables to be assessed include adverse events, including Adverse Events of Special Interest, laboratory assessments and ECG at Follow-up Visit at study end and as clinically indicated, vital signs, and physical examination. These will be performed on patients receiving HSP-130 without (Cycle 0) or with chemotherapy (Cycles 1-4).

Cycle 0:

Safety assessment includes assessment of vital signs, concomitant medications, laboratory assessments including chemistry and hematology (CBC and platelets), ECG, physical exam, and any AEs occurring post-dose administration through Day 30. After completion of Cycle 0, each of the subjects in these dosing groups will have completed their

participation in assessment of HSP-130. The site will be offered reimbursement for treatment with EU-approved Neulasta in accordance with local standard of care by the Investigator with subsequent non-study chemotherapy regimen.

Cycles 1-4:

To begin full-dose chemotherapy on Day 1 of the next cycle (≥ Day 21 of the previous cycle), ANC must have recovered to ≥ 1.5 x 10^9/L and platelet counts to ≥ 100 x 10^9/L. If these requirements are not met, postponement of the following cycle for up to 2 weeks will be acceptable. Both ANC and platelets will be determined on Day 15 and Day 20 of each cycle by a central laboratory so that results are available at the beginning of the next cycle.

In subjects who experience FN and/or ANC < 0.5 x 10^9/L for > 1 week, severe or cumulative cutaneous reactions, or severe (grade 3 or 4) peripheral neuropathy during therapy, the chemotherapy timing and dose will be modified as deemed appropriate by treating physician. Changes in patients TAC chemotherapy regimen will be determined by the patients treating physician in the context of known TAC toxicity profile and management. Subjects who withdraw prior Cycle 2 may be replaced to support the full complement subjects (minimum of 8 evaluable subjects) for primary endpoint data generation for Cycle 1.

Anti- antibody assessments:

Cycle 0:

Blood samples (7.0 mL) for anti-HSP-130 antibodies assessment will be collected on Day 1 (prior to dose), on Day 14 and Day 20.

Cycles 1-4:

Blood samples (7.0 mL) for anti-HSP-130 antibodies assessment will be collected on Day 2 (prior to study drug dose) and on Day 20 in Cycles 1 and 4.

Statistical Methods:

Analysis Populations:

Safety Population: All subjects who receive at least one dose of HSP-130 will be included in the Safety Population. All safety analyses will be conducted on the Safety Population.

Full analysis set (FAS): All subjects who receive at least one dose of HSP-130 in the context of concomitant chemotherapy will be included in the FAS. In analysis of a particular parameter for a particular cycle(s), only those subjects who have sufficient data in the cycle(s) to calculate the parameter will be included. Sufficient data is defined as having more than 3 measurable values where the parameter can be reliably calculated. Subjects who have confirmed positive anti-HSP-130 antibody results will not be included.

Sample Size Estimation:

No formal sample size calculation was conducted.

Pharmacodynamic analysis:

Descriptive statistics including number of observations (N), mean, standard deviation (SD) and associated coefficient of variation (CV), minimum and maximum for each PD parameter by treatment will be reported.

If the PD response ($AUEC_{ANC}$ and/or $AUEC_{CD34+}$) of 3 mg HSP-130 and 6 mg HSP-130 in Cycle 0 indicate that the 3 mg dose level is sub-therapeutic, the 3 mg dose level will not be included in Cycle 1-4 assessment. This design feature will ensure that no patient with chemotherapy will be treated with sub-therapeutic dose of HSP-130.

The primary PD parameters of $AUEC_{ANC}$ results from Cycle 0 and DSN results from Cycle 1 will be assessed to determine appropriate doses for Phase 3 studies. Additional PD results may be assessed as appropriate.

Pharmacokinetic analysis:

Descriptive statistics including N, mean, SD, minimum and maximum for each PK parameter by treatment will be reported.

Safety analysis:

Treatment emergent adverse events will be summarized by system organ class and preferred terms. Descriptive statistics including N, mean, SD, minimum and maximum for numerical data, and counts and frequency for categorical data, will be tabulated for laboratory tests, and vital signs by treatment group. Grading of laboratory abnormalities will be according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (6).

PRINCIPAL CONTACTS

Clinical Protocol and Conduct Inquiries	PPD Global Clinical Operations PPD Office: +PPD Mobile: +PPD Fax: +PPD PPD, PhD Global Clinical Development PPD Office: +PPD Mobile: +PPD Fax: +PPD
Clinical Safety Inquiries	PPD, MD, PhD Global Clinical Development PPD Office: +PPD Mobile: +PPD
Reporting of Serious Adverse Events (SAEs)	Hospira Global Product Safety Phone: +PPD Email: PPD Global Product Safety Fax: +PPD

Note: Full contact details for all parties and individuals referenced above can be found in the Investigator Site File/Regulatory Binder.

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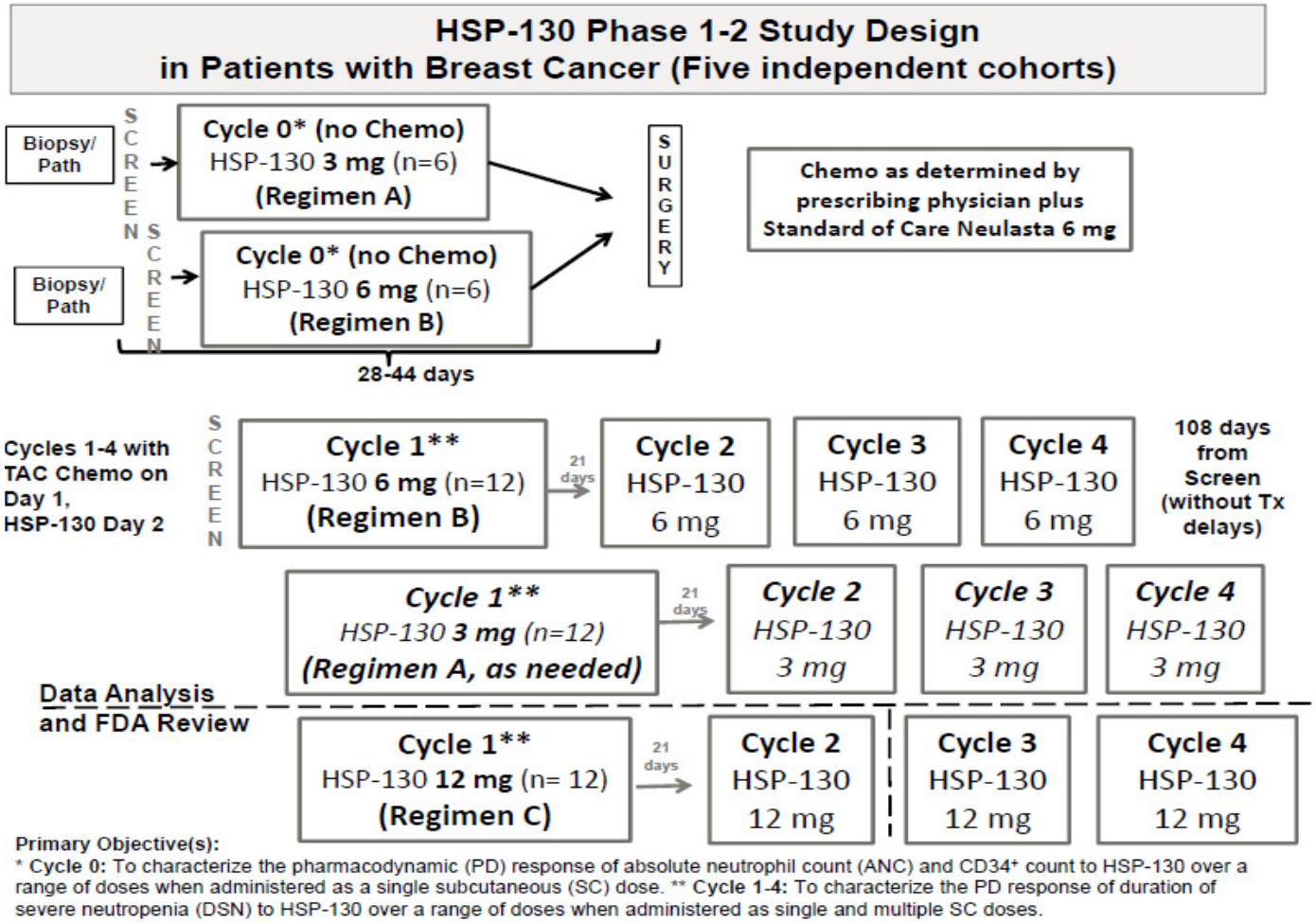
Figure 1 Study Design Schematic



Note that the 12 mg cohort will not be initiated until after discussion with the FDA as defined in Section 6.3.2

28-44 days are guideline time period based on site scheduling and procedures.

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Table 1. Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy

Evaluation	Screening	Site Visit									Follow-up Visit
Study Day	-14 to -1	1	2	3	5	7	9	11	14	20	30 (± 2)
Clinical Assessments/Activities											
Written Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical History	X										
Physical Examination	X										X
Body Weight & Height	X										
Vital Signs [a]	X	X	X	X	X	X	X	X	X	X	X
WHO Performance Status	X	X	X	X	X	X	X	X	X	X	X
CISNE [b]		X				X				X	X
FACT-N [c]		X								X	X
Pregnancy Test [d]	X										X
HSP-130 Administration		X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram	X										X
Chest X-ray (if none within 1 month)	X										
Laboratory Assessments [e]											

Table 1. Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy

Evaluation	Screening	Site Visit									Follow-up Visit
Study Day	-14 to -1	1	2	3	5	7	9	11	14	20	30 (± 2)
Clinical Chemistry	X			X		X		X		X	X
Hematology (including complete blood count + Platelets)	X			X		X			X	X	X
Serology (anti-HIV Abs)	X										
Urinalysis	X										X
Spot urine for protein/creatinine ratio (PCR)	X			X				X		X	X
Pharmacodynamic Sampling [f]		X		X	X	X	X	X	X		
Pharmacokinetic Sampling [g]		X	X	X	X	X	X	X	X		
Anti-HSP-130 antibody Sampling [h]		X							X	X	

a. Vital Signs will be measured pre-dose, at approximately the same time at Day 1, each day of PK/PD sampling (Day 2-Day 14), Day 20 and at Follow-up Visit

b. Clinical Index of Stable Febrile Neutropenia (CISNE) : assessment will be completed for each episode of febrile neutropenia

c. As available in local language

d. Serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization

e. The total blood volume for all laboratory assessments is approximately 100 mL

f. Pharmacodynamic sampling for absolute neutrophil count (ANC), $CD34^+$ count will be collected within 1 hour prior to dose administration and at 48, 96, 144, 192, 240, and 312 hours post-dose

g. Pharmacokinetic sampling will be collected within 1 hour prior to dose at Day 1, and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose

h. Anti-HSP-130 antibody sampling will be collected pre-dose on Day 1 as well as on Day 14 and Day 20.

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Table 2. Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg¥ SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Screening	Site Visit											Follow-up Visit[i] (Cycle 4)
Study Day	**-14 to -1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**11**	**12**	**15**	**20**	**30 (± 2)**
Clinical Assessments/Activities													
Written Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Medical History	X												
Physical Examination	X												X
Vital Signs [a]	X	X	X	X	X	X	X	X		X	X	X	X
WHO Performance Status	X	X	X	X	X	X	X	X		X	X	X	X
CISNE [b]		X					X						
FACT-N [c]		X											X
Pregnancy Test [d]	X												X
HSP-130 Administration [e]			X										
Adverse Events	X	X	X	X	X	X	X	X		X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X	X
12-lead Electrocardiogram	X												X
Chest X-Ray (if none within 1 month)	X												

Table 2. Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg[¥] SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Screening	Site Visit											Follow-up Visit[i] (Cycle 4)
Study Day	**-14 to -1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**11**	**12**	**15**	**20**	**30 (± 2)**
Chemotherapy		X											
Laboratory Assessments [f]													
Clinical Chemistry	X			X		X		X	X	X		X	X
Hematology (including complete blood count + platelets)	X			X		X		X	X	X	X	X	X
Serology (anti-HIV Abs)	X												
Urinalysis	X												X
Spot urine for protein/creatinine ratio (PCR)	X			X				X				X	X
Pharmacodynamic Sampling [g]			X		X	X	X	X		X	X		
Pharmacokinetic Sampling [h]			X	X	X	X	X	X		X	X		
Anti-HSP-130 antibody Sampling [i]			X									X	

[¥] Enrollment in the 12 mg cohort will occur only after

- review with the FDA of data from Cycle 0 cohorts, and the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and
- only if the exposure pattern of the PK/PD response suggest that higher doses are required. Additional details are available regarding the 12 mg cohort and associated stopping rules in section 6.3.2.

*If decision is made to carry out Regimen A in Cycles 1 and 4, subjects will follow same activities listed above

a. Vital Signs will be measured pre-dose, at approximately the same time at Day 2, and each day of PK/PD sampling (Day 3-Day 15), Day 18, Day 20, and at Follow-up Visit

b. Clinical Index of Stable Febrile Neutropenia (CISNE): assessment will be completed for each episode of febrile neutropenia
c. As available in local language
d. Serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization
e. In Cycles 1 and 4, subjects will receive treatment with HSP-130 on Day 2 (no less than 24 hours after administration of chemotherapy)
f. The total blood volume for all laboratory assessments is approximately 250 mL
g. Pharmacodynamic sampling for absolute neutrophil count (ANC) will be collected within 1 hour prior to dose administration and at 48, 96, 144, 192, 240, and 312 hours post-dose
h. Pharmacokinetic sampling will be collected within 1 hour prior to dose and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose
i. Anti-HSP-130 antibody sampling will be collected pre-dose on Day 2 and on Day 20
j. These assessments will be carried out at the end of Cycle 4 or at the time of subject termination during the planned course of the study

[redacted]

Hospira

Table 3. Schedule of Study Activities: Cycles 2 and 3 for Subjects Receiving 6 mg or 12 mg¥ SC injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Site Visit								
Study Day	**1**	**2**	**3**	**6**	**10**	**11**	**12**	**15**	**20**
Clinical Assessments/Activities									
Clinical Chemistry [a]			X	X	X	X	X		X
Hematology (including complete blood count + platelets) [a]			X	X	X	X	X	X	X
Vital Signs	X	X		X				X	X
WHO Performance Status	X	X		X				X	X
CISNE [b]		X							
FACT-N [c]		X							
HSP-130 Administration**		X							
Adverse Events	X	X		X				X	X
Concomitant Medications	X	X		X				X	X
Chemotherapy	X								

¥ Enrollment in the 12 mg cohort will occur only after

- review with the FDA of data from Cycle 0 cohorts, and the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and
- only if the exposure pattern of the PK/PD response suggest that higher doses are required. Additional details are available regarding the 12 mg cohort and associated stopping rules in section 6.3.2.

*If decision is made to carry out Regimen A in Cycles 2 and 3, subjects will follow the same activities listed above
** In Cycles 2-3, subjects will receive treatment with HSP-130 on Day 2 (no less than 24 hours after administration of chemotherapy). Dose levels to be administered in Cycle 1-4 will be determined from the results of Cycle 0. This determination will be based on the following considerations:

1. Evidence of effect of Regimen A (HSP-130 3 mg, single SC injection) on ANC and $CD34^+$ counts in Cycle 0 is commensurate as defined by the protocol with that observed for Regimen B (HSP-130, 6 mg, single SC injection). If data for subjects receiving Regimen A in Cycle 0 demonstrate lack

of effect or significantly diminished effect, Regimen A will not be brought forward to be studied further. Lack of effect of the lowest dose of HSP-130 studied in subjects not receiving a myelosuppressive chemotherapy regimen will preclude use in subjects receiving myelosuppressive chemotherapy (taxane/cyclophosphamide-based regimen, i.e., TAC).

2. Lack of safety concerns as defined by the Medical Monitor based on the specific safety considerations for any of the dose regimens.

a. On Days 3, 10, 11, and 12, blood samples will be collected for Clinical Chemistry and Hematology and does not necessitate a site visit.
b. Clinical Index of Stable Febrile Neutropenia (CISNE): assessment will be completed for each episode of febrile neutropenia
c. As available in local language

GLOSSARY OF ABBREVIATIONS

Abbreviation/Acronym	Definition
AEs	adverse events
ANC	absolute neutrophil count
ANC_E_{max}	maximum effect for ANC
ANC_T_{max}	time of maximum effect for ANC
ARDS	acute respiratory distress syndrome
$AUC_{0-\infty}$	area under the serum HSP-130 versus time curve from the time of dose administration to time infinity
AUC_{0-t}	area under the serum HSP-130 versus time curve from the time of dose administration to time of last measurable concentration
AUEC	area under the effect curve
$AUEC_{ANC}$	area under the effect curve for ANC
$AUEC_{CD34+}$	area under the effect curve for $CD34^+$
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD34+_E_{max}	maximum effect for $CD34^+$ count
CD34+_T_{max}	time of maximum effect for $CD34^+$ count
CFR	U.S. Code of Federal Regulations
CIN	chemotherapy-induced neutropenia
CISNE	clinical index for stable febrile neutropenia
CL	apparent clearance
C_{max}	maximum observed serum HSP-130 concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DSN	duration of severe neutropenia
E. Coli	*Escherichia coli*
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation/Acronym	Definition
EDC	electronic data capture
FACT-N	Functional Assessment of Cancer Therapy - Neutropenia
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FN	febrile neutropenia
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HIVAb	human immunodeficiency virus antibody
HRQOL	health-related quality of life
HSP-130	Hospira Pegylated Recombinant Human Methionyl G-CSF or Hospira pegylated filgrastim
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kD	kilodaltons
MASCC	Multinational Association for Supportive Care in Cancer
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	milligram
mL	milliliter
mPEG	monomethoxypolyethylene glycol
N	number of observations
NAb	neutralizing antibody
PCR	protein/creatinine ratio
PD	pharmacodynamics
PFS	pre-filled syringes
PK	pharmacokinetics
PS	performance status
PT	preferred term

Abbreviation/Acronym	Definition
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SPC	Summary of Product Characteristics
SMQ	standard MedDRA queries
SOP	standard operating procedure
TAC	docetaxel, doxorubicin, and cyclophosphamide
$t_{1/2}$	elimination half-life
TEAEs	treatment-emergent adverse events
T_{max}	time to maximum serum HSP-130 concentration
ULN	upper limit of normal
USPI	United States Package Insert
WBC	white blood cells
WHO	World Health Organization
WHO PS	World Health Organization Performance Status (also known as ECOG PS or Eastern Cooperative Oncology Group PS or Zubrod PS)
WMA	World Medical Association
λz	elimination rate constant

[redacted]

1 BACKGROUND AND RATIONALE

1.1 Background to the Disease

Neutropenia is a laboratory diagnosis and is defined as the reduction in the absolute number of neutrophils in the peripheral blood or circulation. Neutrophils are mature phagocytic leukocytes of the granulocyte series; are formed by bone marrow and released into circulation; are the predominant component of circulating white cells, and are the predominant leukocyte involved in inflammation. Circulating neutrophils actually represent only approximately 3% of the body's total neutrophil numbers, with the vast majority in the bone marrow reserve pool and the remainder in the tissue and marginated pool attached to vascular endothelial cells (7),(8).

Neutropenia is generally characterized as mild, moderate, or severe based on the circulating absolute neutrophil count (ANC) (7), (9), (10).

- Mild neutropenia: ANC 1.0-1.5 $\times 10^9$/L
- Moderate neutropenia: ANC 0.5-1.0 $\times 10^9$/L
- Severe neutropenia: ANC $< 0.5 \times 10^9$/L

In general, only subjects with severe neutropenia have been found to be at risk for major pyogenic infections and life-threatening infections, regardless of the underlying etiology of the neutropenia, congenital or acquired (11).

Myelosuppressive chemotherapy is an important iatrogenic cause of neutropenia. While within a given individual, many chemotherapeutic agents can be associated with neutropenia, there are a number of agents that are consistently associated with elevated risk for its development. These are listed in Table 4 and are consistent with the medical literature as well as national and international guidelines for management of chemotherapy-induced neutropenia (CIN) (9).

Low ANC increases the risk of fevers (febrile neutropenia) and life-threatening infections (12), (13). Febrile neutropenia is defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, categorized as Grades 3 to 5 as follows (6):

- Grade 3: ANC $< 1000/mm^3$ and a single temperature of $> 38.3°C$ (101°F) or a sustained temperature of $\geq 38°C$ (100.4°F) for > 1 hour
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

Table 4. Factors to Consider in Assessing Risk of a Febrile Neutropenic Episode in Patients Undergoing Cytotoxic Chemotherapy for Malignancy

Factor	Effect on Risk	Reported FN Rate (%)	95% CI (%)
Patient Characteristics			
Advanced age	Risk increases if age ≥ 65 years	--	--
ECOG PS	Risk increases if PS ≥ 2	--	--
Nutritional status	Risk increases if albumin < 35 g/L	--	--
Prior FN episode	Risk in cycles 2-6 is 4x greater if FNE occurs in cycle 1	--	--
Comorbidities	FN odds increase by 27%, 67%, and 125%, respectively, for 1, 2, or ≥ 3 comorbidities	--	--
Underlying malignancy	--	--	--
Cancer diagnosis [a]	--	--	--
Acute leukemia/MDS	--	85 to 95	--
Soft tissue sarcoma	--	27	19 to 34.5
NHL/myeloma	--	26	22 to 29
Germ cell carcinoma	--	23	16.6 to 29
Hodgkin lymphoma	--	15	6.6 to 24
Ovarian carcinoma	--	12	6.6 to 17.7
Lung cancers	--	10	9.8 to 10.7
Colorectal cancers	--	5.5	5.1 to 5.8
Head and neck carcinoma	--	4.6	1.0 to 8.2
Breast cancer	--	4.4	4.1 to 4.7
Prostate cancer	--	1	0.9 to 1.1
Cancer stage	Risk increases for advanced stage (≥ 2)	--	--
Remission status	Risk increases if not in remission	--	--
Treatment response	Risk is lowest if patient has a CR If patient has a PR, FN risk is greater for acute leukemia than for solid tissue malignancies FN risk is higher if persistent, refractory, or progressive disease despite treatment	--	--
Treatment for malignancy		--	--

Table 4. Factors to Consider in Assessing Risk of a Febrile Neutropenic Episode in Patients Undergoing Cytotoxic Chemotherapy for Malignancy

Factor	Effect on Risk	Reported FN Rate (%)	95% CI (%)
Cytotoxic regimen	Risk is higher with regimens that administer:	--	--
	Anthracyclines at doses ≥ 90 mg/m^2	--	--
	Cisplatin at doses ≥ 100 mg/m^2	--	--
	Ifosfamide at doses ≥ 9 g/m^2	--	--
	Cyclophosphamide at doses ≥ 1 g/m^2	--	--
	Etoposide at doses ≥ 500 mg/m^2	--	--
	Cytarabine at doses ≥ 1 g/m^2	--	--
	High dose-density (e.g., CHOP-14)	--	--
	Anthracycline + taxane + cyclophosphamide, or anthracycline + gemcitabine for breast cancer	--	--
Dose-intensity	Increased risk if > 85% of scheduled doses are administered [b]	--	--
Degree and duration of GI and/or oral mucositis	Risk is increased if NCI mucositis grade ≥ 3 (GI) or if peak OMAS score ≥ 2	--	--
Degree and duration of:		--	--
Neutropenia	ANC < 500/µL ≥ 7 days	--	--
Lymphopenia	ALC < 700/µL (ANC surrogate)	--	--
Monocytopenia	AMC < 150/µL (ANC surrogate)	--	--
Prophylactic use of WBC growth factors	Reduced risk for patients selected as in ASCO guideline	--	--

[a] Highest to lowest risk

[b] Note that the Panel recommends against routine decreases in dose-intensity as a means of preventing FN

ALC: absolute lymphocyte count; AMC: absolute monocyte count; ANC: absolute neutrophil count; ASCO: American Society of Clinical Oncology; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CR: complete response; ECOG: Eastern Cooperative Oncology Group; FN: fever and neutropenia; FNE: febrile neutropenic episode; GI: gastro intestinal; MDS: myelodysplastic syndrome; NCI: National Cancer Institute; NHL: non-Hodgkin lymphoma; OMAS: Oral Mucositis Assessment Scale; PR: partial response; PS: performance status; WBC: white blood cells.

Source: Reference (9).

Implications of CIN and febrile neutropenia are manifold and include infection and overwhelming sepsis and its associated complications, including death, increased risk for hospitalization as well as compromised oncologic outcomes including treatment delays, reduction in chemotherapeutic dose, or both. Neutropenia is a common dose-limiting adverse effect. As a result, patients can receive suboptimal cancer therapy leading to compromised

outcomes, including increased morbidity and mortality and decreased survival (11), (12), (13), (14), (15), (16). International guidelines for prevention and management of CIN include the consistent recommendation of use of supportive care with myeloid growth factors in patients undergoing myelosuppressive chemotherapy with a specified threshold of risk, generally of risk for at least 20% of patients receiving the myelosuppressive agent or regimen (7), (16), (17).

Endogenous granulocyte-colony stimulating factor (G-CSF) is the primary regulating factor for neutrophils (18). The G-CSF acts by binding to G-CSF receptors located on the cell surface of the whole neutrophil lineage, resulting in stimulated proliferation, differentiation, commitment, and end cell functional activation. Endogenous G-CSF is known to stimulate proliferation of the mitotic cells, to reduce the maturation time of the non-mitotic cells in the bone marrow and to prolong the life-span and enhance the function of mature neutrophils. Endogenous G-CSF is produced by different cell types including macrophages, monocytes, fibroblasts, stromal cells in bone marrow, and endothelial cells (7). Endogenous G-CSF is triggered by inflammatory agents as well as by lipopolysaccharide released from bacteria.

Recombinant human G-CSFs can vary slightly based on whether it is produced in *Escherichia coli* (*E. coli*) [filgrastim] or Chinese hamster ovary (CHO) cells [lenograstim]. The former is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Filgrastim is a water soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD) and is obtained from the bacterial fermentation of a strain of *E. coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. Also based on production in *E. coli*, filgrastim is non-glycosylated, in contrast to endogenous G-CSF, which is glycosylated (19).

Filgrastim has been shown to enhance neutrophil production and to mobilize hematopoietic stem cells from bone marrow to the blood in human subjects (19). Based on its circulating half-life, filgrastim must be given daily to prevent or treat CIN.

Protein pegylation is widely utilized to prolong the circulating half-life of biologic agents. Hospira has developed a pegylated G-CSF, referred to as HSP-130 (Hospira Pegylated Recombinant Human Granulocyte Colony-Stimulating Factor). The proposed pegylated recombinant human G-CSF is a covalent conjugate of recombinant methionyl G-CSF and a 20 kD monomethoxypolyethylene glycol (mPEG) molecule. The mPEG is covalently bound to the N-terminal methionyl residue of filgrastim.

The proposed clinical development program is designed to establish the safety and efficacy of HSP-130 as supportive care to decrease the incidence of infection in subjects with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia and to reduce the duration of neutropenia in patients with non-myeloid malignancies treated with cytotoxic/myelosuppressive agents.

1.2 Investigational Medicinal Products

The Investigational Medicinal Product, HSP-130, is a pegylated recombinant human methionyl G-CSF, also referred to as pegylated filgrastim. It is a conjugate of filgrastim and a 20 kD mPEG molecule. The mPEG is covalently bound to the N-terminal methionyl residue of filgrastim. For this study, 3 mg or 6 mg will be administered subcutaneously. If 12 mg of HSP-130 is determined to be appropriate to study, the 12 mg dose will be administered subcutaneously, as 2 concurrent injections of 6 mg on the same arm separated by approximately 2 to 3 inches.

1.3 Non-clinical Data

The nonclinical studies to support this Phase 1-2 clinical study have been completed and results summary is provided in the Investigational Brochure.

1.4 Clinical Experience

This is the first human study to be conducted with HSP-130. There is no clinical experience with HSP-130.

1.5 Rationale for the Study

1.5.1 Design Features

This is an open-label parallel group study characterizing the PD, PK, and safety of HSP-130 in subjects with non-distantly metastatic (non-Stage IV) breast cancer who have not previously received chemotherapy at any point prior to enrollment in this study (ZIN-130-1504).

There are two aspects of the study. In the initial part of the study, 6 subjects will be sequentially enrolled to receive HSP-130 treatment (3 mg or 6 mg by SC injection) without concomitant or background chemotherapy. This treatment setting will, therefore, be referred to as Cycle 0. Patients in Cycle 0 will receive HSP-130 during the period between biopsy and definitive surgery.

Hospira's rationale for choosing this setting includes optimizing the homogeneity of the study population. Factors potentially causing heterogeneity in the post-operative setting include:

- Variability in the postoperative clinical course of patients
- Known postoperative immunosuppression of variable degrees and duration
- Potential perioperative variable effects of endogenous G-CSF

Advice from experts in the field and review of published data has indicated that a period of approximately 1-1.5 months is not inconsistent with real world treatment intervals between biopsy and surgery. The post-biopsy/pre definitive surgery approach will, per protocol, not exceed 44 days. This maximum duration is based on a protocol-defined maximum of 14 days for screening, 20 days of study assessments, and the Day 30 (±2) Follow-up Visit. Further, with a

cooperative partnership between the surgeon(s) and principal investigator, this period might be further reduced.

The second group of subjects will receive up to 4 cycles of HSP-130, with concomitant background chemotherapy. Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Chemotherapy will consist of every 3 week taxane/cyclophosphamide-based regimen, i.e., docetaxel, doxorubicin and cyclophosphamide (TAC).

The initial component of the study with patients receiving HSP-130 at doses of 3 mg and 6 mg without concomitant background chemotherapy is based on the considerations of patient safety. Based on the preponderance of published non-clinical and clinical data for the class of pegylated filgrastim, it is most likely that a dose of 3 mg could be sub-therapeutic. Both ANC and $CD34^+$ will be assessed to address aspects of the known effect of pegylated filgrastim as a class on demargination of neutrophils as well as effect on the marrow, respectively.

A variety of both fixed and weight-based doses was evaluated in the development of US-approved Neulasta (20). The approved dose of 6 mg US-approved Neulasta provided adequate production of neutrophils and hence weight-based dosing was not required (1), (20), (21).

Assessment of PD and PK parameters after single and multiple doses of HSP-130 at 3 ascending doses (3 mg, 6 mg or 12 mg, with the latter only if agreed to after data review at 3 and 6 mg as detailed in Section 6.3.2.) will provide an adequate separation in doses to characterize the exposure/response sufficiently to support dosing recommendations in future clinical studies.

Based on the dose-response curve published by B. Yang and A. Kido (1), the average concentration (C_{av}) of pegfilgrastim (calculated from the time of pegfilgrastim administration to the time of ANC nadir) for the 6 mg dose was 72 ng/mL, which corresponds to 90% of maximum response (EC_{90}). For a 3 mg dose, the estimated C_{av} was about 21 ng/mL, which corresponds approximately 70% of maximum response (EC_{70}). The expected response for a 3 mg dose (EC_{70}) is 77.8% of that from a 6 mg dose (EC_{90}). It is expected that approximately 30% of patients receiving 3 mg of pegfilgrastim would have a C_{av} value below the EC_{50} value. Because the dose of 3 mg of HSP-130 is potentially sub-therapeutic in breast cancer patients, this dose will be tested in Cycle 0 without chemotherapy first. If the PD response (ANC and/or $CD34^+$) of 3 mg HSP-130 and 6 mg HSP-130 in Cycle 0 indicate that the 3 mg dose level is sub-therapeutic, the 3 mg dose level will not be included in Cycles 1-4 assessment. This design future will ensure that no patient with chemotherapy will be treated with sub-therapeutic dose of HSP-130.

As noted above, the second component of the ZIN-130-1504 study includes up to 4 cycles of HSP-130, with concomitant background chemotherapy. The basis for the selection of breast cancer for the current Phase 1-2 study in patients is multifactorial and includes the large clinical trial experience with pegylated filgrastim in breast cancer (22).

1.5.2 Study Population

Female, chemotherapy-naïve, non-distantly metastatic (non-Stage IV) breast cancer subjects aged ≥ 18 years will be selected for this study as an appropriate population to assess the PD, PK and safety properties of HSP-130. Study population is limited to women for this Phase 1-2 study based on the small total population numbers (approximately 36 to 48) and need for adequate homogeneity to inform dose selection for Phase 3 superiority and non-inferiority studies.

1.5.3 Dosing Regimen and Treatment Duration

Subjects receiving HSP-130 during Cycle 0 will receive a single dose of HSP-130 (3 mg or 6 mg) and be in the study for approximately 30 (± 2) days and will not receive concomitant background chemotherapy.

Subjects receiving HSP-130 during Cycles 1-4 will receive up to 4 doses of HSP-130 in the context 4 cycles of chemotherapy (≥ 21 days per cycle). Exclusive of chemotherapy-related treatment delays, these subjects will participate in the study for approximately 94 days (including Follow-up Visit).

1.5.4 Selection of Pharmacodynamic Endpoints

The mechanism of stimulation of the production of neutrophils by G-CSFs is well understood. The G-CSF acts by binding to G-CSF receptors located on the cell surface of the whole neutrophil lineage, resulting in stimulated proliferation, differentiation, commitment, and end cell functional activation. Endogenous G-CSF is known to stimulate proliferation of the mitotic cells, to reduce the maturation time of the non-mitotic cells in the bone marrow and to prolong the life-span and enhance the function of mature neutrophils. Endogenous G-CSF is produced by different cell types including macrophages, monocytes, fibroblasts, stromal cells in bone marrow, and endothelial cells (7). Both filgrastim and pegfilgrastim act on hematopoietic cells by binding to specific cell surface receptors, which in turn stimulate proliferation, differentiation and end cell functional activation to produce neutrophils (19), (23).

ANC is a direct measure of the therapeutic effect measured in the treatment of neutropenia. Assessment of $CD34^+$ count in Cycle 0 will address any differences in marrow response between 6 mg and 3 mg (a potentially sub-therapeutic dose) to limit the risk of treatment of subjects receiving myelosuppressive chemotherapy in Cycles 1-4 determined to have risk of ≥ 20% for febrile neutropenia (FN).

Cycle 0:

Area under the effect curve for ANC ($AUEC_{ANC}$) was selected as the primary endpoint for Cycle 0 because the production of neutrophils is the primary therapeutic effect measured in the treatment of neutropenia. Evaluation of ANC as a measure of PD for pegylated filgrastim is well established via clinical trials of pegfilgrastim (1), (23), (24), (25). Area under the effect curve is a more appropriate parameter than any measure at a single time because it assesses the overall response to the administered dose.

The sampling schedule for ANC and $CD34^+$ count is of sufficient density and duration to adequately characterize the PD response following single and multiple dose administration of HSP-130. The $AUEC_{ANC}$ from baseline through Day 20 after single dose provides a sufficient duration to characterize PD response to HSP-130 (1), (24), (25).

Secondary PD parameters include maximum effect for ANC (ANC_E_{max}), time of maximum effect for ANC ($ANC\ T_{max}$), area under the effect curve for $CD34^+$ ($AUEC_{CD34+}$), maximum effect for $CD34^+$ count ($CD34^+\_E_{max}$), time of maximum effect for $CD34^+$ count ($CD34^+\ T_{max}$).

Cycles 1-4:

Duration of severe neutropenia (DSN) was selected as the PD parameter for Cycles 1-4 to characterize the effect of HSP-130 in decreasing the neutropenic effect of myelosuppressive chemotherapy. Duration of severe neutropenia is defined as days with grade 4 neutropenia ($ANC < 0.5 \times 10^9/L$).

Primary PD parameter includes DSN in Cycle 1. Secondary PD parameters include DSN in Cycle 4, ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of febrile neutropenia, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour and $ANC < 1.0 \times 10^9/L$, incidence of severe neutropenia (grade 4, $ANC < 0.5 \times 10^9/L$) and time to ANC recovery (the first day with $ANC \geq 2.0 \times 10^9/L$ after any day with $ANC < 2.0 \times 10^9/L$) in Cycle 1 and Cycle 4.

1.5.5 Selection of Pharmacokinetic Endpoints

The sampling schedule for PK measurement will fully define the PK characteristics of the 3 doses of HSP-130 administered.

Cycle 0:

The primary PK endpoints are area under the serum HSP-130 versus time curve from the time of dose administration to time infinity ($AUC_{0-\infty}$) and the maximum observed serum HSP-130 concentration (C_{max}). The secondary PK parameters include area under the serum HSP-130 versus time curve from the time of dose administration to the time of last measurable concentration (AUC_{0-t}), the time of maximum serum HSP-130 concentration (T_{max}), elimination half-life ($t_{1/2}$), elimination rate constant (λ_z) and apparent clearance (CL). The sampling through Day 20 provides sufficient samples to calculate $AUC_{0-\infty}$, AUC_{0-t} and C_{max} for all the dose levels planned (1), (24), (25).

Cycles 1-4:

The primary PK endpoints are AUC_{0-t} and C_{max}. The secondary PK endpoints include $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λ_z, and CL. The sampling through Day 20 provides sufficient samples to calculate AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for all the dose levels planned.

1.6 Risk/Benefit

Chemotherapy naïve, non-distantly metastatic (non-Stage IV) breast cancer subjects with age ≥ 18 years will be enrolled for this study. It is expected that subjects will be getting the therapeutic benefit due to HSP-130 while participating in the study.

The general pharmacologic class risks associated with use of G-CSFs are informed by the US-approved Neupogen® Package Insert and US-approved Neulasta Package Insert and EU-approved Neulasta Summary of Product Characteristics include but are not limited to allergic reactions including systemic symptoms involving at least 2 body systems of skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia); splenic rupture which can present as left upper abdominal and/or shoulder tip pain with enlarged spleen or splenic rupture; acute respiratory distress syndrome (ARDS) presenting with fever, lung infiltrates or respiratory distress as this may be secondary to an influx of neutrophils to sites of inflammation in the lungs; sickle cell crisis in subjects with sickle cell disorders; leukocytosis and immunogenicity. Additional potential risks include cutaneous vasculitis, thrombocytopenia, capillary leak syndrome and cytokine release syndrome (19), (23).

A more detailed description of the side effects with the use of pegylated G-CSF is described in the US-approved Neulasta Package Insert and the EU-approved Neulasta Summary of Product Characteristics (See Appendix H and Appendix F, respectively) (23).

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Endpoints

2.1.1 Primary Objective (s)

Cycle 0:

- To characterize the PD response of ANC and $CD34^+$ count to HSP-130 at doses of 3 mg and 6 mg when administered as a single SC dose without chemotherapy to determine whether it is appropriate to study multiple doses of 3 mg with the context of background chemotherapy

Cycles 1-4:

- To characterize the PD response of duration of severe neutropenia (DSN) in Cycle 1 to HSP-130 over a range of doses when administered as single and multiple SC doses

2.1.2 Pharmacodynamic Endpoints

The PD endpoints are based on the following variables:

Cycle 0:

- **Primary Variable:** Area under the effect curve for ANC ($AUEC_{ANC}$)
- **Secondary Variables:** Maximum effect for ANC (ANC_E_{max}), time of maximum effect for ANC ($ANC\ T_{max}$), area under the effect curve for $CD34^+$ ($AUEC_{CD34+}$), maximum effect for $CD34^+$ count ($CD34+\_E_{max}$), time of maximum effect for $CD34^+$ count ($CD34+\ T_{max}$)

The PD variables will be calculated using non-compartmental methods.

Cycles 1-4:

- **Primary Variable:** Duration of severe neutropenia (DSN). DSN is defined as days with grade 4 neutropenia (ANC < 0.5×10^9/L) in Cycle 1
- **Secondary Variables:** DSN in Cycle 4. ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of FN, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour with ANC < 1.0×10^9/L, incidence of severe neutropenia (grade 4, ANC < 0.5×10^9/L) and time to ANC recovery (the first day with ANC ≥ 2.0×10^9/L after any day with ANC < 2.0×10^9/L) in Cycle 1 and Cycle 4

The PD variables will be calculated using non-compartmental methods.

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objective (s)

Cycle 0:

- To characterize the PK of HSP-130 at doses of 3 mg and 6 mg when administered as a single SC dose without background chemotherapy
- To characterize the safety of HSP-130 at doses of 3 mg and 6 mg when administered as a single SC dose without background chemotherapy

Cycle 1-4:

- To characterize the PD response of ANC to HSP-130 in Cycles 1 and 4 over a range of doses when administered as single and multiple SC doses
- To characterize the PK of HSP-130 in Cycles 1 and 4 over a range of doses when administered as single and multiple SC doses
- To characterize the safety of HSP-130 over a range of doses when administered as single and multiple SC doses

2.2.2 Pharmacokinetic Endpoints

The PK endpoints are based on the following variables:

Cycle 0:

- **Primary Variables:** Area under the serum HSP-130 versus time curve from the time of dose administration to time infinity ($AUC_{0-\infty}$) and the maximum observed serum HSP-130 concentration (C_{max})
- **Secondary Variables:** Area under the serum HSP-130 versus time curve from the time of dose administration to the time of last measurable concentration (AUC_{0-t}), the time of maximum serum HSP-130 concentration (T_{max}), elimination half-life ($t_{1/2}$), elimination rate constant (λz), and apparent clearance (CL)

The PK variables will be calculated using non-compartmental methods.

Cycles 1–4:

- **Primary Variables:** AUC_{0-t} and C_{max}
- **Secondary Variables:** $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λz, and CL

The PK variables will be calculated using non-compartmental methods.

2.3 Safety Variables

Enrolled subjects who receive at least one dose of HSP-130 will be included in the safety analyses. The safety variables to be assessed include adverse events (AEs), AEs of special interest, laboratory assessments and electrocardiogram (ECG) at Follow-up Visit at study end and as clinically indicated, vital signs, and physical examination. Please refer to Section 6.3.2 for additional detail regarding safety assessments and dose escalation criteria.

Cycle 0:

Subjects will be chemotherapy naïve and will not be receiving background chemotherapy during Cycle 0. Safety variables to be assessed include AEs, including AEs of special interest, laboratory assessments and including ECG at Follow-up Visit at study end and as clinically indicated, vital signs, and physical examination.

Cycles 1-4:

To begin full-dose chemotherapy on Day 1 of the next cycle (≥ Day 21 of the previous cycle), ANC must have recovered to ≥ 1.5 x 10^9/L and platelet counts to ≥ 100 x 10^9/L. If these requirements are not met, postponement of the following cycle for up to 2 weeks will be acceptable. Both ANC and platelets will be determined on Day 15 and on Day 20 of Cycles 1-4 by a central laboratory so that results were available at the beginning of the next cycle.

The following are generally accepted approaches to modification of chemotherapy regimens to be following in the context of febrile neutropenia or severe or prolong neutropenia with or without fever. In subjects who experience FN and/or ANC < 0.5 x 10^9/L for > 1 week, severe or cumulative cutaneous reactions, or severe (grade 3 or 4) peripheral neuropathy during therapy, the chemotherapy timing and dose will be modified as deemed appropriate by the treating physician. Changes in patients TAC chemotherapy regimen will be determined by the patients treating physician in the context of known TAC toxicity profile and management. Subjects who withdraw prior to Cycle 2 may be replaced to support the full complement subjects (minimum of 8 evaluable subjects) for primary endpoint data generation for Cycle 1.

It is recommended that rescue management for subjects who develop FN during the study be consistent with several recent publications (2), (3), (4) and recent Cochrane review (5). Management of FN should also include consideration of locale-driven susceptibility patterns.

2.4 Anti-HSP-130 Antibody Assessment

Cycle 0:

Blood samples (7.0 mL) for anti-HSP-130 antibodies assessment will be collected prior to dose on Day 1 (prior to dose), on Day 14, and on Day 20.

Cycles 1-4:

Blood samples (7.0 mL) for anti-HSP-130 antibodies assessment will be collected on Day 2 (prior to HSP-130 dose) and on Day 20 in Cycles 1 and 4.

2.5 Additional Assessments

2.5.1 Performance Status

Performance status (PS) is an assessment of a subject's level of function and capability of self-care and has repeatedly been shown to be an important prognostic factor for survival in several major cancer forms, e.g., breast cancer (26), ovarian cancer (27), small cell lung cancer (28), and non-small cell lung cancer (29). As a result, PS is consistently integrated into oncology clinical trial. The most widely used are Karnofsky's Scale of PS (30) based on a scale of 0 to 100 and the simpler scale, the Zubrod (also known as WHO or Eastern Cooperative Oncology Group [ECOG]) Scale of PS (31), (32). The WHO scale will be used in this protocol and will be assessed at each study visit per the Schedule of Study Activities in Tables 1-3 and is defined in Table 5.

Table 5. The WHO/Zubrod/ECOG Scale

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

2.5.2 Clinical Index of Stable Febrile Neutropenia

Chemotherapy-induced FN is a frequent, potentially life-threatening toxicity that predisposes patients with cancer to serious infections and limits the delivery of optimal therapeutic doses of chemotherapy. The rate of major complications in the context of FN is approximately 25% to 30%, and mortality is as high as 11% in some patient groups (33). Appropriate treatment of patients with FN also includes prevention of over-treatment of low-risk episodes of FN with resultant patient-centric stress, implications of antimicrobial over-treatment and burden to healthcare systems (34).

The most widely validated prognostic tool used to select low-risk patients with FN is the Multinational Association for Supportive Care in Cancer (MASCC) score, which has been shown to be more accurate than the Talcott classification (35), (36), (37).

As has been pointed out by Carmona-Bayonas et al (2015) (2), these models are not specific to patients with solid tumors. In addition, the ability of the MASCC score to predict serious complications is not optimal, because they occur in up to 9% to 15% of patients predicted to be at low risk (35), (38).

In response to this perceived need, Carmona-Bayonas et al (2) developed the Clinical Index of Stable Febrile Neutropenia (CISNE), with 6 explanatory variables associated with serious complications: WHO performance status ≥ 2 (2 points), chronic obstructive pulmonary disease (1 point), chronic cardiovascular disease (1 point), mucositis of grade ≥ 2 (National Cancer Institute Common Toxicity Criteria; 1 point), monocytes < 200 per µL (1 point), and stress-induced hyperglycemia (2 points). These factors were integrated into a score ranging from 0 to 8, which classifies patients into 3 prognostic classes: low (0 points), intermediate (1 to 2 points), and high risk (≥ 3 points). The validation study was published in early 2015 based on the outcomes of 1,133 patients recruited from Sept 2012 to July 2014 with seemingly stable FN from 25 hospitals (24 Spain, 1 Chile).

Complication, mortality, and bacteremia rates by risk category are summarized in Table 6. Areas under the receiver operating characteristic curves in the validation subset were 0.652 (95% confidence interval [95% CI], 0.598 to 0.703) for Talcott, 0.721 (95% CI, 0.669 to 0.768) for MASCC, and 0.868 (95% CI, 0.827 to 0.903) for CISNE (P = 0.002 for comparison between CISNE and MASCC).

With a cutoff of ≥ 3 points, CISNE showed good discriminatory power to predict major complications, with the following parameters: sensitivity, 77.7%; specificity, 78.4%; Positive Predictive Value (PPV), 36.1%; Negative Predictive Value (NPV), 95.7%; Positive likelihood ratio (pLR), 3.6; and Negative likelihood ratio (nLR), 0.28.

The use of the CISNE is potentially and important tool in decision making in patient experiencing febrile neutropenia and will be assessed prospectively in the study per the Schedules of Study Activities in Tables 1-3, i.e., on Days 1, 7, 20, and 30 (Follow-up Visit) for subjects in Cycle 0; on Days 1 and 8 for Cycles 1 and 4; and on Day 2 for Cycles 2 and 3 based on country-specific translation availability.

Table 6. Outcomes by CISNE by Risk Categories (n = 1,133)

Risk Category (Class)	Training Subsets	Validation Subsets
Complications		
I (0 points)	1.1	1.1
II (1-2 points)	6.1	6.2
III (≥ 3 points)	32.5	32.5
Mortality		
I (0 points)	0.0	0.0
II (1-2 points)	1.6	0.0
III (≥ 3 points)	4.3	3.1
Bacteremia		
I (0 points)	3.2	9.1
II (1-2 points)	9.7	9.0
III (≥3 points)	17.6	15.5

2.5.3 Functional Assessment of Cancer Therapy – Neutropenia

The Functional Assessment of Cancer Therapy - Neutropenia (FACT- N) is widely used and validated self-report instrument to assess neutropenia-specific concerns and health-related quality of life (HRQOL) (39), (40). Tools to assess HRQOL are incorporated less commonly in Phase 1 or 2 studies than in Phase 3 studies. However, this will be assessed in the current study per the Schedule of Study Activities in Tables 1-3, i.e., on Days 1, 20, and 30 (Follow-up Visit) for subjects in Cycle 0; on Day 1 and at Follow-up Visit for Cycles 1 and 4; and on Day 2 for Cycles 2 and 3 to help assess the variables included in the subject assessment based on first use in humans of this specific pegylated filgrastim. These will be assessed based on country-specific translation availability.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an open-label, parallel group study characterizing the PD, PK, and safety of HSP-130 in subjects with non-distantly metastatic (non-Stage IV) breast cancer who have not previously received chemotherapy at any point prior to enrollment in this study. The dose groups of 3 mg, 6 mg, and 12 mg for HSP-130 are selected for the purpose of the study. However, 12 mg will only be studied, after discussion with the FDA, as defined in Section 6.3.2.

There are two aspects of the study. In the initial part of the study, 6 subjects will be sequentially enrolled to receive HSP-130 treatment (3 mg or 6 mg by SC injection) without concomitant or background chemotherapy. This treatment setting will, therefore, be referred to as Cycle 0. Patients in Cycle 0 will receive HSP-130 during the period between biopsy and definitive surgery.

The second group of subjects will receive up to 4 cycles of HSP-130, with concomitant background chemotherapy. Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Chemotherapy will consist of every 3 week taxane/cyclophosphamide-based regimen, i.e., TAC.

Specifics of these two groups are addressed below.

Subjects in Cycle 0:

Subject eligibility will be determined during a 14-day Screening Period. Eligible subjects will be enrolled sequentially to each of the HSP-130 dose groups as follows:

Regimen A: HSP-130, 3 mg, single SC injection in the deltoid region (n = 6)

Regimen B: HSP-130, 6 mg, single SC injection in the deltoid region (n = 6)

Dose escalation from Regimen A to B will be based on safety assessments in the first 5 evaluable subjects receiving Regimen A. This will include assessment of vital signs, concomitant medications, laboratory assessments including chemistry and hematology (complete blood count [CBC] and platelets), ECG, physical exam, and any AEs occurring post-dose administration through Day 30. The specific safety criteria for assessment for dose escalation are listed in Section 6.3.2 of the protocol. If, based on these assessments, there is no contraindication for dose escalation, screening for the subsequent dose level (Regimen B) can be initiated.

In Cycle 0, Day 1 is the day that the subject receives HSP-130. Subjects obtain a baseline assessment of ANC and $CD34^+$ count on Day 1 prior to receipt of HSP-130. Subjects will return for ANC, $CD34^+$ measurement, and PK assessment for up to a maximum of 7 visits after HSP-130 dosing.

After completion of Cycle 0, each of the subjects in these dosing groups will have completed their participation in assessment of HSP-130. The site will be offered reimbursement for treatment with EU-approved Neulasta in accordance with local standard of care by the Investigator with subsequent non-study chemotherapy regimen.

Assessment of Regimen A (3 mg) for Cycles 1-4 will be conducted as follows:

Based on the dose-response curve published by B. Yang and A. Kido (1), the average concentration (C_{av}) of pegfilgrastim (calculated from the time of pegfilgrastim administration to the time of ANC nadir) for the 6 mg dose was 72 ng/mL, which corresponds to 90% of maximum response (EC_{90}).

For a 3 mg dose, the estimated C_{av} was about 21 ng/mL, which corresponds approximately 70% of maximum response (EC_{70}). The expected response for a 3 mg dose (EC_{70}) is 77.8% of that from a 6 mg dose (EC_{90}).

It is expected that approximately 30% of subjects receiving 3 mg of pegfilgrastim would have a C_{av} value below the EC_{50} value. Because the dose of 3 mg of HSP-130 is potentially sub-therapeutic in breast cancer patients, this dose will be tested in Cycle 0 without chemotherapy first.

If the PD response (ANC and/or $CD34^+$) of 3 mg HSP-130 and 6 mg HSP-130 in Cycle 0 indicate that the 3 mg dose level is sub-therapeutic, the 3 mg dose level will not be included in Cycles 1-4 assessment. This design feature will ensure that no subject with chemotherapy will be treated with sub-therapeutic dose of HSP-130.

If, however, the individual PD measurement (ANC and/or $CD34^+$) of the treatment with HSP-130 3 mg in Cycle 0 is commensurate with that of 6 mg, as defined by the protocol, then treatment with Regimen A with background chemotherapy will be initiated.

Subjects in Cycles 1-4:

When enrollment of the 6 subjects receiving Regimen B in Cycle 0 is completed, an additional 12 subjects will be enrolled on Regimen B and entered in Cycles 1-4 as defined below. Eligible subjects will be enrolled sequentially to each of the HSP-130 dose groups as follows:

> **Regimen B:** HSP-130, 6 mg, single SC injection in the deltoid region, at least 24 hours after administration of chemotherapy in Cycle 1, Cycle 2, Cycle 3, and Cycle 4 (n=12).
>
> **Potential Regimen A (3 mg) with background chemotherapy:** Inclusion of this cohort will be based on assessment of comparability between Regimens A and B in Cycle 0 for ANC and $CD34^+$ as defined above. If performed, this regimen will be HSP-130, 3 mg, single SC injection in the deltoid region, at least 24 hours after administration of chemotherapy in Cycle 1, Cycle 2, Cycle 3, and Cycle 4 (n=12), as appropriate.

While noted in the protocol schema which is included for completeness, the 12 mg cohort will not be initiated until Hospira has analyzed the data from the Cycle 0 for 3 mg and 6 mg

cohorts and the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and reviewed the results with the FDA. Escalation to 12 mg will only proceed if the exposure pattern of the PK/PD responses suggests that higher doses are required. Please see section 6.3.2 for additional details.

During Cycles 1-4 for each of the regimens, subjects will receive treatment with HSP-130 at 24 hours after administration of chemotherapy (Day 2). Subjects will return for ANC measurement and PK assessment for up to an additional 7 visits after dosing.

Subjects will return for a Follow-up Visit 30 (±2) days after the dose of HSP-130 in Cycle 4.

3.2 Number of Sites and Subjects

Subjects will be enrolled at hospital sites (approximately 10 sites) within Europe.

A total of 24-36 patients will be enrolled initially; a further 12 patients totaling approximately 36-48 patients will be treated if the 12 mg cohort is enrolled, as defined in Section 6.3.2.

- The number of 24 patients includes 12 patients in Cycle 0 and 12 patients in the Cycles 1-4 6 mg cohort.
- The number of 36 patients includes the additional 12 patients if the second 3 mg cohort is included in the Cycles 1-4 part of the study.
- The number of 48 patients includes the potential for 12 patients in the 12 mg cohort if, after review of the data in the up to 36 patients with the FDA, a decision is jointly made based on the exposure pattern of the PK/PD responses that higher doses are required.

Approximately 12 subjects will be enrolled into two cohorts to receive ascending doses of HSP-130 (6 subjects on Regimen A [3 mg] and 6 subjects on Regimen B [6 mg]) without background chemotherapy.

Twelve subjects will be enrolled into 6 mg cohort in the setting of background chemotherapy. As mentioned, enrollment in a 12 mg cohort will not be initiated until criteria addressed in section 6.3.2 are met.

An additional 12 subjects will be enrolled into Regimen A (3 mg) as defined in Section 1.5.1.

3.3 Estimated Study Duration

Subjects receiving HSP-130 during Cycle 0 will receive a single dose of HSP-130 (3 mg or 6 mg) and be in the study for approximately 30 (± 2) days and will not receive concomitant background chemotherapy. Patients in Cycle 0 will receive HSP-130 during the period between biopsy and definitive surgery.

Subjects receiving HSP-130 during Cycles 1-4 will receive up to 4 doses of HSP-130 in the context of 4 cycles of chemotherapy (≥ 21 days per cycle). Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Each of these subjects will have treatment duration, if there

are no chemotherapy-related treatment delays, of approximately 108 days (including Screening Period and Follow-up Visit).

[redacted]

4 STUDY POPULATION SELECTION

4.1 Study Population

Subjects will undergo screening procedures within 14 days prior to initial HSP-130 administration. Subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the study.

4.2 Inclusion Criteria

A subject will be eligible for study participation if all of the following criteria are met at Screening:

1. Is informed, has been given ample time and opportunity to read about participation in the study and has signed and dated the written informed consent form approved by an Independent Ethics committee (IEC) prior to any study related activities

2. Females ≥ 18 years

3. Histologically confirmed and documented invasive breast cancer

4. Breast cancer without evidence of distant metastases (non-Stage 4) based on staging work-up

5. Chemotherapy naïve, who have not received chemotherapy in the neoadjuvant setting and who are candidates for chemotherapy in the adjuvant setting of taxane/cyclophosphamide-based regimen, i.e., TAC, as background chemotherapy

6. Zubrod/WHO/ECOG performance status ≤ 2

7. Adequate bone marrow, hepatic, and renal function reserve as evidenced by:

    a. Hemoglobin ≥ 10 mg/dL

    b. ANC ≥ 1.5 x 10^9/L

    c. Platelet count of ≥ 100 x 10^9/L

    d. Total bilirubin ≤ 2 mg/dL

    e. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 3 x the upper limit of normal (ULN) of the reference lab

    f. Serum creatinine of ≤ 1.5 x ULN for reference lab or estimated glomerular filtration rate (eGFR) of ≥ 60 mg/min

8. Body mass index (BMI) of 19 to 40 kg/m^2, inclusive

9. Subjects of childbearing potential, and their partners, agree to pregnancy prevention throughout the duration of the study (through the Follow-up Visit). Specific type of pregnancy prevention should be discussed with, and acceptable to, the treating oncologist in the context of the tumoral hormone receptor status. Subjects and their partners must agree to use of an effective method of contraception, to avoid impregnation of females throughout the course of the study

   Medically acceptable forms of birth control can include, with approval of the treating physician:

   a. Barrier methods (condom or diaphragm with spermicide)

   b. Intrauterine device (IUD)

   c. Hormone contraceptives (such as oral [pill], injection, skin patch, implant, cervical ring)

   d. Subjects using oral contraceptives must be on a stable regimen for at least 3 months prior to Screening. Sexually active subjects must use contraception while on HSP-130 from admission to the final Follow-up Visit

10. Able to understand verbal or written instructions and comply with all study requirements, to communicate effectively with study personnel and is available for the planned duration of the study

4.3 Exclusion criteria

A subject will NOT be eligible for study participation if any of the following criteria are met at Screening:

1. Previous G-CSF exposure, including filgrastim, lenograstim, pegfilgrastim, lipegfilgrastim, granulocyte/macrophage colony stimulating growth factor (GM-CSF), or any other branded or biosimilar G-CSF

2. Prior autologous stem cell harvest of any type

3. Drug sensitivity, allergic reaction, or known hypersensitivity or idiosyncratic reaction to *E. coli*-derived proteins, filgrastim, other G-CSFs, or pegylated agents

4. Known hypersensitivity to docetaxel, polysorbate 80, or doxorubicin

5. For subjects receiving doxorubicin, no concurrent use of inhibitors and inducers of CYP3A4, CYP2D6, and/or P-gp or with trastuzumab due to increased risk of cardiac dysfunction

6. Chemotherapy other than that included in this study (taxane/cyclophosphamide-based regimen, i.e., TAC) or neoadjuvant chemotherapy; or known immunosuppressive agents including chronic oral corticosteroid use, or radiation therapy within 4 weeks of first dose

of HSP-130, prior bone marrow or stem cell transplantation, or malignancy within 5 years

7. Known $HER2^{+}$ (overexpressing breast cancer)

8. Known triple negative (estrogen receptor-negative, progesterone receptor-negative and HER2-negative) breast cancer

9. ≥ Grade 2 underlying neuropathy

10. Current diagnosis of active tuberculosis or other severe infection, such as sepsis, abscesses or opportunistic infections

11. Treatment with systemically active antibiotics within 72 hours before chemotherapy

12. Known infection with HIV

13. Known sickle cell disease

14. Known severe persistent drug-induced myelosuppression

15. New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, clinically significant ECG abnormalities) or MI within the previous 6 months before the first administration of HSP-130

16. Any malignancy other than breast cancer, with exception of adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ, within 5 years before the first administration of the HSP-130

17. Current or recent treatment (within 30 days before the first administration of the HSP-130) with any other investigational medicinal product

18. Pregnancy or lactation; Subjects planning to be pregnant or to breastfeed before, during, or within 12 months after administration of the HSP-130 are not permitted to enroll in the study

19. Received a live, live-attenuated, or non-live vaccine within 4 weeks before the first administration of the HSP-130

20. Patient has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding or clinical lab finding giving reasonable suspicion of a disease or condition that contraindicated the use of an HSP-130, or patient is high risk for treatment complication

4.4 Inclusion of Subjects Incapable of Informed Consent

Subjects incapable of giving informed consent will not be enrolled in this study.

4.5 Recruitment Methods

Recruitment methods that will be employed include, but are not limited to, advertising, and use of the clinical unit database to identify potential candidates for this study.

5 STUDY TREATMENT

5.1 CCI

5.1.1 CCI

CCI

5.1.2 CCI

CCI

CCI

[redacted]

5.1.3 Shipping, Storage, Retention, and Handling

HSP-130 must be stored at 2° to 8°C (36° to 46°F). Do not freeze or shake. HSP-130 should be protected from light, so must be stored in its carton until usage. The investigational products are for investigational use only and are to be used only within the context of this study. The drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or retained as a reserve sample.

5.1.4 Replacement Procedures for Investigational Medicinal Product

Sufficient HSP-130 will be shipped to the investigative site prior to the start of the study such that replacement supplies should not be required.

5.1.5 Accountability, Destruction, and Return of Study Supplies

The site pharmacist, or designated qualified personnel, will verify that HSP-130 supplies are received intact and in the correct amounts. This will be documented by signing and dating the shipping request form and returning a copy to Hospira or its designee. An accurate running inventory of HSP-130 supplies will be kept by the site, including the amount of drug dispensed and the date HSP-130 was dispensed for each subject. Overall accountability of HSP-130 supplies will be performed throughout the study and at the site closeout visit, and verified by the study monitor. All used and unused supplies must be inventoried and accounted for by the study monitor. When notified by Hospira that it is appropriate, all used, partially used, or unused PFS may be destroyed according to site-specific standard operating procedure (SOP) for clinical supply destruction after accountability has been completed by the study monitor.

5.1.6 Unblinding Procedures

This is an open-label study; therefore, this section is not applicable.

5.1.7 Dosage, Preparation, Administration, Schedule, and Compliance

The doses of HSP-130 to potentially be administered in this study are 3 mg, 6 mg and 12 mg. Inclusion of the 12 mg dose will only occur as defined in Section 6.3.2. Each subject will receive one of the following: 3 mg, 6 mg [or 12 mg] of HSP-130 as SC injection on Study Day 1. Please refer to Section 3.1 for detailed description of the administration schedule.

HSP-130 will be administered in the morning at approximately 8.00 on Day 1 in Cycle 0 and at 24 hours after chemotherapy in Cycle 1-4. HSP-130 will be administered by qualified medical personnel. The time of drug administration will be recorded to the nearest minute in each period.

Before administration, HSP-130 formulation should be inspected visually for particulate matter. Only a solution that is clear and colorless to slightly yellow should be injected.

Excessive shaking may aggregate pegylated G-CSF, rendering it biologically inactive.

The syringe should be allowed to reach room temperature before injecting.

For detailed instructions on preparation and proper use of HSP-130, see Pharmacy Manual.

Treatment compliance will be ensured by the following study procedures:

- HSP-130 will be administered by a qualified health care professional.
- HSP-130 administration will be recorded in the source documents and entered in the appropriate section of the electronic Case Report Form (eCRF). Any problems with the injection will be recorded in the source documents and in the eCRFs.

5.1.8 Treatment of Overdose

This is first use of HSP-130 in humans. The maximum amount of HSP-130 that can be safely administered has not been determined. Hence, a dose escalating design has been planned to evaluate the safety of the product in the previous dose before administering the next higher dose.

As per Neulasta Package Insert, pegylated G-CSF overdosage can cause leukocytosis, which should be managed with discontinuation or reduction of pegylated-G-CSF dosage. The duration of leukocytosis ranged from 6 to 13 days. The effectiveness of leukapheresis in the management of symptomatic individuals with pegylated-G-CSF-induced leukocytosis has not been studied (23).

5.2 Subject Obligations

In addition to the requirements of the study, subjects will also be required to participate in a Follow-up Visit 30 (± 2) days after HSP-130 administration in Cycle 4, as described in the Section 6.3.4. The subject must continue to comply with the protocol requirements from the time of final visit (Day 20) until the time of the Follow-up Visit (Day 30 [± 2]).

5.3 Definition of End of Study

The end of study is defined as the day the last subject completes the Follow-up Visit, 30 days after last dose of HSP-130, in Cycle 4 or is discontinued.

6 TREATMENT PROCEDURES

6.1 Subject Informed Consent

Prior to any study-related activities, an Institutional Review Board (IRB)/IEC approved Informed Consent Form (ICF) must be signed and personally dated by the subject. The format and content of the ICF and subject information sheet must be agreed upon by the Principal Investigator(s), appropriate IRB/IEC and Hospira and/or designee, and include as a minimum the elements of consent described in International Conference on Harmonization for Good Clinical Practice (ICH E6, GCP), and FDA 21CFR§50.25. The ICF should be available in the language of the potential subject. The risks and benefits of participating in the study will be explained by the study investigator/delegate and all questions asked by the subject will be addressed before the subject signs the ICF. The time and date of the informed consent process/discussion/signing taking place will be recorded in the source documents.

It is the Investigator's responsibility to obtain consent only after the subject has received an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any study procedures are started. The subject should be given a copy of the IRB/IEC-approved ICF. The original copy of the signed and dated ICF must be retained in the clinic's records, and is subject to inspection by representatives of Hospira, and/or representatives from regulatory authorities. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed and dated copy. Elements of Informed Consent are specified in Appendix C.

6.2 Study Activities

6.2.1 Subject Demographics

Basic demographic information including date of birth, sex, ethnicity, and race will be recorded at the Screening visit.

6.2.2 Medical History

A complete medical history, including alcohol, nicotine-containing product, and drug abuse histories, will be recorded at Screening.

The medical history obtained on Screening will serve as the baseline for clinical assessment.

6.2.3 Prior and Concomitant Therapy Collection

All medications (prescription and non-prescription drugs) taken within 7 days (or 5 half-lives, whichever is longer) prior to Screening visit will be recorded at Screening, and at each study visit through end of the study.

All medications taken will be documented on the source document and recorded on the eCRF.

6.2.4 Physical Examination

A physical examination will be performed at Screening and at the Follow-up Visit (after Cycle 0 and after Cycle 4) or upon subject discontinuation. Physical examination will specifically include physical assessment of the spleen.

Height and weight, without shoes, will be measured at Screening only.

The physical examination performed at Screening will serve as the baseline physical examination for clinical assessment. Any changes to or worsening of existing physical examination findings, or new abnormal physical examination findings after dosing will be recorded as AEs per the Investigator's judgment.

6.2.5 Vital Signs

Body temperature (tympanic or axillary), heart rate (sitting), blood pressure (sitting systolic and diastolic) and respiratory rate will be measured at Screening, at each study visit in Cycles 0-4 (at approximately the same time of each day at each visit) and at Follow-up Visit after Cycle 0 and after Cycle 4 or upon subject discontinuation.

Vital signs should be measured pre-dose on the dosing day (Day 1 in Cycle 0; Day 2 in Cycles 1-4). Vital signs should be recorded prior to collection of blood samples for ANC measurement and PK assessment. The last available vital sign measurements prior to the start of HSP-130 will serve as the baseline measurements for clinical assessment.

Blood pressure and pulse rate will be measured after the subject has been sitting at rest for at least 5 minutes.

6.2.6 12-Lead Resting ECG and Chest X-ray

A 12-lead resting ECG will be obtained at Screening and at the Follow-up Visit after Cycle 0 and after Cycle 4 or upon subject discontinuation and read by qualified site personnel.

Chest X-ray will be obtained at Screening and read by qualified site personnel.

6.2.7 Adverse Event Monitoring

Recording of any AEs will proceed as documented in Section 8 of this protocol.

6.2.8 Clinical Laboratory Tests

Samples will be obtained for the central clinical laboratory tests (Clinical chemistry and Hematology) as outlined in Table 8 and in the Schedule of Study Activities (Tables 1-3).

Table 8 Clinical Laboratory Tests

<table>
<tr><th>Hematology</th><th colspan="2">Clinical Chemistry</th></tr>
<tr><td rowspan="6">Complete Blood Count (including):
Red blood cell (RBC) count
White blood cell (WBC) count
Hematocrit
Hemoglobin
Neutrophils*
Lymphocytes*
Monocytes*
Basophils*
Eosinophils*
Platelet count
(estimate not acceptable)</td><td>Blood urea nitrogen
Alanine aminotransferase
Aspartate aminotransferase
Alkaline phosphatase
Lactate dehydrogenase
Gamma glutamyl transpeptidase</td><td>Total protein
Albumin
Creatinine
Glucose
Phosphate
Uric acid</td></tr>
<tr><td>Pregnancy Test:</td><td>Immunogenicity:</td></tr>
<tr><td>Serum pregnancy test (at Screening and at Follow-up Visit)**</td><td>Anti-HSP-130 antibodies testing</td></tr>
<tr><td colspan="2">Serology: Screening only</td></tr>
<tr><td colspan="2">Serology (anti-HIVAb)</td></tr>
<tr><td colspan="2">Urinalysis: specific gravity, pH, protein, glucose, ketones, blood, leukocyte esterase, nitrite, bilirubin, urobilinogen, WBC, and RBC</td></tr>
<tr><td></td><td colspan="2">Spot urine for protein/creatinine ratio (PCR)</td></tr>
</table>

*absolute counts and percentage
** serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization

For subjects enrolled in Cycle 0, samples will be obtained for clinical chemistry at Screening, Days 3, 7, 11, 20, and at Follow-up Visit. For subjects enrolled Cycles 1 and 4, samples will be obtained for clinical chemistry at Screening and at Days 3, 6, 10, 11, 12, 20, and at the Follow-up Visit after Cycle 4 or upon subject discontinuation. In addition, samples will be collected for clinical chemistry on Days 3, 6, 10, 11, 12, and 20 in Cycles 2 and 3.

For subjects in Cycle 0, samples will be obtained for hematology at Screening, Day 3, Day 7, Day 14, Day 20, and Follow-up Visit. For subjects in Cycles 1-4, samples will be obtained for hematology at Screening, and on Days 3, 6, 10, 11, 12, 15, 20, and at the Follow-up Visit after Cycle 4 or upon subject discontinuation. In addition, samples will be obtained for hematology on Days 3, 6, 10, 11, 12, 15, and 20 in Cycles 2 and 3. For subjects in Cycle 0, Cycles 1 and 4, samples will be obtained for urinalysis at Screening, and at Follow-up Visit.

A certified central laboratory will be used to process and provide results for the clinical laboratory tests. The baseline laboratory test results for clinical assessment of a particular analyte will be defined as the last measurement prior to the initial dose of HSP-130.

The total blood volume drawn for clinical laboratory outlined above for all visits will be approximately 100 mL for subjects enrolled in Cycle 0 and 250 mL for subjects enrolled in Cycles 1-4, respectively.

Sample collection, handling, and shipment instructions are provided in the Laboratory Manual supplied to the site.

Additional laboratory tests will be obtained if clinically significant abnormalities are present on the previous evaluation. Clinically significant abnormalities observed after HSP-130 administration are to be followed to resolution (i.e., become stable, return to baseline or are explainable). All abnormal laboratory results are to be coded for clinical significance per the judgment of the Investigator.

Laboratory abnormalities will be considered as AEs only if they result in discontinuation from the study, necessitate therapeutic intervention, and/or if the Investigator considers them to be AEs. Grading of laboratory abnormalities will be according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (6).

6.2.9 HIVAb Testing

Subjects will have blood tested by a certified laboratory for the presence of HIVAb at Screening. Only those subjects negative for the presence of antibodies will be allowed to enroll in the study. This exclusion is based on the fact that the current study is intended to assess the effect of HSP-130 in subjects undergoing myelosuppressive chemotherapy and response to treatment may be confounded in this setting. The results of the HIVAb testing will be retained by the study site under confidential restriction.

6.2.10 Anti-HSP-130 Antibody Testing

Cycle 0:

Blood samples for anti-HSP-130 antibody testing will be collected by venipuncture into 7 mL evacuated collection tubes on Day 1 (prior to dose), on Day 14, and on Day 20.

Cycle 1-4:

Blood samples for anti-HSP-130 antibody testing will be collected by venipuncture into 7 mL evacuated collection tubes on Day 2 (prior to HSP-130 dose) and on Day 20 in Cycles 1 and 4.

Blood samples for antibody analysis will be collected - 7 mL of blood to provide approximately 3 mL serum. The serum will be split into 3 polypropylene cryovials (1 mL each). One cryovial will be used for the analysis and 2 cryovials will be retained as a backup.

6.2.11 Pregnancy Test

A pregnancy test will be performed for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization at Screening and at the Follow-up Visit after Cycle 0 and after Cycle 4.

6.2.12 Total Blood Volume to be Collected During the Study

For subjects who enroll in Cycle 0 group the total blood volume sampled is approximately 224 mL, which breaks down as follows:

- 100 mL of blood collected for clinical laboratory assessments
- 32.9 mL of blood collected for PD assessments
- 70 mL of blood collected for PK analyses
- 21 mL of blood collected for anti-HSP-130 antibody testing

For subjects enroll in Cycles 1-4 group the total blood volume sampled is approximately 456 mL, which breaks down as follows:

- 250 mL of blood collected for clinical laboratory assessments
- 37.8 mL of blood collected for PD assessments
- 140 mL of blood collected for PK analyses
- 28 mL of blood collected for anti-HSP-130 antibody testing

Total blood volume for subjects will include an additional 10-15 mL taken for pregnancy testing.

Any additional blood that may be taken is unlikely to cause the total volume of blood to exceed approximately 239 mL for Cycle 0 group and 471 mL for Cycles 1-4 group.

6.3 Study Procedures

6.3.1 Screening Visit (Day -14 to Day -1)

Subjects will undergo Screening procedures within 14 days prior to HSP-130 administration. All Screening procedures will be completed prior to assignment to treatment. Subjects satisfying all inclusion/exclusion criteria may be enrolled in the study.

6.3.2 Dose Escalation Assessment

The safety of administered HSP-130 will be assessed throughout the study and will include AEs, AEs of special interest, laboratory assessments, vital signs and physical examination.

Escalation to the next dose will be allowed based on the pre-specified safety evaluation within a minimum of 5 evaluable subjects. Appropriateness of escalation to the next dose will be based on assessment of vital signs, concomitant medications, laboratory assessments, and any AEs occurring post-dose administration through Day 20 of the HSP-130 dosing periods. If, there is no contraindication based on these assessments within 5 evaluable subjects, screening for the subsequent dose level can be initiated.

Cycle 0 (3 mg to 6 mg):

The ability to dose escalate will specifically include consideration of the following:

1. Dose escalations will not occur under the following conditions:

    - If ≥ 3 subjects experience any of the following (based on the small study numbers [n = 6] upon which escalation decisions are made):

        - Each of these subjects experience the same serious adverse event (or SAE reflecting an analogous medical event), unless unrelated to the study drug. In addition, Hospira will assess aggregate SAE profiles of subjects and identify emerging patterns consistent with a potential unexpected causal drug event association.

        - Each of these subjects experiences severe lab abnormalities including

            - Transaminase elevations (ALT or AST) (e.g., > 5 times ULN) without underlying alternative explanation

            - Significant decreases in renal function from baseline (e.g., 50% decrease in eGFR)

            - Clinically significant leukocytosis (e.g., > 50 x 10^9/L)

            - Clinically significant thrombocytopenia (e.g., < 30 x 10^9/L)

            - Onset of clinically evident splenomegaly within the 30 day assessment period

2. Additionally, concomitant medications will be assessed to see if there is any consistent altered pattern of medication use for treatment emergent SAEs. If observed, this finding will be assessed for implications for dose escalation.

3. If Adverse Events of Special Interest are reported as SAEs and are reported in disproportionate numbers than would be expected based on published safety profiles (United States Product Information [USPI] or Summary of Product Characteristics [SPC]) for approved pegfilgrastims, this will be assessed for implications for dose escalation.

Cycles 1-4 (6 mg to 12 mg):

The ability to dose escalate will specifically include consideration of the following:

1. Dose escalation to 12 mg will be not be considered until Hospira has analyzed the data from the previous Cycle 0 for 3 mg and 6 mg cohorts as well as the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and the data are submitted to the FDA for review. At this point, escalation to the 12 mg cohort may only proceed if the exposure pattern of the PK/PD responses suggests that higher doses are required and both Hospira and the FDA agree to proceed.
2. If the decision is jointly made with the FDA to study a 12 mg dose, Hospira will stop patient enrollment in the 12 mg cohort with criteria jointly agreed upon during that review but will include criteria such as the following.

   Patient enrollment in the 12 mg cohort will be stopped if any of the following occur:

   a. If any patient experiences a grade 5 toxicity suspected to be related to HSP-130
   b. If ≥ 2 of the planned 12 subjects in the cohort experience any of the following:

      - Each of these subjects experiences the same serious adverse event (or SAE reflecting an analogous medical event), unless unrelated to the study drug. In addition, Hospira will assess aggregate SAE profiles of subjects and identify emerging patterns consistent with a potential unexpected causal drug event association.
      - Each of these subjects experiences severe lab abnormalities including:
        - Transaminase elevations (ALT or AST) (e.g., > 5 times ULN) without underlying alternative explanation
        - Significant decreases in renal function from baseline (e.g., 50% decrease in eGFR)
        - Clinically significant leukocytosis (e.g., > 50 x 10^9/L)
        - Clinically significant thrombocytopenia (e.g., < 30 x 10^9/L)
        - Onset of clinically evident splenomegaly within the 30 day assessment period

   c. If ≥ 2 patients in the 12 mg cohort experience grade 3 or 4 known G-CSF-related toxicities as informed by the known safety profiles of approved pegylated or non-pegylated filgrastims.
   d. If Adverse Events of Special Interest are reported as SAEs and are reported in disproportionate numbers than would be expected based on published safety profiles (USPI or SPC) for approved pegfilgrastim.
3. Additionally, concomitant medications will be assessed to see if there is any consistent altered pattern of medication use for treatment emergent SAEs. If observed, this finding will be assessed for implications for dose escalation.
4. If Adverse Events of Special Interest are reported as SAEs and are reported in disproportionate numbers than would be expected based on published safety profiles

(USPI or SPC) for approved pegfilgrastims, this will be assessed for implications for dose escalation.

If subject safety would be compromised by further subject enrollment at a specific dose level (3 mg, 6 mg, or 12 mg) as determined by the Medical Monitor, further enrollment at that dose of HSP-130 may be terminated.

6.3.3 Follow-up Visit

Cycle 0:

Subjects will come for a Follow-up Visit 30 (± 2) days after HSP-130 administration in Cycle 0. After completion of Cycle 0, each of the subjects in these dosing groups will have completed their participation in assessment of HSP-130. The site will be offered reimbursement for treatment with EU-approved Neulasta in accordance with local standard of care by the Investigator with subsequent non-study chemotherapy regimen.

Cycles 1-4:

Subjects will come for a Follow-up Visit 30 (± 2) days after HSP-130 administration in Cycle 4, after which they will be considered to have completed the study. Any information related to treatment associated with an AE will also be collected at the time of Follow-up Visit.

6.4 Pharmacodynamic and Pharmacokinetic Evaluation

6.4.1 Collection of Samples for Analysis

Sample collection, handling, and shipment instructions will be provided in the Laboratory Manual supplied to site.

The total amount of blood required per subject for PD and PK analysis for subjects enroll in Cycle 0 is approximately 126 mL and for subjects enroll in Cycles 1-4 is approximately 196 mL.

Pharmacodynamic sampling

Cycle 0

Blood samples for ANC (2.7 mL) and $CD34^+$ count (2.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 48, 96, 144, 192, 240, and 312 hours post-dose.

The total number of samples planned for PD analysis (ANC and $CD34^+$ count) in Cycle 0 is 7, resulting in approximately 32.9 mL of blood volume.

Cycles 1-4

Blood samples for ANC (2.7 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be only applied to Cycles 1 and 4 with HSP-130 treatment groups.

The total number of samples planned for PD analysis (ANC) in Cycles 1 and 4 is 14, resulting in approximately 37.8 mL of blood volume.

Pharmacokinetic sampling

Cycle 0

Blood samples (7.0 mL) for HSP-130 assay will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose.

The total number of samples planned for HSP-130 assay in Cycle 0 is 10, resulting in approximately 70 mL of blood volume.

Cycles 1-4

Blood samples (7.0 mL) for HSP-130 assay will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be applied only to Cycles 1 and 4 with HSP-130 treatment groups.

For PK analysis, 7 mL of blood will be collected at each sampling time point to provide approximately 3 mL serum. The serum will be split into 2 polypropylene cryovials (1.5 mL each). One cryovial will be used for the analysis and 1 cryovial will be retained as a backup.

The timing of blood collections will take priority over all other scheduled study activities except for dosing. The time that each blood sample is collected will be recorded to the nearest minute.

The total number of samples planned for HSP-130 assay in Cycles 1 and 4 is 20, resulting in approximately 140 mL of blood volume.

6.4.2 Pharmacodynamic Variables

Cycle 0

- **Primary Variable:** $AUEC_{ANC}$
- **Secondary Variables:** ANC_E_{max}, ANC T_{max}, $AUEC_{CD34+}$, $CD34^+\_E_{max}$, $CD34^+$ T_{max}

The PD variables will be calculated using non-compartmental methods.

Cycles 1-4

- **Primary Variable:** DSN (defined as days with grade 4 neutropenia [ANC < 0.5 x 10^9/L]) in Cycle 1.
- **Secondary Variables:** DSN in Cycle 4. ANC nadir concentration, Time of nadir concentration, AUEC, incidence of FN, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour with ANC < 1.0 x 10^9/L, incidence of severe neutropenia (grade 4, ANC < 0.5 x 10^9/L) and time to ANC recovery (the first day with ANC ≥ 2.0 x 10^9/L after any day with ANC < 2.0 x 10^9/L) in Cycle 1 and Cycle 4.

The PD variables will be calculated using non-compartmental methods.

6.4.3 Pharmacokinetic Variables

Cycle 0

- **Primary Variables:** $AUC_{0-\infty}$ and C_{max}
- **Secondary Variables:** AUC_{0-t}, T_{max}, $t_{1/2}$, λz and CL

The PK variables will be calculated using non-compartmental methods.

Cycles 1-4

- **Primary Variables:** AUC_{0-t}, and C_{max}
- **Secondary Variables:** $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λz and CL

The PK variables will be calculated using non-compartmental methods

6.5 Measurement Methods

6.5.1 Pharmacodynamic Assay

Analysis of Samples: ANC will be determined at the central clinical laboratory conducting the clinical laboratory tests. $CD34^+$ count will be determined by flow cytometric method.

6.5.2 Pharmacokinetic Assay

Analysis of Serum Samples: Serum pegylated G-CSF concentrations will be determined from an aliquot of human serum using a validated enzyme-linked immunosorbent assay (ELISA) procedure with double-antibody sandwich method with quantitation by absorbance. This method is suitable for determination pegylated G-CSF in human serum over the range of 100 to 5000 pg/mL. The method meets the requirements of the Guidance for Industry Bioanalytical Method Validation: (May 2001) of the FDA and a subsequent revision to the Guidance (September, 2013) (41), (42).

6.5.3 Antibody Assay

Samples for the assessment of anti-HSP-130 antibodies will be assayed in accordance with FDA Guidelines for immunogenicity testing (43), (44).

A validated electrochemiluminescent (ECL) assay will be used to measure sera for the presence of anti-HSP-130 antibodies. Sera that are confirmed as positive will be tested in a cell-based assay for neutralizing antibodies (NAb) that neutralize the biologic activity of HSP-130. In parallel, serum samples will be assessed for anti-PEG binding antibodies using an independent assay both pre- and post-treatment.

6.5.4 Sample Analysis Repeats

Analysis of samples that are considered suspect will be repeated according to the laboratory's operating procedures on sample repeats. A table of repeat values must be included in the analytical report with justification for the repeat analysis and the accepted value.

6.6 Subject Enrollment

Only subjects satisfying the inclusion and exclusion criteria will be enrolled. Prior to administration of the HSP-130, subjects will be given unique numbers and sequentially assigned to 1 of the 3 treatment groups.

6.7 Subject Replacement

A total of 24 to 36 patients will be enrolled initially depending on whether a second 3 mg cohort is required; a further 12 patients totaling approximately 36 to 48 patients will be treated if the 12 mg cohort is enrolled, as defined in Section 6.3.2. Subjects who withdraw prior to Cycle 2 may be replaced to support the full complement of subjects (minimum of 8 evaluable subjects) for primary endpoint data generation for Cycle 1.

7 WITHDRAWAL AND EARLY DISCONTINUATION

7.1 Early Discontinuation of the Study

Hospira may discontinue this study prematurely in its entirety for reasonable cause provided that written notice is submitted at a reasonable time in advance of the intended termination. The Investigator may also discontinue the study at his/her site for reasonable cause after notifying the IRB/IEC and providing written notice to Hospira at a reasonable time in advance of the intended termination. Advanced notice is not required by either party if the study is stopped due to safety concerns.

The study will be terminated by the Sponsor if either of the following occurs:

- Lack of efficacy for 6 mg is demonstrated, i.e., more than 3 patients experience severe neutropenia for a duration of > 5 days, with severe neutropenia as < 0.5 x 10^9/L OR

- If more than 3 patients in the 3 mg cohort or more than 3 patients in the 6 mg cohort experiences grade 3, 4, or 5 known G-CSF related toxicities informed by the known safety profiles of approved pegylated or non-pegylated filgrastims (19), (23)

7.2 Early Discontinuation of Individual Subjects

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care.

Subjects may be discontinued or withdrawn from the study for a number of reasons, which must be recorded on the appropriate eCRF.

A subject will be discontinued from this study if any of the following criteria are met:

- Subject withdrawal of consent
- Clinical presentation consistent with splenic rupture following study drug administration
- Evidence of acute respiratory distress syndrome following study drug administration
- Evidence of serious allergic reaction following study drug administration
- At the discretion of the Principal Investigator or Medical Monitor, the subject presents with a new onset significant condition during study conduct that may influence the subject's welfare or study endpoints.
- At the discretion of the Principal Investigator or Medical Monitor, the subject will be discontinued if deemed appropriate in the best interest of the subject's welfare.

Withdrawal for any reason is considered to be a premature discontinuation. Following discontinuation from the study, the subject will be treated in accordance with the Investigator's best clinical judgment. Once a subject has prematurely discontinued from the

study, end of study assessments will be performed. For subjects who received HSP-130, all study assessments should be completed if possible, inclusive of potential serial blood collection in cases of identified positive anti-HSP-130 antibody results.

Enrolled subjects who discontinue due to an AE will have events documented and will be followed to satisfactory resolution or until the Principal Investigator or sub-investigator deems the event to be chronic or not clinically significant or the subject to be stable. If clinically indicated, a complete laboratory evaluation (chemistry, hematology, urinalysis and spot urine for PCR) will be performed.

The date and reason for a subject's premature discontinuation from the study will be recorded in the source document and entered in the appropriate section of the eCRF.

8 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

The Investigator will monitor each subject for clinical and laboratory evidence of AE on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to HSP-130, an alternate etiology for events not considered related to HSP-130, final diagnosis, if known, and any action(s) taken. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All Serious AEs will be followed to resolution or until the Principal Investigator or sub-investigator deems the event to be chronic or not clinically significant or the subject to be stable.

8.1 Definitions

8.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the investigational product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Clinically significant abnormalities are to be followed to resolution (i.e. become stable, return to normal, return to baseline, or become explainable).

Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been planned prior to study entry, including kidney transplants. However, if the pre-existing condition deteriorates unexpectedly during the study (i.e., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

8.1.2 Adverse Events of Special Interest

The following events are considered AEs of Special Interest for HSP-130. See Section 10.2.5.1 for definitions and clarification.

1. Potential Allergic Reactions

2. Splenomegaly
3. Splenic rupture
4. Acute Respiratory Distress Syndrome
5. Alveolar Hemorrhage
6. Hemoptysis
7. Leukocytosis
8. Thrombocytopenia
9. Capillary Leak Syndrome
10. Cytokine Release Syndrome
11. Cutaneous Vasculitis

8.1.3 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Hospira as a SAE within 24 hours of occurrence or notification of the study site:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an out-patient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Other	Both spontaneous and elective abortions are to be treated as SAEs.

A list of AEs that must always be reported as SAEs during this study is provided in Appendix E.

8.1.4 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected. Investigators will be notified of SUSARs in a manner and timeframe consistent with applicable national regulatory requirements.

The study will comply with all local regulatory requirements. This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.

8.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

8.3 Causality of Adverse Events

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as related and unrelated, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

- An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE;

generally the facts (evidence) or arguments to suggest a causal relationship should be provided.

- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor.

- If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.4 Adverse Event Collection Period

AE data, whether elicited or spontaneously reported by the subject, will be collected from time of informed consent up to and including the Follow-up Visit (Day 30) after HSP-130 administration in Cycle 4 or early discontinuation. A medical history will be taken at Screening and any changes in the health of the subject prior to receiving HSP-130 should be recorded as a change in the medical history.

Serious adverse events will also be collected for any subject from the time the subject signs the study-specific informed consent up to and including the Follow-up Visit (Day 30) after HSP-130 administration in Cycle 4 or early discontinuation.

8.5 Serious Adverse Event Reporting

In the event of a SAE, whether related to HSP-130 or not, the Principal Investigator or representative must make an accurate and adequate report within 24 hours by telephone, email, or fax to Hospira Global Product Safety.

Hospira Global Product Safety
Phone: +PPD
Email: PPD
Global Product Safety Fax: +PPD

In addition, the Principal Investigator will submit the SAE reports to the IRB/IEC in accordance with applicable requirements within 15 calendar days of discovering the SAE.

In the EU, the sponsors reports all SUSARs to the relevant Competent Authority and, IEC with 7 calendar days for all fatal and life threatening events and 15 calendar days for all other seriousness criteria.

Copies of each report will be kept in the site's study files, and adequate documentation will be provided to Hospira, including documentation of IRB/IEC notification, as applicable.

A subject experiencing 1 or more SAEs will receive treatment and Follow-up evaluations by the Principal Investigator or may be referred to another appropriate physician for treatment and Follow-up.

8.6 Pregnancy

Hospira must be notified immediately if a female study subject becomes pregnant during the study. The Investigator must report the pregnancy by telephone to the Safety Medical Monitor listed in Section 8.5. The Investigator must also complete and send the Clinical Trial Pregnancy Report Form within 5 working days of initial sponsor notification. The Investigator will follow the course of the subject's pregnancy and submit reports to Hospira on the health of the subject and fetus at least each trimester, at birth, and once after delivery, within 3 to 6 months.

Pregnancy in a study patient is not considered an AE or SAE. Study subjects who become pregnant will be discontinued from the study. The medical outcome of an elective or a spontaneous abortion in a female study subject is considered an SAE, and must be reported to Hospira within 24 hours of learning of the event, as noted in Section 8.5.

Adequate methods of contraception to prevent pregnancy are to be maintained throughout the course of the study in study subjects as defined by the protocol.

9 PROTOCOL DEVIATIONS

The Investigator or other physician(s) in attendance should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator or other physician(s) in attendance should consult with Hospira, and the IRB, as required, to determine the appropriate course of action. Deviations from the inclusion/exclusion criteria will not be permitted.

The site should document all protocol deviations in the subject's source documents and a description of the departure from the protocol and the reason(s) for it must be recorded on the appropriate form. In the event of a significant deviation, the site should notify Hospira or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments. These would include subjects who entered into the study even though they did not satisfy the entry criteria, developed withdrawal criteria during the study but were not withdrawn, received the wrong treatment or the incorrect dose or received an excluded concomitant treatment.

If there is any question by the investigative site as to whether a deviation meets the reporting requirements of a significant deviation, site personnel should contact Hospira.

When a significant deviation from the protocol has occurred for an individual subject, the Investigator or other physician(s) in attendance must contact the Hospira Medical Monitor listed below. Such contact must be made as soon as possible to permit a decision as to whether or not the subject is allowed to continue in the study. A description of the departure from the protocol and the reason(s) for it must be recorded on the appropriate eCRF.

PPD, MD, PhD
Global Clinical Development
PPD
Office: PPD
Mobile: PPD
Email: PPD

10 STATISTICAL CONSIDERATIONS

The sections below summarize the intended statistical methods and analyses for the study. A more detailed statistical analysis plan (SAP) will be written prior to finalization of the clinical trial database. Any changes to the planned methods and analyses will be described and justified in the protocol and/or in the final clinical study report, as appropriate.

10.1 Statistical Methods

The SAP describing in detail the statistical analysis methods used will be prepared and finalized prior to study database lock.

For continuous variables, number of observations (N), mean, median, standard deviation (SD), minimum and maximum will be presented. For categorical variables, N and percent will be shown.

10.1.1 Subject Population/Data Sets to be Evaluated

Safety and PK analyses will be based on the actual treatment each subject received. PD analysis will be based on assigned treatment. Any subject receiving treatment other than that of the assigned Treatment Group will be listed in the clinical study report.

Safety Population:

All subjects who receive at least 1 dose of HSP-130 will be included in the Safety Population. All safety analyses will be conducted on the Safety Population.

Full Analysis Set (FAS):

All subjects who receive at least one does of HSP-130 are included in FAS. In analysis of a particular parameter for a particular cycle(s), only those subjects who have sufficient data in the cycle(s) to calculate the parameter will be included. Sufficient data is defined as having more than 3 measurable values where the parameter can be reliably calculated. Subjects who have confirmed positive anti-HSP-130 antibody results will not be included.

10.1.2 Sample Size Determination

No formal sample size calculation was conducted.

10.1.3 Data and Interim Analyses

There will be no interim analyses performed in this study.

10.1.4 Handling of Missing Data

Missing data will not be imputed. All subjects in FAS with available data will be included in summaries of each PK/PD parameter or concentration time point. All subjects' data will be listed.

10.2 Statistical Analyses

10.2.1 Subject Disposition and Demography

The number of subjects enrolled and the reason for discontinuation from the study will be summarized by treatment.

The demographics and the medical history will be summarized.

10.2.2 Assessment of Efficacy

Efficacy parameters will be summarized by treatment. Individual subject's efficacy data will be listed.

10.2.3 Assessment of Pharmacodynamics and Pharmacokinetics

Pharmacodynamic Assessment

The primary PD parameters of $AUEC_{ANC}$ results from Cycle 0 and DSN results from Cycle 1 will be assessed to determine appropriate doses for Phase 3 studies. Additional PD results may be assessed as appropriate.

Cycle 0:

Pharmacodynamic parameters of $AUEC_{ANC}$, ANC_E_{max}, ANC T_{max}, $AUEC_{CD34+}$, $CD34^+$_E_{max}, and $CD34^+$ T_{max} will be calculated for assessment.

If the PD response ($AUEC_{ANC}$ and/or $AUEC_{CD34+}$) of 3 mg HSP-130 and 6 mg HSP-130 in Cycle 0 indicate that the 3 mg dose level is sub-therapeutic, the 3 mg dose level will not be included in Cycles 1-4 assessment. This design feature will ensure that no subject with chemotherapy will be treated with sub-therapeutic dose of HSP-130. Additional PD results may be assessed as appropriate.

Cycles 1-4:

Pharmacodynamic parameters of DSN (defined as days with grade 4 neutropenia [ANC $< 0.5 \times 10^9$/L]) in Cycle 1, DSN in Cycle 4, ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of febrile neutropenia, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour and ANC $< 1.0 \times 10^9$/L, incidence of severe neutropenia (grade 4, ANC $< 0.5 \times 10^9$/L) and time to ANC recovery (the first day with ANC $\geq 2.0 \times 10^9$/L after any day with ANC $< 2.0 \times 10^9$/L) in Cycle 1 and Cycle 4 will be calculated for assessment.

Descriptive statistics including number of observations (N), mean, SD and associated coefficient of variation (CV), minimum and maximum for each PD parameter by treatment will be reported.

Pharmacokinetic Assessment

Cycle 0:

Pharmacokinetic parameters of $AUC_{0-\infty}$, C_{max}, AUC_{0-t}, T_{max}, $t_{1/2}$, λz, and CL will be calculated for assessment.

Cycles 1-4:

Pharmacokinetic parameters of AUC_{0-t}, C_{max}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λz, and CL will be calculated for assessment.

Descriptive statistics including N, mean, SD, minimum and maximum for each PK parameter by treatment will be reported.

10.2.4 Additional Assessments

Data collected in with WHO Performance Status, CISNE, and FACT-N, will be summarized by treatment and listed for individual subjects. Descriptive statistics including N, mean, SD, minimum and maximum for numerical data, and counts and frequency for categorical data, will be presented.

10.2.5 Assessment of Safety

Treatment emergent adverse events (TEAEs) will be summarized by system organ class and preferred terms (PT). Descriptive statistics including N, mean, SD, minimum and maximum for numerical data, and counts and frequency for categorical data, will be tabulated for laboratory tests, and vital signs by treatment group. Grading of laboratory abnormalities will be according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (6).

10.2.5.1 Adverse Events

The Medical Dictionary for Drug Regulatory Activities (MedDRA) will be used to map AE descriptions to preferred terms (PT) and system organ classes. MedDRA version 17.1 or later will be used.

AEs of Special Interest will be identified prospectively based on the safety information of the Neulasta, as described in the Neulasta (Amgen) Package Insert, and grouped by similar medical constructs. The AEs of Special Interest are further informed based on the known extension of the pharmacology of the drug as manifested by known clinical adverse reactions with G-CSFs.

The following events are considered AEs of Special Interest for HSP-130 and will be summarized by the medical concept (narrow standard MedDRA queries [SMQ] and PT as appropriate):

1. Potential Allergic Reactions

2. Splenomegaly
3. Splenic rupture
4. Acute Respiratory Distress Syndrome
5. Alveolar Hemorrhage
6. Hemoptysis
7. Leukocytosis
8. Thrombocytopenia
9. Capillary Leak Syndrome
10. Cytokine Release Syndrome
11. Cutaneous Vasculitis

Definitions of Adverse Events of Special Interest

MedDRA version 17.1 or later is employed in this study to code event terms. Adverse Events of Special Interest are defined in the Statistical Analysis Plan. The Adverse Events of Special Interest were identified based on the safety profile of the originator product in accordance with the US prescribing information for approved US-approved G-CSFs (pegfilgrastim and filgrastim, Neulasta and Neupogen, respectively) and any potential preclinical or clinical Nivestim (EU-approved Hospira filgrastim) data that may inform the safety characterization for HSP-130.

The methodology employed to medically group together similar medical constructs within MedDRA was as follows: where a SMQ in MedDRA 17.1 or later exists to summarize the adverse event of interest, the SMQ was employed to medically group together the PTs. In order to ensure adequate specificity, the SMQ narrow in MedDRA 17.1 or later was employed to offer a sensitive, but adequately specific approach to summarizing the adverse event of special interest. If an SMQ was not available in MedDRA 17.1 or later to summarize the adverse event of interest, a selection of PTs was identified by the sponsor to provide a medically comprehensive grouping of the medical concept.

An AE will be considered to be treatment-emergent if the event started or worsened in severity after the HSP-130 administration up to and including 30 days post HSP-130 administration. For TEAEs, the number and percentage of subjects who reported each PT will be summarized by treatment groups. Category of severity (mild, moderate, severe) and relationship to HSP-130 (related, not related) will be summarized by treatment group for TEAEs. Adverse events missing an indicated relationship to HSP-130 will be considered related to HSP-130.

SAEs will be summarized by each treatment group and listed by each subject.

10.2.5.2 Concomitant Therapy

Concomitant therapies will be coded to their generic name using the latest version of World Health Organization (WHO) drug dictionary. Medications will be listed according to treatment group. The number of subjects taking medication prior to HSP-130 dosing and concomitant therapies taken after HSP-130 dosing will be tabulated by treatment group.

10.2.5.3 Vital Signs

Baseline is defined as the last non-missing measurement prior to the start of HSP-130.

Descriptive statistics will be applied to summarize blood pressure, heart rate, and temperature for each treatment group.

10.2.5.4 Clinical Laboratory Measurements

All laboratory values outside the normal range will be flagged in the data listing.

10.2.5.5 Physical Examination, Chest X-ray, and ECG

Physical examination data recorded at Screening and at Follow-up Visit (Day 30) after HSP-130 administration in Cycle 4 will be listed. Chest X-ray and ECG data will be listed.

10.2.5.6 Antibody Assay

Antibody data will be listed.

10.2.6 Deaths

Deaths will be summarized by each treatment group and listed by each subject.

11 REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

11.1 Declaration of Helsinki

The Investigator and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki (See Appendix D), GCP, ICH Guidelines and the applicable laws and regulations.

11.2 Good Clinical Practice

The study will be conducted in accordance with SOPs that meet the current regulatory requirements and guidelines laid down by the ICH GCP in clinical studies and all applicable local regulatory requirements and laws.

11.3 Ethical Approval

11.3.1 Initial Approval

Prior to the release of HSP-130 for administration and the enrollment of subjects, IRB/IEC written approval of the following must be obtained: the conduct of the study at named site(s), the protocol and any amendment(s), the subject information sheet and ICF, any other written information that will be provided to the subjects, any advertisements that will be used and any subject compensation.

11.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to Hospira for review and submitted to the IRB/IEC for approval as applicable. Amendments requiring regulatory authority and/or IRB/IEC approval may be implemented only after a copy of the necessary approval letter(s) has been transmitted to Hospira.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Hospira and/or IRB/IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

11.3.3 End of Trial Notifications

The appropriate regulatory authorities and IRB/IECs will be informed about the end of the trial within the required timelines.

11.4 Regulatory Authority Approval

The study will be performed in compliance with applicable regulatory requirements. Clinical trial authorization from the appropriate regulatory authority must be obtained prior to the start of the study. In addition, the applicable regulatory authorities must approve amendments (as instructed by Hospira), receive suspected unexpected serious adverse reactions (SUSAR) reports and annual safety reports, when applicable, and be notified of the end of the trial.

11.5 Other Required Approvals

In addition to IRB/IEC and regulatory approval, all other required approvals (e.g. approval from local Research and Development Board or Scientific Committee) will be obtained prior to recruitment of subjects into the study and shipment of the HSP-130.

11.6 Insurance

Hospira has civil liability insurance, which covers this study in all applicable countries.

11.7 Pre-study Documentation Requirements

The requirements and guidelines for authorization to ship HSP-130, as outlined in the applicable Hospira (and/or designee) SOPs, will be met prior to the release and use of the HSP-130, to include the collection of the essential documents outlined in ICH E6, Section 8.2, which are required prior to the start of the study (See Appendix B).

11.8 Informed Consent

It is the Investigator's responsibility to obtain a signed ICF from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any study procedures are commenced. As detailed in Section 6.1, the subject should be given a copy of the approved subject information sheet and informed consent in their native language. The original copy of the signed and dated ICF must be retained in the clinic's records, and is subject to inspection by representatives of Hospira, and/or representatives from regulatory authorities. (See Appendix C)

11.9 Contact with General Practitioner

It is the Investigator's responsibility to inform the subject's General Practitioner (where applicable) by letter that the subject is taking part in the study, provided the subject agrees to this and information to this effect is included in the subject information sheet and informed consent. A copy of this letter will be filed in the Investigator Site File.

11.10 Subject Confidentiality

The Investigator must ensure that the subject's privacy is maintained. On the eCRF or other documents submitted to Hospira, subjects will be identified by a screening and/or enrollment number only. Documents that are not submitted to Hospira (e.g., signed informed consent) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit direct access to subject's records and source documents for the purposes of monitoring, auditing, or inspection by Hospira, authorized representatives of Hospira, regulatory authorities and IRB/IECs only.

11.11 Data Protection

All personnel involved in the study will observe or work within the confines of applicable local data protection regulations.

11.12 Study Documentation and Data Storage

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation for inspection by Hospira and representatives of regulatory authorities for at least 2 years after the last approval of a marketing application in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of HSP-130. It is the responsibility of Hospira to inform the Investigator when these documents no longer need to be retained.

A subject screening/enrollment log is to be completed at each investigative site. Data recorded on the screening/enrollment log are to include a subject identifier, the date of screening, and the reason the subject was not entered (if applicable). All subjects initially screened are to be recorded in this log.

Documents will be stored in such a way that they can be easily accessed/data retrieved at a later date. Consideration should be given to security and environmental risks. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from Hospira prior to the transfer.

11.13 Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of Hospira. The Investigator may use this information for the purposes of the study only.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study. This list will be maintained at the site, and will not be retrieved by Hospira or its designee.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Hospira in connection with the development of HSP-130. This information may be disclosed as deemed necessary by Hospira to other clinical investigators, other pharmaceutical companies, to the FDA and to other governmental agencies. In addition, the information collected during this study may be added to research databases and used in the future by the Sponsor and its affiliated companies to study better measures of safety and effectiveness, study other therapies for subjects, develop a better understanding of disease(s) included in the study, or improve the efficiency, design and study methods of future clinical trials. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

It is understood by the Investigator that Hospira will use information developed in this clinical study in connection with the development of HSP-130 and therefore may disclose it as required to other clinical investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Hospira.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from Hospira.

11.14 Publication

Hospira intends to publish the results of the study as a whole once all subjects have completed the study and the study has been analyzed. The Investigator may not publish the results until the study has been submitted for publication and must have prior written permission from Hospira.

The Investigator or Hospira may not submit for publication or present the results of this study without allowing each of the other parties 30 days in which to review and comment on the pre-publication manuscript.

The Investigator may not submit the results of the study for publication without the prior written consent of Hospira.

12 ADMINISTRATIVE OBLIGATIONS

12.1 Source Data Access

The Investigator/institution will permit study-related monitoring, audits/inspections, IRB/IEC review and regulatory inspection providing direct access to source documents.

12.2 Language

Electronic CRFs will be in English. Generic names for concomitant therapies should be recorded in the eCRF wherever possible.

All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

12.3 Data Collection

Subject data will be collected in this study using an Electronic Data Capture (EDC) system.

Hospira, or its designee, will supply to the site personnel access to the eCRFs. These forms will be used to transmit information collected during the study to Hospira or its designee and regulatory authorities, as applicable. The Investigator may formally designate authority to complete eCRFs to qualified staff by completing the signature log and requesting access rights to the EDC system for the designee. Every user of the system will be made aware of the fact that user name and password should never be shared and their electronic signature constitutes the legally binding equivalent of a hand-written signature.

Electronic CRFs must be completed for each enrolled subject who signs the informed consent document for the study. Screening study data will be collected on the eCRF for all subjects. The system automatically records all changes in an electronic audit trail and requires a “reason for change” to be picked from a pre-defined list. If the reason for the correction is not obvious, a brief explanation (e.g. transcription error) should accompany the change. All information recorded on the eCRFs forms must reflect the information in the subject source documents.

For screen failed subjects, the Investigator or designee will capture in source the subject’s demographic data, data collected from all completed screening procedures, and reason for screen failure. Only the subject’s demographic data, informed consent, reason for screen failure and SAEs will be entered in the EDC.

The Investigator will review the eCRFs for completeness and accuracy and electronically sign each set of eCRFs. Hospira personnel (or their representatives) will periodically review the eCRFs for completeness and accuracy. Hospira personnel (or their representatives) will be allowed access to all source documents in order to verify eCRF entries.

12.4 Monitoring

It is understood that monitors from Hospira (and/or their designee), and any authorized personnel contracted to Hospira, may contact and visit the Investigator, and that they will be allowed to inspect the various records of the study on request (eCRFs, source documents and any other related data), provided that subject confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy, consistency of the data, and adherence to regulatory requirements and ICH GCP guidelines.

The Investigator agrees to co-operate with the monitor to ensure that any issues detected during the course of these monitoring visits will be resolved in a timely manner.

12.5 Independent Data Monitoring Committee

An independent data monitoring committee will not be utilized in this study.

12.6 Quality Control and Quality Assurance

Quality Control will be performed according to applicable SOPs. The study may be audited by Quality Assurance representative(s) of Hospira (or their designee). All necessary related data and documents will be made available for inspection.

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14 APPENDICES

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies Sponsored by Hospira are subject to the regulations of the US FDA. The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the Sponsor (Hospira), summarizing the Investigator's qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Hospira, except when necessary to protect the safety, rights, or welfare of subjects.
2. To personally conduct or supervise the described investigation(s).
3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IEC/IRB review and approval in 21 CFR Part 56 are met.
4. To report to Hospira adverse experiences that occurs in the course of the investigation(s) in accordance with 21 CFR 312.64.
5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.
6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Hospira, the IEC/IRB, and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Hospira.
8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.
9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Hospira to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix B. Documents Required Prior to Initiation of the Study

As Sponsor of a clinical study, Hospira has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the Investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the Investigator will be asked to provide the following documentation.

1. A signed and dated protocol for the study.
2. A signed and dated Form FDA 1572 certifying the Investigator's agreement to comply with the appropriate regulations governing the conduct of the study.
3. A current curriculum vitae of the Investigator. If sub-investigators will participate in the study, curriculum vitae for each.
4. A current medical license for the Investigator and each sub-investigator.
5. Requirements for the IEC/IRB.
6. A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and ICF were approved (unless separate documentation that the informed consent was approved is provided). The letter must also specify the version number and/or date of the approved ICF.
7. A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.
8. If the Investigator and/or sub-investigator are a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or ICF.
9. A model copy of the IEC/IRB-approved informed consent document to be used in the study.
10. Dated, documented approval/favorable opinion of IRB of an Advertisement for patient recruitment.
11. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
12. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.
13. A copy of the lab director’s curriculum vitae and current medical license.

Financial Disclosure forms must be completed by each Investigator and all sub-investigators identified on the Form FDA 1572. A Financial Disclosure, EU consent, is required to be completed for each Investigator and/or sub-investigator who is a resident of the European Union.

Appendix C. Elements of the Informed Consent Form

Hospira requires that all informed consent and assent statements used in studies comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH GCP Consolidated Guidance. To ensure compliance, the required elements of informed consent are listed below to aid the investigator in drafting an acceptable informed consent. Hospira will review a proposed informed consent prior to its submission to the IRB/IEC; alternatively, Hospira will supply to the Investigator a draft informed consent statement that may be submitted to the review committee.

Signed informed consent will be obtained from all subjects participating in this study, or from the subject's legally authorized representatives. This informed consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of subjects involved in the trial.
4. The expected duration of the subject's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The subject's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the subject and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that the study may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the subject for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the subject, this should be stated.
13. The anticipated prorated payment, if any, to the subject for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
15. A statement that the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatments are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research subject's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the subject.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally authorized representative is authorizing such access.

21. Information regarding safeguards to be used against disclosure of subject information to non-clinical research-related personnel.
22. A statement that the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the subjects' participation in the trial may be terminated.
24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the subject may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the informed consent is given to the subject.
29. The statement, "I agree to participate..."
30. A place for the subject or the subject's legally authorized representative to print their name, sign and date.
31. A place for the person who conducted the informed consent discussion to print their name, sign and date.
32. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as www.ClinicalTrials.gov.

[redacted]

Appendix D. Declaration of Helsinki

World Medical Association (WMA) Declaration of Helsinki- Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on Paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The WMA has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the Sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any SAEs. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research

cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

[redacted]

Appendix E. Adverse Events – Categorized as SAEs

A: Abortion (non-elective)**;** Acute respiratory (pulmonary) failure**;** Adrenal hemorrhage**;** Agranulocytosis**;** Anemia, aplastic**;** Anaphylaxis, anaphylactic shock; Anaphylactoid reaction**;** Aorto-oesophageal fistula, Aplastic bone marrow**;** Apnea (all ages)**;** Asphyxia (all ages)**;** Asystole**;** Attempted suicide**;** AV Block, third degree (aka, complete heart block)

B: Acute blindness; Brain death

C: Cardiac arrest/circulatory arrest/cardiorespiratory arrest; Cavernous sinus thrombosis; Cerebral edema; Cerebral vascular accident (stroke) includes hemorrhagic, thrombotic, embolic strokes to any region of the brain; Congenital anomalies (non-trivial); Coma (all types); Creutzfeldt-Jakob Disease

D: Deafness, acute; Death (all types); Disseminated Intravascular Coagulation (DIC), Dysplasia; Deep vein thrombosis (DVT)

E: Encephalomyelitis; Encephalopathy **F:** Fibrillation, ventricular; Fetal distress, demise

G: Gangrene; Gastrointestinal obstruction; Gastrointestinal perforation; Gastrointestinal rupture; Genitourinary obstruction; Genitourinary tract rupture; Genitourinary tract perforation; Glaucoma

H: Hemorrhage, neonatal; Hemorrhage, retroperitoneal; Hepatitis, infectious and non-infectious; Hemopericardium; Hepatic encephalopathy; Hepatic failure, necrosis; Hepatocellular damage, neonatal; Hepato-renal syndrome; Hyperpyrexia, Malignant ("Malignant Hyperthermia")

I: Intestinal ischemia, necrosis or death; Intrauterine death; Infarction (myocardial, pulmonary, etc.)

L: Laryngeal edema; Leukemia; Liver failure; Leukoencephalopathy, reversible or posterior multifocal; Lymphoma

M: Malignancy, primary occurrence. Excludes non-melanotic skin cancer; Malignant hypertension; Meningitis; MS aggravation or MS-like syndrome; Myelitis; Myeloproliferative disorder

N: Neuroleptic Malignant Syndrome

P: Pancytopenia; Pleural fibrosis; Pregnancy, ectopic; Pulmonary hypertension, primary; Pulmonary fibrosis; Pulmonary hemorrhage; Pulmonary edema (acute); Psychosis, acute onset

Q: Quadriplegia

R: Red cell aplasia; Renal failure, acute; Respiratory Distress Syndrome (neonatal)**;** Respiratory arrest; Respiratory depression, neonatal; Respiratory paralysis; Respiratory obstruction; Respiratory tract perforation; respiratory tract rupture; Retrobulbar neuritis; Retinopathies; Retroperitoneal Fibrosis; Reye's syndrome

S: Sagittal sinus thrombosis; Sepsis/Septicemia; Status asthmaticus; Status epilepticus; Stevens-Johnson Syndrome; Stillbirth; Sudden Infant Death Syndrome (SIDS)

T: Thrombocytopenia with platelet count <50,000 (severe); Thrombosis (excluding superficial sites); Torsades De Pointes; Toxic Epidermal Necrolysis

U: Uterine perforation

V: Vascular occlusion

W: Wallenberg Syndrome

[redacted]

Appendix F. Neulasta® (pegfilgrastim, Amgen) Summary of Product Characteristics

Summary of Product Characteristics Updated May-2015| Amgen Ltd

NEULASTA

Summary of Product Characteristics Updated 24-Jun-2015 | Amgen Ltd

1. Name of the medicinal product

Neulasta 6 mg solution for injection.

2. Qualitative and quantitative composition

Each pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only**.

*Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG).

** The concentration is 20 mg/ml if the PEG moiety is included.

The potency of this product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1

Excipient(s) with known effect:

Each pre-filled syringe contains 30 mg sorbitol (E420)

Each pre-filled syringe contains less than 1 mmol (23 mg) sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

Clear, colourless solution for injection.

4. Clinical particulars

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Neulasta therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

Posology

One 6 mg dose (a single pre-filled syringe) of Neulasta is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.

Method of administration

Neulasta is injected subcutaneously. The injections should be given into the thigh, abdomen or upper arm. For instructions on handling of the medicinal product before administration, see section 6.6.

Paediatric population

The safety and efficacy of Neulasta in children has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made

Patients with renal impairment

No dose change is recommended in patients with renal impairment, including those with end stage renal disease.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Limited clinical data suggest a comparable effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (see section 5.1). However, the long-term effects of Neulasta have not been established in acute myeloid leukaemia; therefore, it should be used with caution in this patient population.

Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

The safety and efficacy of Neulasta have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (AML); therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

The safety and efficacy of Neulasta administration in *de novo* AML patients aged < 55 years with cytogenetics t (15;17) have not been established.

The safety and efficacy of Neulasta have not been investigated in patients receiving high dose chemotherapy. This medicinal product should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Pulmonary adverse events

Uncommon (≥1/1,000 to < 1/100) pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see section 4.8).

The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). In such circumstances Neulasta should be discontinued at the discretion of the physician and the appropriate treatment given (see section 4.8).

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome

Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and splenic rupture

Uncommon but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 4.8). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Thrombocytopenia and anaemia

Treatment with Neulasta alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

Sickle cell anaemia

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease (see section 4.8). Therefore, physicians should use caution when prescribing Neulasta in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/l or greater have been observed in less than 1% of patients receiving Neulasta. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicine. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10^9/l after the expected nadir, this medicine should be discontinued immediately.

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with Neulasta. Permanently discontinue Neulasta in patients with clinically significant hypersensitivity. Do not administer Neulasta to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

The safety and efficacy of Neulasta for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

The needle cap of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging findings. This should be considered when interpreting bone-imaging results.

Neulasta contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Neulasta contains less than 1 mmol (23 mg) sodium per 6 mg dose, i.e. essentially 'sodium-free'.

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the trade name of the administered product should be clearly recorded in the patient file.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neulasta should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, Neulasta has been safely administered 14 days before chemotherapy. Concomitant use of Neulasta with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of Neulasta and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

Possible interactions with other haematopoietic growth factors and cytokines have not been specifically investigated in clinical trials.

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

The safety and efficacy of Neulasta have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression e.g., nitrosoureas.

Specific interaction or metabolism studies have not been performed, however, clinical trials have not indicated an interaction of Neulasta with any other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Neulasta is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women who become pregnant during Neulasta treatment are encouraged to enrol in Amgen's Pregnancy Surveillance Programme. Contact details are provided in section 6 of the Package leaflet.

Breast-feeding

There is insufficient information on the excretion of Neulasta / metabolites in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Neulasta therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Women who are breast-feeding during Neulasta treatment are encouraged to enrol in Amgen's Lactation Surveillance programme. Contact details are provided in section 6 of the Package leaflet.

Fertility

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area) (see section 5.3).

4.7 Effects on ability to drive and use machines

Neulasta has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were bone pain (very common [≥ 1/10]) and musculoskeletal pain (common). Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythaema, flushing, and hypotension occurred on initial or subsequent treatment with Neulasta (uncommon [≥ 1/1,000 to < 1/100]). Serious allergic reactions, including anaphylaxis can occur in patients receiving Neulasta (uncommon) (see section 4.4).

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony-stimulating factors; see section 4.4 and section “Description of selected adverse reactions” below.

Splenomegaly, generally asymptomatic, is uncommon.

Splenic rupture including some fatal cases is uncommonly reported following administration of pegfilgrastim (see section 4.4).

Uncommon pulmonary adverse reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Uncommonly, cases have resulted in respiratory failure or Acute Respiratory Distress Syndrome (ARDS), which may be fatal (see section 4.4).

Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients) (see section 4.4).

Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**				
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
Blood and lymphatic system disorders		Thrombocytopenia[1] Leukocytosis[1]	Sickle cell crisis[2]; Splenomegaly[2];		

			Splenic rupture[2]		
Immune system disorders			Hypersensitivity reactions; Anaphylaxis		
Metabolism and nutrition disorders			Elevations in uric acid		
Nervous system disorders	Headache[1]				
Vascular disorders			Capillary leak syndrome[1]		
Respiratory, thoracic and mediastinal disorders			Acute Respiratory Distress Syndrome[2]; Pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis)		
Gastrointestinal disorders	Nausea[1]				
Skin and subcutaneous tissue disorders			Sweet's syndrome (acute febrile dermatosis)[1,2]; Cutaneous vasculitis[1,2]		
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculo-skeletal pain, neck pain)			
General disorders and administrative site conditions		Injection site pain[1] Non-cardiac chest pain	Injection site reactions[2]		
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1]; Transient elevations in LFT's for ALT or AST[1]		
Renal and urinary disorders			Glomerulonephritis[2]		

[1] See section “Description of selected adverse reactions” below.

[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults. The frequency category was estimated from a statistical calculation based upon 1576 patients receiving Neulasta in nine randomized clinical trials.

Description of selected adverse reactions

Uncommon cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Uncommon events of cutaneous vasculitis have been reported in patients treated with Neulasta. The mechanism of vasculitis in patients receiving Neulasta is unknown.

Injection site reactions, including injection site erythaema (uncommon (≥ 1/1000 to < 1/100)) as well as injection site pain (common events ≥ 1/100 to < 1/10) have occurred on initial or subsequent treatment with Neulasta.

Common (≥ 1/100 to < 1/10) cases of leukocytosis (White Blood Count [WBC] > 100 x 10^9/l) have been reported (see section 4.4).

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were uncommon; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon in patients receiving Neulasta following cytotoxic chemotherapy.

Nausea and headaches were very commonly observed in patients receiving chemotherapy.

Uncommon elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

Common cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony-stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Paediatric population

The experience in children is limited. A higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. The most common adverse reaction reported was bone pain (see section 5.1 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Single doses of 300 µg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factor; ATC Code: L03AA13

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

In two randomised, double-blind, pivotal studies in patients with high risk stage II-IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once per cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to7 days, and a 30-40% incidence of febrile neutropenia. In one study (n = 157), which used a 6mg fixed dose of pegfilgrastim the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group (difference 0.23 days, 95% CI -0.15, 0.63). Over the entire study, the rate of febrile neutropenia was 13% of pegfilgrastim-treated patients compared with 20% of filgrastim-treated patients (difference 7%, 95% CI of -19%, 5%). In a second study (n = 310), which used a weight-adjusted dose (100 µg /kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 1.8 days in the filgrastim group (difference 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference 9%, 95% CI of -16.8%,-1.1%).

In a placebo-controlled, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m^2 every 3 weeks for 4 cycles). Nine hundred and twenty eight patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (Day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was lower for patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, $p < 0.001$). The incidence of hospitalisations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was lower in the pegfilgrastim group compared with placebo (1% versus 14%, $p < 0.001$; and 2% versus 10%, $p < 0.001$).

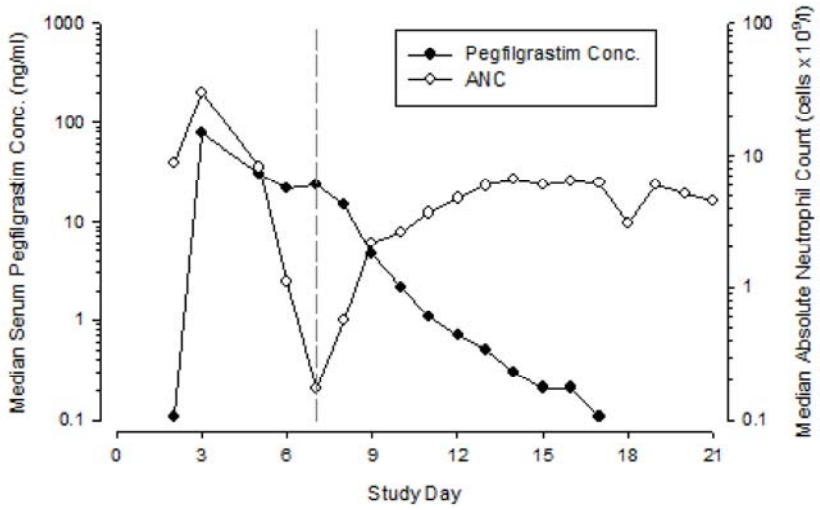
A small (n = 83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied (see section 4.4).

In a phase II (n = 37) multicentre, randomised, open-label study of paediatric sarcoma patients receiving 100 µg/kg pegfilgrastim following cycle 1 of vincristine, doxorubicin and cyclophosphamide (VAdriaC/IE) chemotherapy, a longer duration of severe neutropenia (neutrophils < 0.5 x 10^9) was observed in younger children aged 0-5 yrs (8.9 days) compared to older children aged 6-11 years and 12-21 years (6 days and 3.7 days, respectively) and adults. Additionally a higher incidence of febrile neutropenia was observed in younger children aged 0-5 yrs (75%) compared to older children aged 6-11 years and 12-21 years (70% and 33%, respectively) and adults (see sections 4.8 and 5.2).

5.2 Pharmacokinetic properties

After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see figure 1).

Figure 1. Profile of Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count (ANC) in Chemotherapy Treated Patients after a Single 6 mg Injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In an open label, single dose study (n = 31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

Elderly people

Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

Paediatric population

The pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma, who received 100 µg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (± Standard Deviation) (47.9 ± 22.5 µg·hr/ml) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 µg·hr/ml and 29.3 ± 23.2 µg·hr/ml, respectively) (see section 5.1). With the exception of the youngest age group (0-5 years), the mean AUC in paediatric subjects appeared similar to that for adult patients with high-risk stage II-IV breast cancer and receiving 100 µg/kg pegfilgrastim after the completion of doxorubicin/docetaxel (see sections 4.8 and 5.1).

5.3 Preclinical safety data

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously. The relevance of these findings for humans is not known.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium acetate*

Sorbitol (E420)

Polysorbate 20

Water for injections

*Sodium acetate is formed by titrating glacial acetic acid with sodium hydroxide.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Neulasta may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Neulasta left at room temperature for more than 72 hours should be discarded.

Do not freeze. Accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect the stability of Neulasta.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pre-filled syringe (Type I glass), with a rubber stopper and a stainless steel needle with or without an automatic needle guard.

The needle cap of the pre-filled syringe contains dry natural rubber (a derivative of latex) (see section 4.4).

Each pre-filled syringe contains 0.6 ml of solution for injection. Pack size of one pre-filled syringe, in either a blistered or non-blistered packaging.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before administration, Neulasta solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Amgen Europe B.V.

Minervum 7061

4817 ZK Breda

The Netherlands

8. Marketing authorisation number(s)

EU/1/02/227/001 1 pack blistered syringe

EU/1/02/227/002 1 pack unblistered syringe

EU/1/02/227/004 1 pack blistered syringe with needle guard

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 22 August 2002

Date of latest renewal: 16 July 2007

10. Date of revision of the text

May 2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

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Customer Care direct line
+44 (0)808 0100 321

Appendix G. Protocol Amendment Complete Listing of Changes

The following specific changes have been incorporated into the protocol under this protocol amendment. Sections from the original protocol that have been changed are detailed below and the new text to each changed section has been added. Changes that were strictly editorial (e.g. updating, formatting, correction of spelling errors etc.) are not included.

1. Title Page and Synopsis: Study Title

Existing Text:

A Phase 1-2 ascending dose study to assess the pharmacodynamics, pharmacokinetics, and safety of HSP-130 in subjects with non-metastatic breast cancer following single dose and multiple-dose administration by subcutaneous injection.

Revised Text:

A Phase 1-2 ascending dose study to assess the pharmacodynamics, pharmacokinetics, and safety of HSP-130 in subjects with non-metastatic breast cancer following single-dose and multiple-dose administration by subcutaneous injection.

Rationale for Change:

Inserted hyphen for grammatical correction and as well as for consistency.

2. Modified Protocol Version and Date

Existing Text:

IND Number	124793
EudraCT Number	2015-002057-35
Sponsor	Hospira, Inc. (Hospira)
	Hospira, Inc. 275 North Field Drive Lake Forest, IL 60045
Original Protocol v 2.0	31 July 2015
Amendment #2, Protocol v 2.6	17 December 2015

Revised Text:

IND Number	124793
EudraCT Number	2015-002057-35
Sponsor	Hospira, Inc. (Hospira)
	Hospira, Inc. 275 North Field Drive Lake Forest, IL 60045
Original Protocol v 2.0	31 July 2015
Amendment#2, Protocol v 3.0	21 December 2015

Rationale for Change:

Updated for accuracy.

Sections Changed:

Header and Title page

3. Signature Page

Existing Text:

_____ Date: _____

PPD , MD
PPD , Global Pharmacovigilance and Safety

Revised Text:

_____ Date: _____

PPD , MD, MPH
PPD , Global Pharmacovigilance and Safety

Rationale for Change:

Provided information about the new Global Medical Director, Pharmacovigilance and Safety

Existing Text:

_____ Date: _____

PPD
PPD , Global Medical Operations

Revised Text:

PPD name has been removed.

Rationale for Change:

Change in the requirement for protocol approval from Function Head of Clinical Operations to the VP, Clinical Operations/equivalent.

4. Synopsis: Study Design, Section 1.5.1 Design Features, Section 1.5.2 Study Population, Section 1.6 Risk/Benefit and Section 3.1 Study Design

Existing Text:

An open-label, parallel group study characterizing the PD, PK, and safety of HSP-130 in subjects with non-metastatic breast cancer who have not previously received chemotherapy at any point prior to enrollment in this study (ZIN-130-1504).

Revised Text:

An open-label, parallel group study characterizing the PD, PK, and safety of HSP-130 in subjects with non-distantly metastatic (non-Stage IV) breast cancer who have not previously received chemotherapy at any point prior to enrollment in this study (ZIN-130-1504).

Rationale for Change:

To clarify what is meant by metastatic to specifically mean non-distantly metastatic (non-Stage IV) versus, e.g., local/regional lymph node metastases.

5. Synopsis: Study Design and Section 1.5.1: Design Features

Existing Text:

The second group of subjects will receive up to 4 cycles of HSP-130, with concomitant background chemotherapy. Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Chemotherapy will consist of every 3 week taxane/cyclophosphamide-based regimen, e.g., docetaxel, doxorubicin and cyclophosphamide (TAC) or docetaxel and cyclophosphamide (TC).

Revised Text:

The second group of subjects will receive up to 4 cycles of HSP-130, with concomitant background chemotherapy. Patients in Cycles 1-4 will receive HSP-130 after definitive surgery. Chemotherapy will consist of every 3 week taxane/cyclophosphamide-based regimen, i.e., docetaxel, doxorubicin and cyclophosphamide (TAC).

Rationale for Change:

Choice of one specific regimen to limit chemotherapy-induced heterogeneity.

6. Synopsis: Key Inclusion Criteria for all study subjects and Section 4.2: Inclusion criteria

Existing Text:

Chemotherapy naïve, who have not received chemotherapy in the neoadjuvant setting and who are candidates for chemotherapy in the adjuvant setting of taxane/cyclophosphamide-based regimen, e.g.,TAC or TC as background chemotherapy

Revised Text:

Chemotherapy naïve, who have not received chemotherapy in the neoadjuvant setting and who are candidates for chemotherapy in the adjuvant setting of taxane/cyclophosphamide-based regimen, i.e.,TAC as background chemotherapy

Rationale for Change:

Choice of one specific regimen to limit chemotherapy-induced heterogeneity.

7. Synopsis: Key Exclusion Criteria and Section 4.3: Exclusion criteria

Existing Text:

Chemotherapy other than that included in this study (i.e., taxane/cyclophosphamide-based regimen, e.g., TAC or TC) or neoadjuvant chemotherapy; or known immunosuppressive agents including chronic oral corticosteroid use, or radiation therapy within 4 weeks of first dose of HSP-130, prior bone marrow or stem cell transplantation, or malignancy within 5 years

Revised Text:

Chemotherapy other than that included in this study (i.e., taxane/cyclophosphamide-based regimen, i.e., TAC) or neoadjuvant chemotherapy; or known immunosuppressive agents including chronic oral corticosteroid use, or radiation therapy within 4 weeks of first dose of HSP-130, prior bone marrow or stem cell transplantation, or malignancy within 5 years

Rationale for Change:

Choice of one specific regimen to limit chemotherapy-induced heterogeneity.

8. Synopsis: Duration of Treatment, Safety Assessments, Section 1.5.3: Dosing Regimen and Treatment Duration, Section 2.3: Safety Variables and Section 3.3: Estimated Study Duration

Existing Text:

Subjects receiving Regimen B (6 mg), and, if performed, multiple dose Regimen A (3 mg) [and Regimen C (12 mg) if the decision is made with the FDA to pursue a 12 mg dose. See Section 6.3.2 for details], will receive up to 4 doses of HSP-130 in the context of 4 cycles of chemotherapy (21 days per cycle).

Revised Text:

Subjects receiving Regimen B (6 mg), and, if performed, multiple dose Regimen A (3 mg) [and Regimen C (12 mg) if the decision is made with the FDA to pursue a 12 mg dose. See Section 6.3.2 for details], will receive up to 4 doses of HSP-130 in the context of 4 cycles of chemotherapy (≥ 21 days per cycle).

Rationale for Change:

To clarify that chemotherapy cycles will be at least 21 days in duration.

9. Synopsis: Pharmacodynamics and Pharmacokinetics of HSP-130

Existing Text:

Cycle 0:

Pharmacodynamic Sampling/Collection:

Blood samples for ANC (4.0 mL) and $CD34^+$ count (4.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 48, 96, 144, 192, 240, and 312 hours post-dose.

Cycles 1-4:

Pharmacodynamic Sampling/Collection:

Blood samples for ANC (4.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be applied to Cycles 1 and 4 with HSP-130 treatment groups.

Revised Text:

Cycle 0:

Pharmacodynamic Sampling/Collection:

Blood samples for ANC (2.7 mL) and $CD34^+$ count (2.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 48, 96, 144, 192, 240, and 312 hours post-dose.

Cycles 1-4:

Pharmacodynamic Sampling/Collection:

Blood samples for ANC (2.7 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be applied to Cycles 1 and 4 with HSP-130 treatment groups.

Rationale for Change:

Different collection tube size allowed for smaller volume to be collected.

10. Synopsis: Safety Assessments and Section 2.3 Safety Variables

Existing Text:

Cycles 1-4:

In subjects who experience FN and/or ANC $< 0.5 \times 10^9$/L for > 1 week, severe or cumulative cutaneous reactions, or severe (grade 3 or 4) peripheral neuropathy during therapy, the dose of docetaxel will be reduced by 20% or as deemed appropriate by treating physician. Doxorubicin will be reduced by 25% in subjects with FN and /or ANC $< 0.5 \times 10^9$/L for > 1 week or as deemed appropriate by treating physician. In subjects with a platelet count of $< 20 \times 10^9$/L and/or failure to recover to $\geq 100 \times 10^9$/L by Day 20 of a cycle, dosages of doxorubicin and docetaxel will to be reduced by 25% in subsequent cycles or as deemed appropriate by treating physician. If reactions continue at the reduced chemotherapy doses, study treatment will be discontinued and the subject will be withdrawn.

Revised Text:

Cycles 1-4:

In subjects who experience FN and/or ANC $< 0.5 \times 10^9$/L for > 1 week, severe or cumulative cutaneous reactions, or severe (grade 3 or 4) peripheral neuropathy during therapy, the chemotherapy timing and dose will be modified as deemed appropriate by treating physician.

Changes in patients TAC chemotherapy regimen will be determined by the patients treating physician in the context of known TAC toxicity profile and management.

Rationale for Change:

This is a Phase 1-2 ascending dose study to assess the pharmacodynamics, pharmacokinetics, and safety of HSP-130 in subjects with non-metastatic breast cancer following single-dose and multiple-dose administration by subcutaneous injection and not a study of TAC chemotherapy. As such, management of an individual's chemotherapy will be determined by the treating physician not by the ZIN-130-1504 protocol.

11. Principal contacts

Existing Text:

Reporting of Serious Adverse Events (SAEs)	Hospira Global Complaint Management Phone: +PPD Email: PPD Global Product Safety Fax: +PPD

Revised Text:

Reporting of Serious Adverse Events (SAEs)	Hospira Global Product Safety Phone: +PPD Email: PPD Global Product Safety Fax: +PPD

Rationale for Change:

Revised information to reflect that SAEs will be reported to Hospira Global Product Safety instead of Hospira Global Complaint Management. Included updated email ID for SAEs reporting as PPD is the direct mailbox to Global Product Safety who assesses and enters the event information in the Hospira Safety Database. To improve the efficiency of SAE reporting, this direct mailbox is considered more appropriate for clinical studies as the Global Complaint Management.

12. Figure 1 Study Design Schematic

Inserted the following text as footnote in Figure 1

28-44 days are guideline time period based on site scheduling and procedures.

Rationale for Change:

To clarify that 28-44 days is a general guideline and not protocol defined such that if definitive surgery is beyond 44 days, e.g., as inability of surgeon to schedule patient's surgery within 44 days from study drug, this would not be a protocol deviation.

13. Table 1 Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy

Existing Text:

Table 1. Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy

Evaluation	Screening	Site Visit									Follow-up Visit
Study Day	-14 to -1	1	2	3	5	7	9	11	14	20	30 (± 2)
Clinical Assessments/Activities											
Written Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical History	X										
Physical Examination	X										X
Body Weight & Height	X										
Vital Signs [a]	X	X	X	X	X	X	X	X	X	X	X
WHO Performance Status	X	X	X	X	X	X	X	X	X	X	X
CISNE [b]		X				X				X	X
FACT-N		X								X	X
Pregnancy Test [c]	X										X
HSP-130 Administration		X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram	X										X
Chest X-ray (if none within 1 month)	X										
Laboratory Assessments [d]											
Clinical Chemistry	X			X							X
Hematology (including complete blood count + Platelets)	X			X		X			X	X	X
Serology (anti-HIV Abs)	X										

Table 1. Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy											
Evaluation	**Screening**	**Site Visit**									**Follow-up Visit**
Study Day	**-14 to -1**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**14**	**20**	**30 (± 2)**
Urinalysis	X										X
Pharmacodynamic Sampling [e]		X		X	X	X	X	X	X		
Pharmacokinetic Sampling [f]		X	X	X	X	X	X	X	X		
Anti-HSP-130 antibody Sampling [g]		X							X	X	

a. Vital Signs will be measured pre-dose, at approximately the same time at Day 1, each day of PK/PD sampling (Day 2-Day 14), Day 20 and at Follow-up Visit

b. Clinical Index of Stable Febrile Neutropenia (CISNE) : assessment will be completed for each episode of febrile neutropenia

c. Serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization

d. The total blood volume for all laboratory assessments is approximately 200 mL

e. Pharmacodynamic sampling for absolute neutrophil count (ANC), $CD34^+$ count will be collected within 1 hour prior to dose administration and at 48, 96, 144, 192, 240, and 312 hours post-dose

f. Pharmacokinetic sampling will be collected within 1 hour prior to dose at Day 1, and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose

g. Anti-HSP-130 antibody sampling will be collected pre-dose on Day 1 as well as on Day 14 and Day 20.

Revised Text:

Table 1. Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy											
Evaluation	**Screening**	**Site Visit**									**Follow-up Visit**
Study Day	**-14 to -1**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**14**	**20**	**30 (± 2)**
Clinical Assessments/Activities											
Written Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical History	X										
Physical Examination	X										X
Body Weight & Height	X										
Vital Signs [a]	X	X	X	X	X	X	X	X	X	X	X
WHO Performance Status	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Study Activities: Cycle 0: 3 mg or 6 mg SC Injection (s) Without Background Chemotherapy

Evaluation	Screening	Site Visit									Follow-up Visit
Study Day	-14 to -1	1	2	3	5	7	9	11	14	20	30 (± 2)
CISNE [b]		X				X				X	X
FACT-N [c]		X								X	X
Pregnancy Test [d]	X										X
HSP-130 Administration		X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
12-lead Electrocardiogram	X										X
Chest X-ray (if none within 1 month)	X										
Laboratory Assessments [e]											
Clinical Chemistry	X			X		X		X		X	X
Hematology (including complete blood count + Platelets)	X			X		X			X	X	X
Serology (anti-HIV Abs)	X										
Urinalysis	X										X
Spot urine for protein/creatinine ratio (PCR)	X			X				X		X	X
Pharmacodynamic Sampling [f]		X		X	X	X	X	X	X		
Pharmacokinetic Sampling [g]		X	X	X	X	X	X	X	X		
Anti-HSP-130 antibody Sampling [h]		X							X	X	

a. Vital Signs will be measured pre-dose, at approximately the same time at Day 1, each day of PK/PD sampling (Day 2-Day 14), Day 20 and at Follow-up Visit

b. Clinical Index of Stable Febrile Neutropenia (CISNE) : assessment will be completed for each episode of febrile neutropenia

c. As available in local language

d. Serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization

e. The total blood volume for all laboratory assessments is approximately 100 mL

f. Pharmacodynamic sampling for absolute neutrophil count (ANC), $CD34^+$ count will be collected within 1 hour prior to dose administration and at 48, 96, 144, 192, 240, and 312 hours post-dose

g. Pharmacokinetic sampling will be collected within 1 hour prior to dose at Day 1, and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose

h. Anti-HSP-130 antibody sampling will be collected pre-dose on Day 1 as well as on Day 14 and Day 20.

Rationale for Change:

The FACT-N is a licensed, validated patient reported quality of life tool with multiple translations but it is not available in all languages. As of the date of this amendment, there is no Hungarian translation. Will be made available in English, Spanish and, if becomes available, in Hungarian.

The urines to be collected during the study are primarily included for screening for proteinuria. It has been determined that potentially a better option than qualitative urinalysis/dipstick to address this would be for the semi-quantitative spot urine for PCR.

14. Table 2 Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg¥ SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Existing Text:

Table 2. Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg¥ SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Screening	Site Visit											Follow-up Visit[i] (Cycle 4)
Study Day	**-14 to -1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**11**	**12**	**15**	**20**	**30 (± 2)**
Clinical Assessments/Activities													
Written Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Medical History	X												
Physical Examination	X												X
Vital Signs [a]	X	X	X	X	X	X	X	X		X	X	X	X
WHO Performance Status	X	X	X	X	X	X	X	X		X	X	X	X
CISNE [b]		X					X						
FACT-N		X											X
Pregnancy Test [c]	X												X
HSP-130 Administration [d]			X										
Adverse Events	X	X	X	X	X	X	X	X		X	X	X	X

Table 2. Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg[¥] SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Screening	Site Visit											Follow-up Visit[i] (Cycle 4)
Study Day	**-14 to -1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**11**	**12**	**15**	**20**	**30 (± 2)**
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X	X
12-lead Electrocardiogram	X												X
Chest X-Ray (if none within 1 month)	X												
Chemotherapy		X											
Laboratory Assessments [e]													
Clinical Chemistry	X			X		X		X	X	X		X	X
Hematology (including complete blood count + platelets)	X			X		X		X	X	X	X	X	X
Serology (anti-HIV Abs)	X												
Urinalysis	X												X
Pharmacodynamic Sampling [f]			X		X	X	X	X		X	X		
Pharmacokinetic Sampling [g]			X	X	X	X	X	X		X	X		
Anti-HSP-130 antibody Sampling [h]			X									X	

[¥] Enrollment in the 12 mg cohort will occur only after

- review with the FDA of data from Cycle 0 cohorts, and the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and
- only if the exposure pattern of the PK/PD response suggest that higher doses are required. Additional details are available regarding the 12 mg cohort and associated stopping rules in section 6.3.2.

*If decision is made to carry out Regimen A in Cycles 1 and 4, subjects will follow same activities listed above

a. Vital Signs will be measured pre-dose, at approximately the same time at Day 2, and each day of PK/PD sampling (Day 3-Day 15), Day 18, Day 20, and at Follow-up Visit
b. Clinical Index of Stable Febrile Neutropenia (CISNE): assessment will be completed for each episode of febrile neutropenia
c. Serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization
d. In Cycles 1 and 4, subjects will receive treatment with HSP-130 on Day 2 (no less than 24 hours after administration of chemotherapy)
e. The total blood volume for all laboratory assessments is approximately 350 mL

f. Pharmacodynamic sampling for absolute neutrophil count (ANC) will be collected within 1 hour prior to dose administration and at 48, 96, 144, 192, 240, and 312 hours post-dose
g. Pharmacokinetic sampling will be collected within 1 hour prior to dose and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose
h. Anti-HSP-130 antibody sampling will be collected pre-dose on Day 2 and on Day 20
i. These assessments will be carried out at the end of Cycle 4 or at the time of subject termination during the planned course of the study

Revised Text:

Table 2. Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg¥ SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Screening	Site Visit											Follow-up Visit[i] (Cycle 4)
Study Day	**-14 to -1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**11**	**12**	**15**	**20**	**30 (± 2)**
Clinical Assessments/Activities													
Written Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Medical History	X												
Physical Examination	X												X
Vital Signs [a]	X	X	X	X	X	X	X	X		X	X	X	X
WHO Performance Status	X	X	X	X	X	X	X	X		X	X	X	X
CISNE [b]		X					X						
FACT-N [c]		X											X
Pregnancy Test [d]	X												X
HSP-130 Administration [e]			X										
Adverse Events	X	X	X	X	X	X	X	X		X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X	X
12-lead Electrocardiogram	X												X
Chest X-Ray (if none within 1 month)	X												
Chemotherapy		X											
Laboratory Assessments [f]													
Clinical Chemistry	X			X		X		X	X	X		X	X

Table 2. Schedule of Study Activities: Cycles 1 and 4 for Subjects Receiving 6 mg or 12 mg[¥] SC Injection(s) 24 hours Post-Chemotherapy Administration Each Cycle*

Evaluation	Screening	Site Visit											Follow-up Visit[i] (Cycle 4)
Study Day	**-14 to -1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**11**	**12**	**15**	**20**	**30 (± 2)**
Hematology (including complete blood count + platelets)	X			X		X		X	X	X	X	X	X
Serology (anti-HIV Abs)	X												
Urinalysis	X												X
Spot urine for protein/creatinine ratio (PCR)	X			X				X				X	X
Pharmacodynamic Sampling [g]			X		X	X	X	X		X	X		
Pharmacokinetic Sampling [h]			X	X	X	X	X	X		X	X		
Anti-HSP-130 antibody Sampling [i]			X									X	

[¥] Enrollment in the 12 mg cohort will occur only after

- review with the FDA of data from Cycle 0 cohorts, and the Cycles 1-4 for 6 mg cohort (and 3 mg cohort, if performed) and
- only if the exposure pattern of the PK/PD response suggest that higher doses are required. Additional details are available regarding the 12 mg cohort and associated stopping rules in section 6.3.2.

*If decision is made to carry out Regimen A in Cycles 1 and 4, subjects will follow same activities listed above

a. Vital Signs will be measured pre-dose, at approximately the same time at Day 2, and each day of PK/PD sampling (Day 3-Day 15), Day 18, Day 20, and at Follow-up Visit
b. Clinical Index of Stable Febrile Neutropenia (CISNE): assessment will be completed for each episode of febrile neutropenia
c. As available in local language
d. Serum pregnancy test for all subjects except those who are postmenopausal for 5 years or have undergone surgical sterilization
e. In Cycles 1 and 4, subjects will receive treatment with HSP-130 on Day 2 (no less than 24 hours after administration of chemotherapy)
f. The total blood volume for all laboratory assessments is approximately 250 mL
g. Pharmacodynamic sampling for absolute neutrophil count (ANC) will be collected within 1 hour prior to dose administration and at 48, 96, 144, 192, 240, and 312 hours post-dose
h. Pharmacokinetic sampling will be collected within 1 hour prior to dose and at 6, 12, 24, 48, 96, 144, 192, 240, and 312 hours post-dose
i. Anti-HSP-130 antibody sampling will be collected pre-dose on Day 2 and on Day 20
j. These assessments will be carried out at the end of Cycle 4 or at the time of subject termination during the planned course of the study

Rationale for Change:

The FACT-N is a licensed, validated patient reported quality of life tool with multiple translations but it is not available in all languages. As of the date of this amendment, there is no Hungarian translation. Will be made available in English, Spanish and, if becomes available, in Hungarian.

The urines to be collected during the study are primarily included for screening for proteinuria. It has been determined that potentially a better option than qualitative urinalysis/dipstick to address this would be for the semi-quantitative spot urine for PCR.

15. Glossary of Abbreviations:

Existing Text:

Abbreviation/Acronym	Definition
TC	docetaxel and cyclophosphamide

Revised Text:

Deleted TC and added the following abbreviations.

Abbreviation/Acronym	Definition
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
PCR	protein/creatinine ratio
WHO	World Health Organization

Rationale for Change:

Updated for accuracy, completeness, and consistency.

16. Section 1.5.4: Selection of Pharmacodynamic Endpoints

Existing Text:

Secondary PD parameters include DSN in Cycle 4, ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of febrile neutropenia, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour and ANC < 0.5 x 10^9/L,

incidence of severe neutropenia (grade 4) and time to ANC recovery (the first day with ANC $\geq$ 2.0 x 10^9/L after any day with ANC < 2.0 x 10^9/L) in Cycle 1 and Cycle 4.

Revised Text:

Secondary PD parameters include DSN in Cycle 4, ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of febrile neutropenia, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour and ANC < 1.0 x 10^9/L, incidence of severe neutropenia (grade 4, ANC < 0.5 x 10^9/L) and time to ANC recovery (the first day with ANC $\geq$ 2.0 x 10^9/L after any day with ANC < 2.0 x 10^9/L) in Cycle 1 and Cycle 4.

Rationale for Change:

Correction of typographical error for consistency, and accuracy.

17. Section 2.5.1 Performance Status

Existing Text:

Table 5. The WHO/Zubrod Scale

Revised Text:

Table 5. The WHO/Zubrod/ECOG Scale

Rationale for Change:

All of these terms are used for the same performance status scale but can be variously referred to based on local/regional variations. This was revised for clarification.

18. Section 6.2.4: Physical Examination

Existing Text:

A physical examination will be performed at Screening and at the Follow-up Visit (after Cycle 0 and after Cycle 4) or upon subject discontinuation.

Revised Text:

A physical examination will be performed at Screening and at the Follow-up Visit (after Cycle 0 and after Cycle 4) or upon subject discontinuation. Physical examination will specifically include physical assessment of the spleen.

Rationale for Change:

One of the risks associated with use of G-CSFs is that of splenomegaly or splenic rupture. As such it was felt important to underscore the importance that any and all physical examinations that are included in the protocol must include physical assessment of the spleen.

19. Section 6.2.8: Clinical Laboratory Tests and Section 10.2.5: Assessment of Safety

Existing Text:

Laboratory abnormalities will be considered as AEs only if they result in discontinuation from the study, necessitate therapeutic intervention, and/or if the Investigator considers them to be AEs.

Revised Text:

Laboratory abnormalities will be considered as AEs only if they result in discontinuation from the study, necessitate therapeutic intervention, and/or if the Investigator considers them to be AEs. Grading of laboratory abnormalities will be according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (6).

Existing Text:

Treatment emergent adverse events (TEAEs) will be summarized by system organ class and preferred terms (PT). Descriptive statistics including N, mean, SD, minimum and maximum for numerical data, and counts and frequency for categorical data, will be tabulated for laboratory tests, and vital signs by treatment group.

Revised Text:

Treatment emergent adverse events (TEAEs) will be summarized by system organ class and preferred terms (PT). Descriptive statistics including N, mean, SD, minimum and maximum for numerical data, and counts and frequency for categorical data, will be tabulated for laboratory tests, and vital signs by treatment group. Grading of laboratory abnormalities will be according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (6).

Rationale for Change:

Grading of laboratory abnormalities clinically and within the context of clinical trials in oncology utilize the CTCAE and this was added for clarity and completeness.

20. Section 6.2.12: Total Blood Volume to be Collected During the Study

Existing Text:

For subjects who enroll in Cycle 0 group the total blood volume sampled is approximately 347 mL, which breaks down as follows:

- 200 mL of blood collected for clinical laboratory assessments
- 56 mL of blood collected for PD assessments
- 70 mL of blood collected for PK analyses
- 21 mL of blood collected for anti-HSP-130 antibody testing

For subjects enroll in Cycles 1-4 group the total blood volume sampled is approximately 574 mL, which breaks down as follows:

- 350 mL of blood collected for clinical laboratory assessments
- 56 mL of blood collected for PD assessments
- 140 mL of blood collected for PK analyses
- 28 mL of blood collected for anti-HSP-130 antibody testing

Total blood volume for subjects will include an additional 10-15 mL taken for pregnancy testing.

Any additional blood that may be taken is unlikely to cause the total volume of blood to exceed approximately 362 mL for Cycle 0 group and 589 mL for Cycles 1-4 group.

Revised Text:

For subjects who enroll in Cycle 0 group the total blood volume sampled is approximately 224 mL, which breaks down as follows:

- 100 mL of blood collected for clinical laboratory assessments
- 32.9 mL of blood collected for PD assessments
- 70 mL of blood collected for PK analyses
- 21 mL of blood collected for anti-HSP-130 antibody testing

For subjects enroll in Cycles 1-4 group the total blood volume sampled is approximately 456 mL, which breaks down as follows:

- 250 mL of blood collected for clinical laboratory assessments
- 37.8 mL of blood collected for PD assessments
- 140 mL of blood collected for PK analyses
- 28 mL of blood collected for anti-HSP-130 antibody testing

Total blood volume for subjects will include an additional 10-15 mL taken for pregnancy testing.

Any additional blood that may be taken is unlikely to cause the total volume of blood to exceed approximately 239 mL for Cycle 0 group and 471 mL for Cycles 1-4 group.

Rationale for Change:

Different collection tube size allowed for smaller volume to be collected.

21. Section 6.4.1: Pharmacodynamic sampling

Existing Text:

Cycle 0

Blood samples for ANC (4.0 mL) and $CD34^+$ count (4.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 48, 96, 144, 192, 240, and 312 hours post-dose.

The total number of samples planned for PD analysis (ANC and $CD34^+$ count) in Cycle 0 is 7, resulting in approximately 56 mL of blood volume.

Cycles 1-4

Blood samples for ANC (2.7 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be only applied to Cycles 1 and 4 with HSP-130 treatment groups.

The total number of samples planned for PD analysis (ANC) in Cycles 1 and 4 is 14, resulting in approximately 37.8 mL of blood volume.

Revised Text:

Cycle 0

Blood samples for ANC (2.7 mL) and $CD34^+$ count (2.0 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 1 and at 48, 96, 144, 192, 240, and 312 hours post-dose.

The total number of samples planned for PD analysis (ANC and $CD34^+$ count) in Cycle 0 is 7, resulting in approximately 32.9 mL of blood volume.

Cycles 1-4

Blood samples for ANC (2.7 mL) will be collected by venipuncture into evacuated collection tubes within 1 hour prior to dose administration on Day 2 of the chemotherapy cycle and at 48, 96, 144, 192, 240, and 312 hours post-dose. This sample collection schedule will be only applied to Cycles 1 and 4 with HSP-130 treatment groups.

The total number of samples planned for PD analysis (ANC) in Cycles 1 and 4 is 14, resulting in approximately 37.8 mL of blood volume.

Rationale for Change:

Different collection tube size allowed for smaller volume to be collected.

22. Section: 8.1.2 Adverse Events of Special Interest and Section: 10.2.5.1 Adverse Events

Existing Text:

1. Potential Allergic Reactions, including Anaphylactic Reactions, Angioedema, Hypersensitivity
2. Splenomegaly/Splenic Rupture
3. Acute Respiratory Distress Syndrome
4. Alveolar Hemorrhage
5. Hemoptysis
6. Leukocytosis
7. Thrombocytopenia
8. Capillary Leak Syndrome
9. Cytokine Release Syndrome

10. Cutaneous Manifestations

Revised Text:

1. Potential Allergic Reactions
2. Splenomegaly
3. Splenic rupture
4. Acute Respiratory Distress Syndrome
5. Alveolar Hemorrhage
6. Hemoptysis
7. Leukocytosis
8. Thrombocytopenia
9. Capillary Leak Syndrome
10. Cytokine Release Syndrome
11. Cutaneous Vasculitis

Rationale for Change:

Correction for consistency, and accuracy.

23. Section: 8.5 Serious Adverse Event Reporting

Existing Text:

In the event of a SAE, whether related to HSP-130 or not, the Principal Investigator or representative must make an accurate and adequate report within 24 hours by telephone, email, or fax to Hospira Global Complaint Management or Global Product Safety.

Hospira Global Complaint Management Phone: PPD Email: PPD Global Product Safety Fax: PPD

Revised Text:

In the event of a SAE, whether related to HSP-130 or not, the Principal Investigator or representative must make an accurate and adequate report within 24 hours by telephone, email, or fax to Hospira Global Product Safety.

Hospira Global Product Safety Phone: +PPD Email: PPD Global Product Safety Fax: +PPD

Rationale for Change:

Revised information to reflect that SAEs will be reported to Hospira Global Product Safety instead of Hospira Global Complaint Management. Included updated email ID for SAEs reporting as PPD is the direct mailbox to Global Product Safety who assesses and enters the event information in the Hospira Safety Database. To improve the efficiency of SAE reporting, this direct mailbox is considered more appropriate for clinical studies as the Global Complaint Management.

24. Section: 10.2.3 Assessment of Pharmacodynamics and Pharmacokinetics

Existing Text:

Pharmacodynamic parameters of DSN (defined as days with grade 4 neutropenia [ANC $< 0.5 \times 10^9$/L]) in Cycle 1, DSN in Cycle 4, ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of febrile neutropenia, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour and ANC $< 0.5 \times 10^9$/L, incidence of severe neutropenia (grade 4) and time to ANC recovery (the first day with ANC $\geq 2.0 \times 10^9$/L after any day with ANC $< 2.0 \times 10^9$/L) in Cycle 1 and Cycle 4 will be calculated for assessment.

Revised Text:

Pharmacodynamic parameters of DSN (defined as days with grade 4 neutropenia [ANC $< 0.5 \times 10^9$/L]) in Cycle 1, DSN in Cycle 4, ANC nadir concentration, time of nadir concentration, area under the effect curve (AUEC), incidence of febrile neutropenia, defined as tympanic or axillary body temperature > 38.5°C for > 1 hour and ANC $< 1.0 \times 10^9$/L, incidence of severe neutropenia (grade 4, ANC $< 0.5 \times 10^9$/L) and time to ANC recovery (the first day with ANC $\geq 2.0 \times 10^9$/L after any day with ANC $< 2.0 \times 10^9$/L) in Cycle 1 and Cycle 4 will be calculated for assessment.

Rationale for Change:

Correction of typographical error for consistency, and accuracy.

25. Section: 10.2.5.1 Definitions of Adverse Events of Special Interest

Existing Text:

MedDRA version 17.1 is employed in this study to code event terms. adverse events of special interest are defined in the PEG-14-04 Statistical Analysis Plan. The adverse events of special interest were identified based on the safety profile of the originator product in accordance with the US prescribing information for approved US-approved G-CSFs (pegfilgrastim and filgrastim, Neulasta and Neupogen, respectively) and any potential preclinical or clinical Nivestim (Hospira filgrastim) data that may inform the safety characterization for HSP-130.

The methodology employed to medically group together similar medical constructs within MedDRA was as follows: where a SMQ in MedDRA 17.1 exists to summarize the adverse event of interest, the SMQ was employed to medically group together the PTs. In order to ensure adequate specificity, the SMQ narrow in MedDRA 17.1 was employed to offer a sensitive, but adequately specific approach to summarizing the adverse event of special interest. If an SMQ was not available in MedDRA 17.1 to summarize the adverse event of interest, a selection of PTs was identified by the sponsor to provide a medically comprehensive grouping of the medical concept. The adverse events of special interest for HSP-130 are outlined below including the preferred terms summarized within each adverse event of special interest.

Adverse Events of Special Interest:

1. **Potential Allergic Reactions defined by the MedDRA 17.1 SMQ Angioedema (narrow) and Anaphylactic Reactions (narrow) and Hypersensitivity (narrow) with the following PTs:**

Anaphylactic Reactions

Anaphylactic reaction	Anaphylactoid reaction	First use syndrome	Type I hypersensitivity
Anaphylactic shock	Anaphylactoid shock	Kounis syndrome	
Anaphylactic transfusion reaction	Circulatory collapse	Shock	

Angioedema

Allergic oedema	Face oedema	Lip oedema	Small bowel angioedema
Angioedema	Gingival oedema	Lip swelling	Swelling face
Circumoral oedema	Gingival swelling	Oculorespiratory syndrome	Swollen tongue
Conjunctival oedema	Gleich's syndrome	Oedema mouth	Tongue oedema
Corneal oedema	Hereditary angioedema	Oropharyngeal swelling	Tracheal oedema
Epiglottic oedema	Idiopathic urticaria	Palatal oedema	Urticaria

Eye oedema	Laryngeal oedema	Periorbital oedema	Urticaria cholinergic
Eye swelling	Laryngotracheal oedema	Pharyngeal oedema	Urticaria chronic
Eyelid oedema	Limbal swelling	Scleral oedema	Urticaria papular
Mouth swelling	Palatal swelling		

Hypersensitivity

Hypersensitivity	Documented hypersensitivity to administered drug	Oropharyngeal blistering	
Drug hypersensitivity	Drug eruption	Oropharyngeal spasm	
Acute generalised exanthematous pustulosis		Oropharyngeal swelling	
Administration site hypersensitivity	Drug provocation test	Palatal oedema	
Administration site rash	Drug reaction with eosinophilia and systemic symptoms	Palatal swelling	
Administration site urticaria	Eczema	Palisaded neutrophilic granulomatous dermatitis	
Allergic bronchitis	Eczema infantile	Palpable purpura	
Allergic colitis	Eczema nummular	Pathergy reaction	
Allergic cough	Eczema vaccinatum	Periorbital oedema	
Allergic cystitis	Eczema vesicular	Pharyngeal oedema	
Allergic eosinophilia	Eczema weeping	Pruritus allergic	
Allergic gastroenteritis	Encephalitis allergic	Radioallergosorbent test positive	
Allergic granulomatous angiitis	Encephalopathy allergic	Rash	
Allergic hepatitis	Epidermal necrosis	Rash erythematous	
Allergic keratitis	Epidermolysis	Rash follicular	
Allergic myocarditis	Epidermolysis bullosa	Rash generalised	
Allergic oedema	Epiglottic oedema	Rash macular	
Allergic otitis externa	Erythema multiforme	Rash maculo-papular	
Allergic otitis media	Erythema nodosum	Rash maculovesicular	
Allergic pharyngitis	Exfoliative rash	Rash morbilliform	
Allergic respiratory disease	Eye allergy	Rash neonatal	

Allergic respiratory symptom	Eye oedema	Rash papulosquamous	
Allergic sinusitis	Eye swelling	Rash pruritic	
Allergic transfusion reaction	Eyelid oedema	Rash pustular	
Allergy test positive	Face oedema	Rash rubelliform	
Allergy to immunoglobulin therapy	First use syndrome	Rash scarlatiniform	
Allergy to vaccine	Giant papillary conjunctivitis	Rash vesicular	
Alveolitis allergic	Gingival oedema	Reaction to azo-dyes	
Anaphylactic reaction	Gingival swelling	Reaction to colouring	
Anaphylactic shock	Gleich's syndrome	Reaction to drug excipients	
Anaphylactic transfusion reaction	Haemorrhagic urticaria	Reaction to preservatives	
Anaphylactoid reaction	Hand dermatitis	Red man syndrome	
Anaphylactoid shock	Henoch-Schonlein purpura	Rhinitis allergic	
Anaphylaxis treatment	Henoch-Schonlein purpura nephritis	Scleral oedema	
Angioedema	Heparin-induced thrombocytopenia	Scleritis allergic	
Antiallergic therapy	Hereditary angioedema	Scrotal oedema	
Antiendomysial antibody positive		Serum sickness	
Anti-neutrophil cytoplasmic antibody positive vasculitis	Hypersensitivity vasculitis	Serum sickness-like reaction	
Application site dermatitis	Idiopathic urticaria	Shock	
Application site eczema	Immediate post-injection reaction	Skin necrosis	
Application site hypersensitivity	Immune thrombocytopenic purpura	Skin reaction	
Application site rash	Immune tolerance induction	Skin test positive	
Application site urticaria	Implant site dermatitis	Small bowel angioedema	
Arthritis allergic	Implant site hypersensitivity	Solar urticaria	

Aspirin-exacerbated respiratory disease	Implant site rash	Solvent sensitivity	
Atopy	Implant site urticaria	Stevens-Johnson syndrome	
Blepharitis allergic	Incision site dermatitis	Stoma site hypersensitivity	
Blood immunoglobulin E abnormal	Incision site rash	Stoma site rash	
Blood immunoglobulin E increased	Infusion site dermatitis	Swelling face	
Bromoderma	Infusion site eczema	Swollen tongue	
Bronchospasm	Infusion site hypersensitivity	Tongue oedema	
Catheter site dermatitis	Infusion site rash	Toxic epidermal necrolysis	
Catheter site eczema	Infusion site urticaria	Toxic skin eruption	
Catheter site hypersensitivity	Infusion site vasculitis	Tracheal oedema	
Catheter site rash	Injection site dermatitis	Type I hypersensitivity	
Catheter site urticaria	Injection site hypersensitivity	Type II hypersensitivity	
Catheter site vasculitis	Injection site rash	Type III immune complex mediated reaction	
Chronic eosinophilic rhinosinusitis	Injection site urticaria	Type IV hypersensitivity reaction	
Chronic hyperplastic eosinophilic sinusitis	Injection site vasculitis	Urticaria	
Circulatory collapse	Interstitial granulomatous dermatitis	Urticaria cholinergic	
Circumoral oedema	Iodine allergy	Urticaria chronic	
Conjunctival oedema	Kaposi's varicelliform eruption	Urticaria contact	
Conjunctivitis allergic	Kounis syndrome	Urticaria papular	
Contact stomatitis	Laryngeal oedema	Urticaria physical	
Contrast media allergy	Laryngitis allergic	Urticaria pigmentosa	
Contrast media reaction	Laryngospasm	Urticaria vesiculosa	
Corneal oedema	Laryngotracheal	Vaccination site	

	oedema	dermatitis	
Cutaneous vasculitis	Limbal swelling	Vaccination site exfoliation	
Dennie-Morgan fold	Lip oedema	Vaccination site hypersensitivity	
Dermatitis	Lip swelling	Vaccination site rash	
Dermatitis acneiform	Mouth swelling	Vaccination site urticaria	
Dermatitis allergic	Mucocutaneous rash	Vaccination site vesicles	
Dermatitis atopic	Multiple allergies	Vaginal exfoliation	
Dermatitis bullous	Nephritis allergic	Vaginal ulceration	
Dermatitis contact	Nikolsky's sign	Vasculitic rash	
Dermatitis exfoliative	Oculomucocutaneous syndrome	Vulval ulceration	
Dermatitis exfoliative generalised	Oculorespiratory syndrome	Vulvovaginal rash	
Dermatitis herpetiformis	Oedema mouth	Vulvovaginal ulceration	
Dermatitis infected	Oral allergy syndrome		
Dermatitis psoriasiform			
Distributive shock			

2. **Splenomegaly/Splenic Rupture defined by the MedDRA v 17.1 with the following PT:** Splenic rupture/splenomegaly

3. **Acute Respiratory Distress Syndrome (ARDS) defined by the MedDRA v 17.1 with the following PT:** Acute Respiratory Distress syndrome

4. **Alveolar Hemorrhage/Hemoptysis defined by the MedDRA v 17.1 with the following PTs:** Pulmonary alveolar haemorrhage and Pulmonary haemorrhage

5. **Alveolar Hemorrhage / Hemoptysis defined by the MedDRA v 17.1 with the following PT:** Hemoptysis

6. **Leukocytosis defined by the MedDRA v 17.1 with the following PTs:**

Leukocytosis	Lymphocytosis	Neutrophilia	
Granulocytosis	Monocytosis		

7. **Thrombocytopenia defined by the MedDRA v 17.1 with the following PTs:**

Thrombocytopenia	Mean platelet volume decreased		
Platelet production decreased	Platelet count abnormal		

8. **Capillary leak syndrome defined by the MedDRA v 17.1 with the following PT:** Capillary leak syndrome

9. **Cytokine release syndrome defined by the MedDRA v 17.1 with the following PT:** Cytokine release syndrome

10. Cutaneous manifestations defined by the MedDRA v 17.1 with the following PTs:

Drug eruption	Rash pruritic	Drug rash	Skin vasculitis
Rash maculopapular	Allergic rash	Allergic vasculitis	Vasculitis allergic
Hypersensitivity vasculitis	Cutaneous vasculitis	Cutaneous hypersensitivity	

An AE will be considered to be treatment-emergent if the event started or worsened in severity after the HSP-130 administration up to and including 30 days post HSP-130 administration. For TEAEs, the number and percentage of subjects who reported each PT will be summarized by treatment groups. Category of severity (mild, moderate, severe) and relationship to HSP-130 (related, not related) will be summarized by treatment group for TEAEs. Adverse events missing an indicated relationship to HSP-130 will be considered related to HSP-130.

SAEs will be summarized by each treatment group and listed by each subject.

Revised Text:

MedDRA version 17.1 or later is employed in this study to code event terms. Adverse Events of Special Interest are defined in the Statistical Analysis Plan. The Adverse Events of Special Interest were identified based on the safety profile of the originator product in accordance with the US prescribing information for approved US-approved G-CSFs (pegfilgrastim and filgrastim, Neulasta and Neupogen, respectively) and any potential preclinical or clinical Nivestim (EU-approved Hospira filgrastim) data that may inform the safety characterization for HSP-130.

The methodology employed to medically group together similar medical constructs within MedDRA was as follows: where a SMQ in MedDRA 17.1 or later exists to summarize the adverse event of interest, the SMQ was employed to medically group together the PTs. In order to ensure adequate specificity, the SMQ narrow in MedDRA 17.1 or later was employed to offer a sensitive, but adequately specific approach to summarizing the adverse event of special interest. If an SMQ was not available in MedDRA 17.1 or later to summarize the adverse event of interest, a selection of PTs was identified by the sponsor to provide a medically comprehensive grouping of the medical concept.

An AE will be considered to be treatment-emergent if the event started or worsened in severity after the HSP-130 administration up to and including 30 days post HSP-130 administration. For TEAEs, the number and percentage of subjects who reported each PT will be summarized by treatment groups. Category of severity (mild, moderate, severe) and relationship to HSP-130 (related, not related) will be summarized by treatment group for

TEAEs. Adverse events missing an indicated relationship to HSP-130 will be considered related to HSP-130.

SAEs will be summarized by each treatment group and listed by each subject.

Rationale for Change:

Modified text to provide a revised definition for treatment-emergent AEs and the definition for AEs related to the study drug. Updated information to provide better clarity on the basis for the identification of Adverse Events of Special Interest for ZIN 130-1504 study.

The Adverse Events of Special Interest section is revised to remove information on the PTs for each Adverse Event of Special Interest in order to harmonize this protocol with the other protocols across programs. Updated information to reflect that MedDRA version 17.1 or later will be used for coding adverse events and AESIs.

26. Section 13: References

Existing Text:

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Revised Text:

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17. NCCN Clinical Practice Guidelines on Oncology (NCCN guidelines®), Myeloid Growth Factors. Version 1, 2015. Available at http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed on 23 Nov 2015.

19. Neupogen® (Amgen) Prescribing Information, 07/2015. Available at http://pi.amgen.com/united_states/neupogen/neupogen_pi_hcp_english.pdf . Accessed on 23 Nov 2015.

21. Yang BB, Lum P, Neumann T, Nguyen S, Roskos L. Pharmacokinetic rationale for a fixed-dose regimen of a sustained-duration form of filgrastim in cancer patients [abstract]. Blood. 2000;96(11 Suppl. 1):157b.

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Rationale for Change:

Updated for accuracy.

27. Appendix E. Adverse Events – Categorized as SAEs

Existing Text:

A.
Abortion
Acute liver failure
Acute respiratory (pulmonary) failure
Acute renal failure
Acute adrenocortical insufficiency
Adrenal hemorrhage
Acute Respiratory Distress Syndrome (ARDS)
Agranulocytosis
Alveolitis, allergic or fibrosing
Anemia, aplastic
Anemia, hemolytic
Anaphylaxis, anaphylactic shock

Anaphylactoid reaction
Aplastic bone marrow
Apnea (all ages)
Asphyxia, all ages
Asystole
Attempted suicide
AV Block, third degree (aka, complete heart block)

B.

Acute blindness
Brain death
Brain stem hemorrhage

C.

Cardiac arrest/circulatory arrest/cardiorespiratory arrest
Cardiomyopathy
Cavernous sinus thrombosis
Cerebral edema
Cerebral vascular accident (stroke) includes hemorrhagic, thrombotic, embolic strokes to any region of the brain
Cheyne-Stokes Respiration
Colitis, hemorrhagic, pseudomembranous or ulcerative
Coma (all types)
Convulsions (seizures), all types
Creutzfeldt-Jakob Disease

D.

Deafness, acute
Death (all types)
Delirium
Disseminated Intravascular Coagulation (DIC)

E.

Embolism, arterial
Embolism, pulmonary
Encephalomyelitis
Encephalopathy
Epiglottitis
Erythema Multiforme

F.

Fibrillation, ventricular
Fibrosis, mediastinal

Fetal distress, demise

G.

Gangrene
Glomerulonephritis
Goodpasture Syndrome
Guillain-Barre Syndrome

H.

Hemolytic-uremic syndrome
Hemorrhage, all intracranial
Hemorrhage, neonatal
Hemorrhage, retroperitoneal
Hepatitis, infectious and non-infectious
Hemopericardium
Hemothorax
Hepatic encephalopathy
Hepatic failure, necrosis
Hepatocellular damage, neonatal
Hepato-renal syndrome
Hyperpyrexia, Malignant ("Malignant Hyperthermia")

I.

Intestinal ischemia, necrosis or death
Intestinal perforation or stenosis
Intrauterine death

L.

Laryngeal edema
Leukemia
Leukoencephalopathy, reversible or posterior multifocal
Lymphoma

M.

Malignancy, primary occurrence (Excludes non-melanotic skin cancer)
Malignant hypertension
Manic reaction
Meningitis
MS aggravation or MS like syndrome
Myelitis
Myeloproliferative disorder
Myocardial infarction

Myocarditis
Myositis

N.

Neonatal respiratory failure
Nephritis
Nephropathy, toxic
Neuroleptic Malignant Syndrome

O.

Optic nerve atrophy, neuritis

P.

Pancreatitis
Pancytopenia
Pemphigus
Peritonitis
Phlebitis, deep (DVT)
Pleural fibrosis
Polyarteritis Nodosa
Pregnancy, ectopic
Pulmonary hypertension, primary
Pulmonary fibrosis
Pulmonary hemorrhage, infarction
Pulmonary embolism
Pulmonary edema (acute)
Pure Red Cell Aplasia (PRCA)
Purpura
Psychosis, acute onset

Q.

Quadriplegia

R.

Red cell aplasia
Renal failure, acute
Renal Tubular Necrosis
Respiratory distress Syndrome (neonatal)
Respiratory arrest
Respiratory depression, neonatal
Respiratory paralysis
Retrobulbar neuritis

Retroperitoneal Fibrosis
Reye's syndrome
Rhabdomyolysis

S.

Sagittal Sinus Thrombosis
Sclerosing syndromes
Seizure
Serotonin Syndrome
Status asthmaticus
Status epilepticus
Stevens-Johnson Syndrome
Stillbirth
Subarachnoid hemorrhage
Subdural hemorrhage/hematoma
Sudden Infant Death Syndrome (SIDS)

T.

Thrombocytopenia with platelet count < 50,000 (severe)
Thromboembolism
Thrombosis (excluding superficial sites)
Torsades De Pointes
Toxic Epidermal Necrolysis

U.

Uterine perforation

V.

Vasculitis

W.

Wallenberg Syndrome
Withdrawal syndrome

Revised Text:

A: Abortion (non-elective)**;** Acute respiratory (pulmonary) failure**;** Adrenal hemorrhage**;** Agranulocytosis**;** Anemia, aplastic**;** Anaphylaxis, anaphylactic shock; Anaphylactoid reaction**;** Aorto-oesophageal fistula, Aplastic bone marrow**;** Apnea (all ages)**;** Asphyxia (all ages)**;** Asystole**;** Attempted suicide**;** AV Block, third degree (aka, complete heart block)

B: Acute blindness; Brain death

C: Cardiac arrest/circulatory arrest/cardiorespiratory arrest; Cavernous sinus thrombosis; Cerebral edema; Cerebral vascular accident (stroke) includes hemorrhagic, thrombotic,

embolic strokes to any region of the brain; Congenital anomalies (non-trivial); Coma (all types); Creutzfeldt-Jakob Disease

D: Deafness, acute; Death (all types); Disseminated Intravascular Coagulation (DIC), Dysplasia; Deep vein thrombosis (DVT)

E: Encephalomyelitis; Encephalopathy **F:** Fibrillation, ventricular; Fetal distress, demise

G: Gangrene; Gastrointestinal obstruction; Gastrointestinal perforation; Gastrointestinal rupture; Genitourinary obstruction; Genitourinary tract rupture; Genitourinary tract perforation; Glaucoma

H: Hemorrhage, neonatal; Hemorrhage, retroperitoneal; Hepatitis, infectious and non-infectious; Hemopericardium; Hepatic encephalopathy; Hepatic failure, necrosis; Hepatocellular damage, neonatal; Hepato-renal syndrome; Hyperpyrexia, Malignant ("Malignant Hyperthermia")

I: Intestinal ischemia, necrosis or death; Intrauterine death; Infarction (myocardial, pulmonary, etc.)

L: Laryngeal edema; Leukemia; Liver failure; Leukoencephalopathy, reversible or posterior multifocal; Lymphoma

M: Malignancy, primary occurrence. Excludes non-melanotic skin cancer; Malignant hypertension; Meningitis; MS aggravation or MS-like syndrome; Myelitis; Myeloproliferative disorder

N: Neuroleptic Malignant Syndrome

P: Pancytopenia; Pleural fibrosis; Pregnancy, ectopic; Pulmonary hypertension, primary; Pulmonary fibrosis; Pulmonary hemorrhage; Pulmonary edema (acute); Psychosis, acute onset

Q: Quadriplegia

R: Red cell aplasia; Renal failure, acute; Respiratory Distress Syndrome (neonatal)**;** Respiratory arrest; Respiratory depression, neonatal; Respiratory paralysis; Respiratory obstruction; Respiratory tract perforation; respiratory tract rupture; Retrobulbar neuritis; Retinopathies; Retroperitoneal Fibrosis; Reye's syndrome

S: Sagittal sinus thrombosis; Sepsis/Septicemia; Status asthmaticus; Status epilepticus; Stevens-Johnson Syndrome; Stillbirth; Sudden Infant Death Syndrome (SIDS)

T: Thrombocytopenia with platelet count <50,000 (severe); Thrombosis (excluding superficial sites); Torsades De Pointes; Toxic Epidermal Necrolysis

U: Uterine perforation

V: Vascular occlusion

W: Wallenberg Syndrome

Rationale for Change:

The AEs that are always considered SAEs was updated to the current version.

28. Appendix F Neulasta® (pegfilgrastim, Amgen) Summary of Product Characteristics

Existing Text:

Summary of Product Characteristics Updated 22-Aug-2014| Amgen Ltd

Revised Text:

Summary of Product Characteristics Updated May-2015| Amgen Ltd

Rationale for Change:

Updated for accuracy.

Appendix H. Neulasta® (pegfilgrastim, Amgen) Package Insert

The Neulasta Package Insert is appended below

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEULASTA safely and effectively. See full prescribing information for NEULASTA.

NEULASTA® (pegfilgrastim) injection, for subcutaneous use
Initial U.S. Approval: 2002

----------RECENT MAJOR CHANGES----------

• Indications and Usage (1.2)	11/2015
• Dosage and Administration (2.2, 2.3)	11/2015
• Warnings and Precautions (5.6, 5.7, 5.8)	09/2015
• Dosage and Administration (2.4, 2.5)	12/2014
• Warnings and Precautions (5.4)	12/2014

----------INDICATIONS AND USAGE----------

Neulasta is a leukocyte growth factor indicated to

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (1.1)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2)

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

----------DOSAGE AND ADMINISTRATION----------

- Patients with cancer receiving myelosuppressive chemotherapy
  - 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
  - Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
  - Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)
- Patients acutely exposed to myelosuppressive doses of radiation
  - Two doses, 6 mg each, administered subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. (2.2)
  - Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only. (3)
- Injection: 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta.

----------CONTRAINDICATIONS ----------

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim. (4)

----------WARNINGS AND PRECAUTIONS----------

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction (5.4)
- Fatal sickle cell crises: Have occurred. (5.5)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Neulasta if causality is likely. (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *[see Clinical Studies (14.1)]*.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

1.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation *[see Dosage and Administration (2.2) and Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

The recommended dose of Neulasta is two doses, 6 mg each, administered subcutaneously one week apart. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.

Obtain a baseline complete blood count (CBC). Do not delay administration of Neulasta if a CBC is not readily available. Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

2.3 Administration

Neulasta is administered subcutaneously via a single prefilled syringe for manual use or for use with the On-body Injector for Neulasta which is co-packaged with a single prefilled syringe. Use of the On-body Injector for Neulasta has not been studied in pediatric patients.

Pediatric Patients weighing less than 45 kg

The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg

Body Weight	Neulasta Dose	Volume to Administer
Less than 10 kg*	See below*	See below*
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 44 kg	4 mg	0.40 mL

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta.

Visually inspect parenteral drug products (prefilled syringe) for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

The needle cap on the prefilled syringes contains dry natural rubber (derived from latex); persons with latex allergies should not administer these products.

2.4 Special Healthcare Provider Instructions for the On-body Injector for Neulasta

A healthcare provider must fill the On-body Injector with Neulasta using the prefilled syringe and then apply the On-body Injector for Neulasta 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 On-body Injector for Neulasta. Approximately 27 hours after the On-body Injector for Neulasta is applied to the patient's skin, Neulasta will be delivered over approximately 45 minutes. A healthcare provider may initiate administration with the On-body Injector for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the On-body Injector for Neulasta delivers Neulasta no less than 24 hours after administration of cytotoxic chemotherapy.

The prefilled syringe co-packaged in Neulasta Onpro™ kit must only be used with the On-body Injector for Neulasta. The prefilled syringe contains additional solution to compensate for liquid loss during delivery through the On-body Injector for Neulasta. If the prefilled syringe co-packaged in Neulasta Onpro kit is used for manual subcutaneous injection, the patient will receive an overdose. If the single use prefilled syringe for manual use is used with the On-body Injector for Neulasta, the patient may receive less than the recommended dose.

Do not use the On-body Injector for Neulasta to deliver any other drug product except the Neulasta prefilled syringe co-packaged with the On-body Injector for Neulasta.

The On-body Injector for Neulasta should be applied to intact, non-irritated skin on the arm or abdomen.

A missed dose could occur due to an On-body Injector for Neulasta failure or leakage. If the patient misses a dose, a new dose should be administered by single prefilled syringe for manual use, as soon as possible after detection.

Refer to the Healthcare Provider Instructions for Use for the On-body Injector for Neulasta for full administration information.

2.5 Advice to Give to Patients Regarding Administration via the On-body Injector for Neulasta

Advise patients to avoid activities such as traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute delivery period plus an hour post-delivery). Patients should have a caregiver nearby for the first use.

Refer the patient to the dose delivery information written on the Patient Instructions for Use. Provide training to patients to ensure they understand when the dose delivery of Neulasta will begin and how to monitor the On-body Injector for Neulasta for completed delivery. Ensure patients understand how to identify signs of malfunction of On-body Injector for Neulasta. *[see Warnings and Precautions (5.3) and Patient Counseling Information (17)]*.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe for manual use only.
- Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe co-packaged with the On-body Injector for Neulasta (Neulasta Onpro kit).

4 CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

5.4 Allergies to Acrylics

The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction.

5.5 Use in Patients with Sickle Cell Disorders

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

5.6 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving Neulasta. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis

resolved after dose reduction or discontinuation of Neulasta. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Neulasta.

5.7 Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

5.8 Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including Neulasta, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.9 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte-colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture *[See Warnings and Precautions (5.1)]*
- Acute Respiratory Distress Syndrome *[See Warnings and Precautions (5.2)]*
- Serious Allergic Reactions *[See Warnings and Precautions (5.3)]*
- Allergies to Acrylics *[See Warnings and Precautions (5.4)]*
- Use in Patients with Sickle Cell Disorders *[See Warnings and Precautions (5.5)]*
- Glomerulonephritis *[See Warnings and Precautions (5.6)]*
- Leukocytosis *[See Warnings and Precautions (5.7)]*
- Capillary Leak Syndrome *[See Warnings and Precautions (5.8)]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells *[See Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients

were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and <1% Asian, Native American or other.

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Neulasta Patients Compared to Placebo in (Study 3)

System Organ Class Preferred Term	Placebo (N= 461)	Neulasta 6 mg SC on Day 2 (N= 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis
In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
- Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions (5.2)]*
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing *[see Warnings and Precautions (5.3)]*
- Sickle cell crisis *[see Warnings and Precautions (5.5)]*
- Glomerulonephritis *[see Warnings and Precautions (5.6)]*
- Leukocytosis *[see Warnings and Precautions (5.7)]*

- Capillary leak syndrome *[see Warnings and Precautions (5.8)]*
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis

7 DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryolethality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. No evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area) *[see Nonclinical Toxicology (13.3)]*.

8.3 Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Neulasta have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of Neulasta in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*.

The use of Neulasta to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in animals and clinical data supporting the use of Neulasta in patients with cancer receiving myelosuppressive chemotherapy. Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Results from population modeling and simulation indicate that-two doses of Neulasta (Table 1), administered one week apart provide pediatric patients with exposures comparable to that in adults receiving two 6 mg doses one week apart *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

8.5 Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

8.6 Renal Impairment

Renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The maximum amount of Neulasta that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum absolute neutrophil count (ANC) of 55 x 10^9/L, with a corresponding mean maximum WBC of 67 x 10^9/L. The absolute maximum ANC observed was 96 x 10^9/L with a corresponding absolute maximum WBC observed of 120 x 10^9/L. The duration of leukocytosis ranged from 6 to 13 days. The effectiveness of leukapheresis in the management of symptomatic individuals with Neulasta-induced leukocytosis has not been studied.

11 DESCRIPTION

Neulasta (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of *E coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

Neulasta is provided in two presentations:

- Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
- On-body Injector for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta in solution when used with the On-body Injector for Neulasta. The syringe does not bear graduation marks and is only to be used with the On-body Injector for Neulasta.

The delivered 0.6 mL dose from either the prefilled syringe for manual subcutaneous injection or the On-body Injector for Neulasta contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

12.2 Pharmacodynamics

Animal data and clinical data in humans suggest a correlation between pegfilgrastim exposure and the duration of severe neutropenia as a predictor of efficacy. Selection of the dosing regimen of Neulasta is based on reducing the duration of severe neutropenia.

12.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim was studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim was nonlinear and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of Neulasta ranged from 15 to 80 hours after subcutaneous injection. In healthy volunteers, the pharmacokinetics of pegfilgrastim were comparable when delivered subcutaneously via a manual prefilled syringe versus via the On-body Injector for Neulasta.

Specific Populations
No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients (≥ 65 years of age) compared with younger patients (< 65 years of age) *[see Use in Specific Populations (8.5)]*.

Renal Impairment
In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim *[see Use in Specific Populations (8.6)]*.

Pediatric Patients with Cancer Receiving Myelosuppressive Chemotherapy
The pharmacokinetics and safety of pegfilgrastim were studied in 37 pediatric patients with sarcoma in Study 4 *[see Clinical Studies 14.1]*. The mean (± standard deviation [SD]) systemic exposure ($AUC_{0\text{-}inf}$) of Neulasta after subcutaneous administration at 100 mcg/kg was 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11), 22.0 (± 13.1) mcg·hr/mL in the (6 to 11 years age group (n = 10), and 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13). The terminal elimination half-lives of the corresponding age groups were 30.1 (± 38.2) hours, 20.2 (± 11.3) hours, and 21.2 (± 16.0) hours, respectively.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation
The pharmacokinetics of pegfilgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetic data in irradiated non-human primates, the area under the concentration-time curve (AUC), reflecting the exposure to pegfilgrastim in non-human primates following a 300 mcg/kg dose of Neulasta, appears to be greater than in humans receiving a 6 mg dose. Results from population modeling and simulation indicate that two 6 mg doses of Neulasta administered one week apart in adults result in clinically relevant effects on duration of grade 3 and 4 neutropenia. In addition, weight based dosing in pediatric patients weighing less than 45 kg *[see Dosing and Administration, Section 2.3, Table 1]* provides exposures comparable to those in adults receiving two 6 mg doses one week apart.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

13.3 Reproductive and Developmental Toxicology

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of Neulasta. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC $< 0.5 \times 10^9$/L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies, and the efficacy of Neulasta was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the Neulasta arm compared to 1.6 days in the Filgrastim arm [difference in means 0.1 (95% CI -0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature ≥ 38.2°C and ANC $\leq 0.5 \times 10^9$/L) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations

(1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.

Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics *[see Clinical Pharmacology (12.3)]* of Neulasta in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous Neulasta as a single dose of 100 mcg/kg (n= 37) or subcutaneous filgrastim at a dose 5 mcg/kg/day (n=6) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the Neulasta and filgrastim groups. The most common adverse reaction reported was bone pain.

14.2 Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome

Efficacy studies of Neulasta could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting Neulasta's effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy *[see Dosage and Administration (2.1)]*.

The recommended dose of Neulasta is two doses, 6 mg each, administered one week apart for humans exposed to myelosuppressive doses of radiation. For pediatric patients those weighing less than 45 kg, dosing of Neulasta is weight based and is provided in Table 1 *[see Dosage and Administration (2.3)]*. This dosing regimen is based on population modeling and simulation analyses. The exposure associated with this dosing regimen is expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation *[see Clinical Pharmacology (12.3)]*. The safety of Neulasta at a dose of 6 mg has been assessed on the basis of clinical experience in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of Neulasta for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control (n=23) or treated (n=23) cohort. On study day 0, animals (n = 6 to 8 per irradiation day) were exposed to total body irradiation (TBI) of 7.50 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment (control article [5% dextrose in water] or pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the pegfilgrastim group compared to 48% survival (11/23) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Neulasta single use prefilled syringe for manual use

Neulasta is supplied in a prefilled single use syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Neulasta is provided in a dispensing pack containing one sterile 6mg/0.6 mL prefilled syringe (NDC 55513-190-01).

Neulasta prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

Store refrigerated between 36° to 46°F (2° to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

Neulasta Onpro™ kit

Neulasta Onpro kit is provided in a carton containing one sterile prefilled syringe and one sterile On-body Injector for Neulasta (NDC 55513-192-01).

The single use prefilled syringe contains 0.64 mL of solution that delivers 6 mg/0.6 mL of pegfilgrastim when used with the On-body Injector for Neulasta. The prefilled syringe is supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. The syringe does not bear graduation marks and is only to be used with the On-body Injector for Neulasta.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. Because the On-body Injector for Neulasta is at room temperature during the period of use, Neulasta Onpro kit should not be held at room temperature longer than 12 hours prior to use. Discard Neulasta Onpro kit if stored at room temperature for more than 12 hours.

Do not use the On-body Injector for Neulasta if its packaging has been previously opened.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients of the following risks and potential risks with Neulasta:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) that efficacy studies of Neulasta for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals *[see Clinical Studies (14.2)]*.

Advise patients on the use of the On-body Injector for Neulasta:

- Review the Patient Information and Patient Instructions for Use with the patient and provide the instructions to the patient.
- Refer the patient to the dose delivery information written on the Patient Instructions for Use.
- Tell the patient when their dose delivery of Neulasta will begin and when their dose delivery should be completed.
- Advise the patient that serious allergic reactions can happen with Neulasta. Patients should have a caregiver nearby for the first use. Patients should plan to be in a place where they can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an

hour after the delivery. Advise the patient to avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta.

- If the On-body Injector for Neulasta is placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector for Neulasta.
- If a patient calls the healthcare provider regarding any On-body Injector for Neulasta problems, the healthcare provider is advised to call Amgen at 1-800-772-6436.
- Advise the patient:
  - to call their healthcare provider immediately if the status light on the On-body Injector for Neulasta is flashing red (see the Patient Instructions for Use).
  - to inform their healthcare provider if the adhesive on the On-body Injector for Neulasta becomes saturated with fluid, or there is dripping, as this may be evidence of significant product leakage, resulting in inadequate or missed dose (see the Patient Instructions for Use).
  - to keep the On-body Injector for Neulasta dry for approximately the last 3 hours prior to the dose delivery start to better enable potential leak detection.
  - that the On-body Injector for Neulasta should only be exposed to temperatures between 41°F and 104°F (5°C-40°C)
  - to keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector for Neulasta at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
  - that if the needle is exposed after On-body Injector for Neulasta removal, place the used On-body Injector for Neulasta in a sharps disposal container to avoid accidental needle stick and call their healthcare provider immediately.
  - to remove the On-body Injector for Neulasta after the green light shines continuously and to place the used On-body Injector for Neulasta in a sharps disposal container (see the Patient Instructions for Use).
- Advise the patient:
  - do not reapply the On-body Injector for Neulasta if the On-body Injector for Neulasta comes off before full dose is delivered and instead call their healthcare provider immediately.
  - avoid bumping the On-body Injector for Neulasta or knocking the On-body Injector for Neulasta off the body.
  - do not expose the On-body Injector for Neulasta to medical imaging studies, e.g. X-ray scan, MRI, CT scan, ultrasound and oxygen rich environments such as hyperbaric chambers to avoid On-body Injector for Neulasta damage and patient injury.
- Advise the patient to avoid:
  - airport X-ray scans and request a manual pat down instead; remind patients who elect to request a manual pat down to exercise care to avoid having the On-body Injector for Neulasta dislodged during the pat down process.
  - sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta as this may affect On-body Injector for Neulasta performance.
  - getting body lotions, creams, oils and cleaning agents near the On-body Injector for Neulasta as these products may loosen the adhesive.
  - using hot tubs, whirlpools, or saunas and avoid exposing the On-body Injector for Neulasta to direct sunlight as these may affect the drug.
  - peeling off or disturbing the On-body Injector for Neulasta adhesive before delivery of full dose is complete.

AMGEN®

Neulasta® (pegfilgrastim)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License No. 1080

Patent: http://pat.amgen.com/neulasta/

www.neulasta.com
1-800-77-AMGEN (1-800-772-6436)

11/2015
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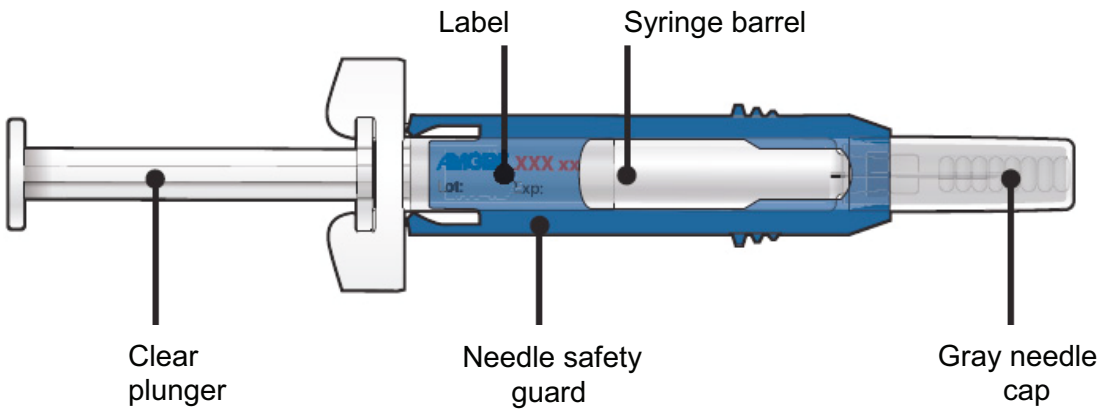
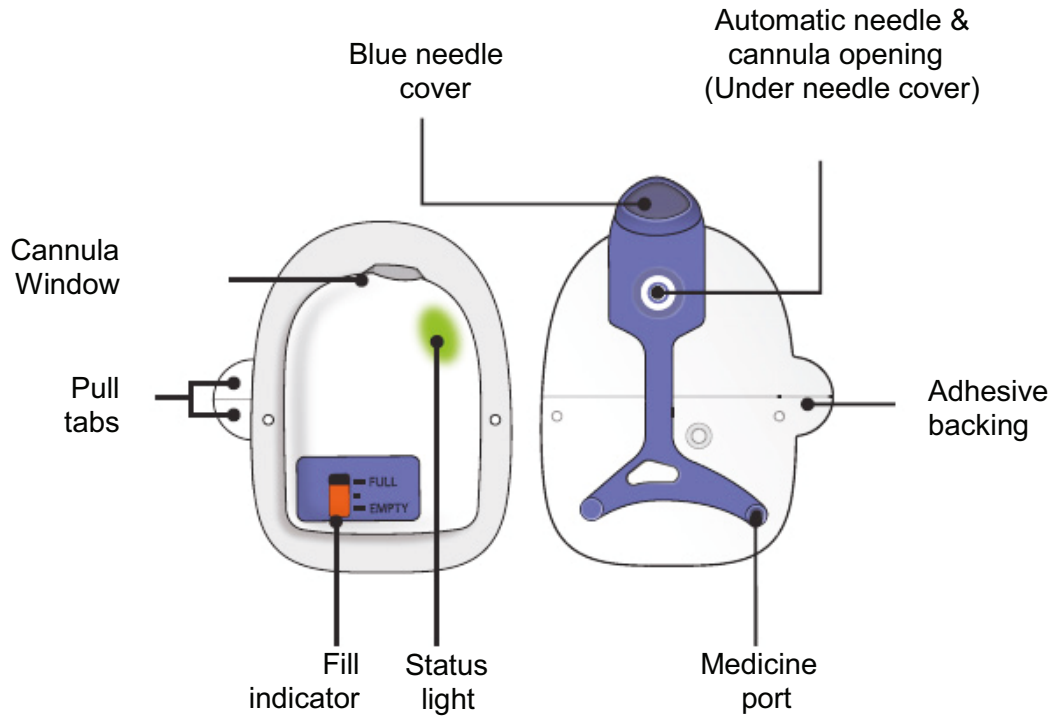
Neulasta® (pegfilgrastim) Onpro™ kit
Healthcare Provider Instructions for Use

Guide to Parts

Neulasta Prefilled Syringe with Manual Needle Guard



On-body Injector for Neulasta



Reference ID: 3846752

Important

READ THE FOLLOWING INSTRUCTIONS BEFORE USING THE ON-BODY INJECTOR

Warning: Do not use Neulasta Onpro kit to deliver any other drug product.

- See Prescribing Information for information on Neulasta.
- The On-body Injector is for adult patients only.
- Store Neulasta Onpro kit in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C) until ready for use. If Neulasta Onpro kit is stored at room temperature for more than 12 hours, do not use. Start again with a new Neulasta Onpro kit.
- Keep the prefilled syringe in the Neulasta Onpro kit carton until use to protect from light.
- For patients who have had severe skin reactions to acrylic adhesives, consider the benefit:risk profile before administering pegfilgrastim via the On-body Injector for Neulasta.
- The On-body Injector should be applied to intact, non-irritated skin on the abdomen or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
- DO NOT:
  - ✘ freeze Neulasta Onpro kit.
  - ✘ shake the prefilled syringe.
  - ✘ separate the components of Neulasta Onpro kit until ready for use.
  - ✘ modify the On-body Injector.
  - ✘ warm Neulasta Onpro kit components using a heat source.
  - ✘ use Neulasta Onpro kit if expiry date on the carton or any of the Neulasta Onpro kit components has passed.
  - ✘ use if the name Neulasta does not appear on the Neulasta Onpro kit carton.
  - ✘ attempt to reapply On-body Injector.
  - ✘ use if either the On-body Injector or prefilled syringe is dropped. Start again with a new Neulasta Onpro kit.

For all questions, call Amgen at 1-800-772-6436. If a patient calls you regarding any On-body Injector problems, call Amgen at 1-800-772-6436.

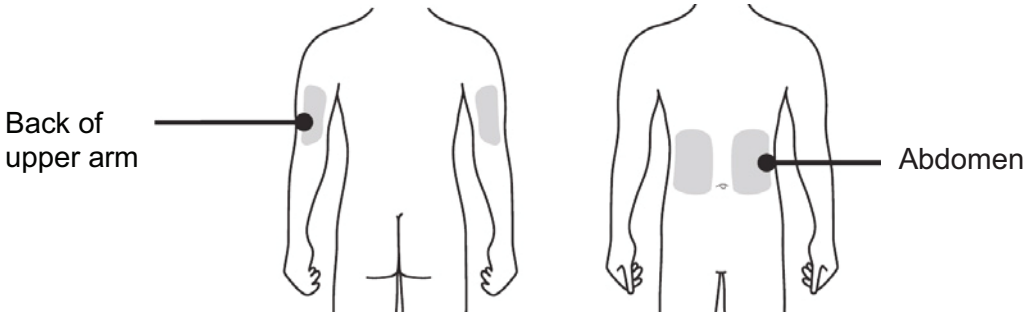
Step 1: Prepare

A Remove Neulasta Onpro kit from refrigerator. Check to make sure it contains:

- One Neulasta prefilled syringe
- One On-body Injector for Neulasta
- Neulasta package insert
- Instructions for use:
  – for healthcare provider
  – for patient
- Reference guide

⃠ DO NOT use On-body Injector if its packaging has been previously opened.

B Wash hands thoroughly. Prepare and clean On-body Injector application site.



Choose the flattest site for On-body Injector application. Consult with your patient regarding their ability to remove and monitor the entire On-body Injector.

You can use:

- Left or right side of abdomen, except for a 2-inch area right around navel.
- Back of upper arm, only if there is a caregiver available to monitor the status of the On-body Injector.

Choose an area larger than the adhesive pad, and clean it with an alcohol swab. Allow skin to completely dry.

⃠ DO NOT touch this area again before attaching On-body Injector.

You should avoid:

✘ Areas with scar tissues, moles, or excessive hair. In case of excessive hair, carefully trim hair to get On-body Injector close to skin.

✘ Areas where belts, waistbands, or tight clothing may rub against, disturb, or dislodge On-body Injector.

✘ Surgical sites.

✘ Areas where On-body Injector will be affected by folds in skin.

STOP

The following is an overview of On-body Injector preparation steps. Read this section first.
When ready, proceed to Step 2: Get Ready Section.

Before you apply On-body Injector to your patient, locate medicine port on blue needle cover to fill the On-body Injector with Neulasta.

Please note: During filling, beeping will sound and the On-body Injector will be activated.

After activation, you will have 3 minutes to:

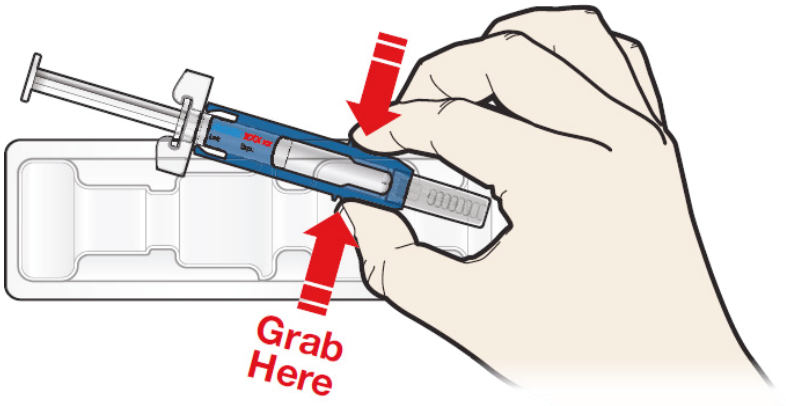
1. Completely empty syringe contents into medicine port.
2. Remove syringe from port and pull down needle safety guard over the exposed needle.
3. Remove blue needle cover from back of On-body Injector.
4. Peel away the two pieces of white adhesive backing from the back of the On-body Injector.
5. Attach On-body Injector to back of patient's upper arm or abdomen.

On-body Injector will deploy cannula in 3 minutes, even if not applied to patient. If not on patient's body in 3 minutes, do not use the On-body Injector. Start again with a new Neulasta Onpro kit.

When you feel you are ready, please continue...

Step 2: Get Ready

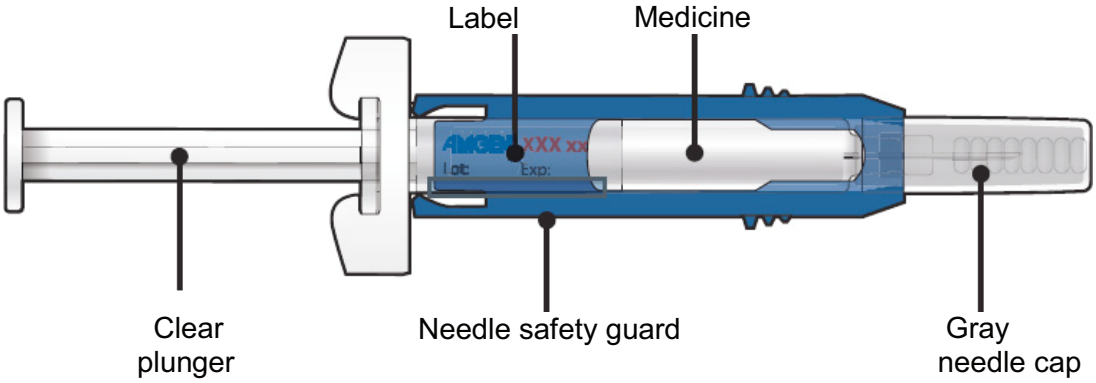
A Remove Neulasta prefilled syringe from tray.



For safety reasons:

- DO NOT grasp gray needle cap.
- DO NOT put the gray needle cap back onto syringe.
- DO NOT grasp clear plunger.

B Inspect medicine and Neulasta prefilled syringe. The Neulasta liquid should always be clear and colorless.

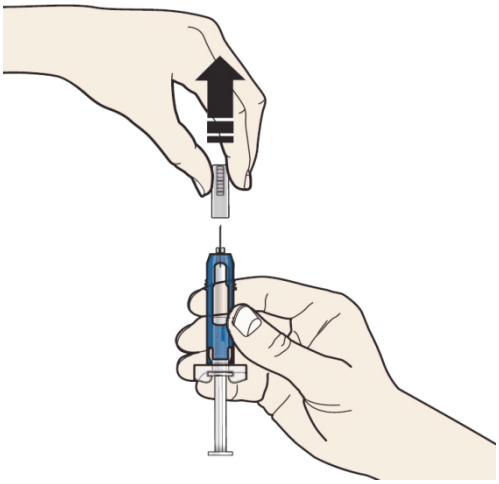


- DO NOT use Neulasta prefilled syringe if:
  - ✘ Liquid contains particulate matter or discoloration is observed prior to administration.
  - ✘ Any part appears cracked or broken.
  - ✘ The gray needle cap is missing or not securely attached.
  - ✘ The expiration date printed on the label has passed.
- DO NOT remove gray needle cap until ready to fill On-body Injector.
- DO NOT pull needle safety guard down over the needle until filling is complete.
- In all the above cases, start again with a new Neulasta Onpro kit. Call Amgen at 1-800-772-

6436.

! The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex.

C **Carefully remove gray needle cap straight out from the syringe and away from your body. Check syringe, and remove air bubbles.**

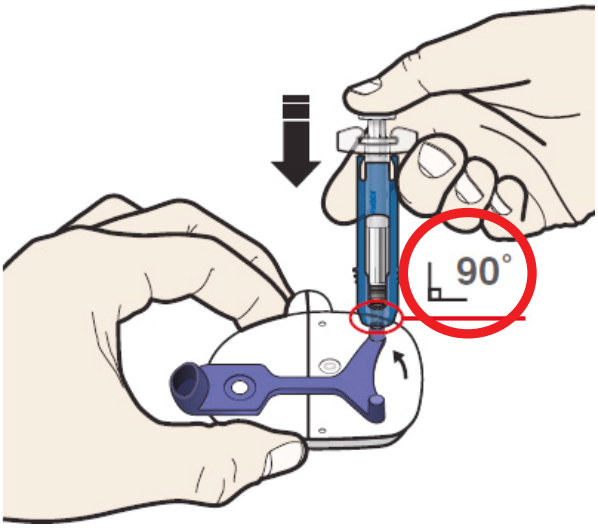


! Take care to expel air only and not medicine.
A small droplet at the tip of the needle during air purging is normal.

⊘ DO NOT recap syringe.

D **Using blue needle cover, to avoid bending the needle and spilling medicine, insert syringe needle at 90 degrees all the way into medicine port. Slowly empty the entire syringe contents. Remove empty syringe from the medicine port.**

When beeping sounds and the status light flashes amber, the 3-minute countdown begins.

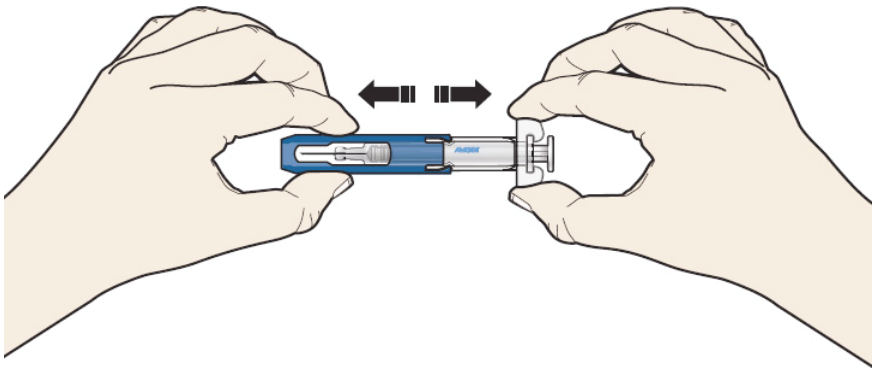


⊘ **DO NOT insert needle into medicine port at other than a 90 degree angle**

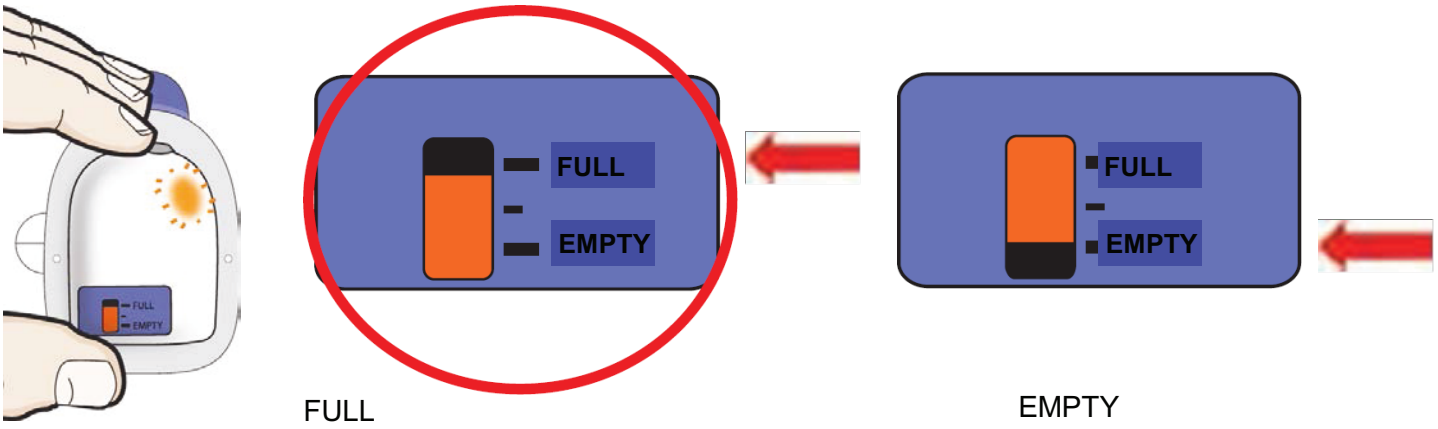
⊘ DO NOT insert needle more than once.

⊘ DO NOT remove blue needle cover before filling the On-body Injector.

E **Pull needle safety guard down until it clicks and covers needle. Dispose of empty syringe in a sharps container.**



F Check to see if the On-body Injector is full.



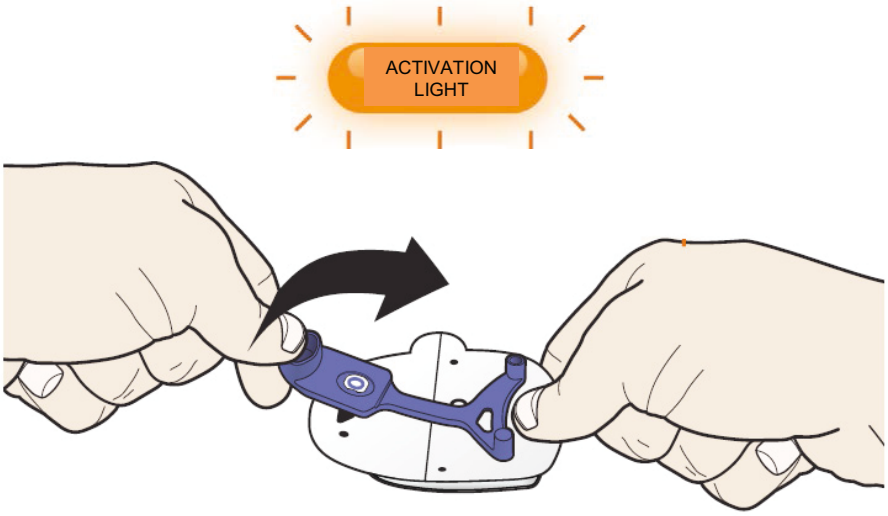
FULL EMPTY

You should see:
- amber status light flashing.
- black line next to FULL on the fill indicator

If this is not the case, do not use. Start again with a new Neulasta Onpro kit, and call Amgen at 1-800-772-6436.

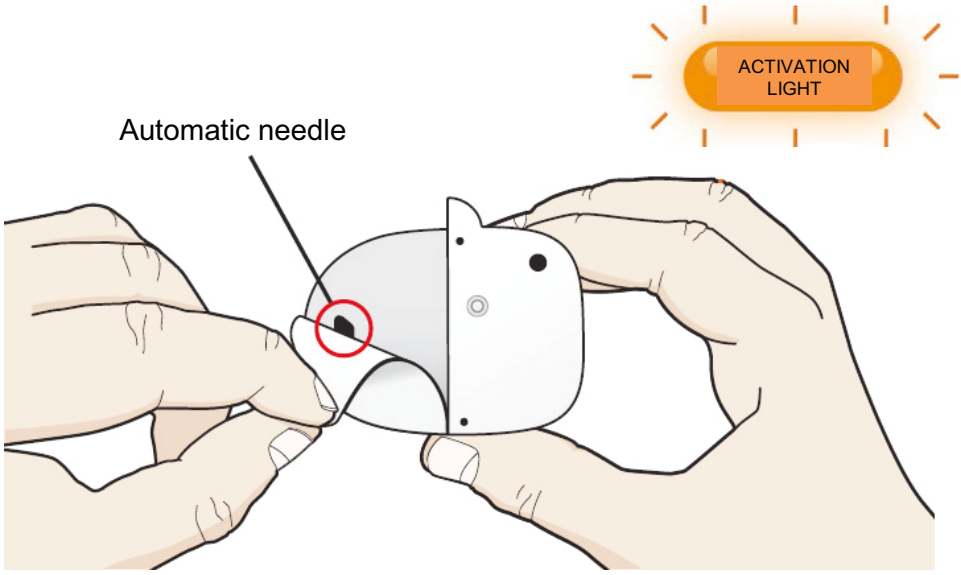
Step 3: Apply

A Firmly lift and remove blue needle cover away from On-body Injector.



A drop of medicine may be visible on needle tip when blue needle cover is removed.

B **To expose the adhesive pad, use both pull tabs, one at a time, to peel the two pieces of white adhesive backing away from On-body Injector.**

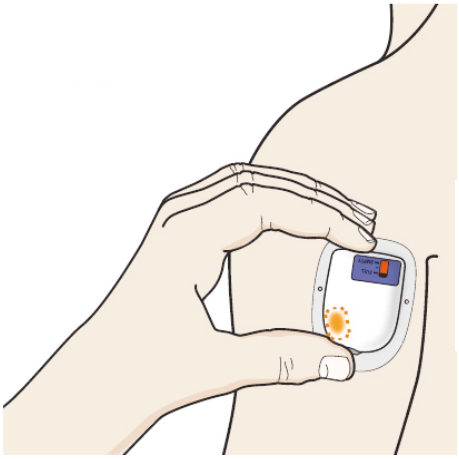


- DO NOT touch or contaminate automatic needle area.
- DO NOT pull off adhesive pad or fold it.
- DO NOT use if the needle or cannula is extended past the adhesive or is extended before the On-body Injector is placed on patient.

! In all cases, start again with a new Neulasta Onpro kit. Call Amgen at 1-800-772-6436.

C **Apply On-body Injector securely to patient with entire On-body Injector visible so it can be monitored by patient or caregiver.**
Before cannula deploys, place On-body Injector on your selected site, and run your finger around entire adhesive pad to make sure it is securely attached.

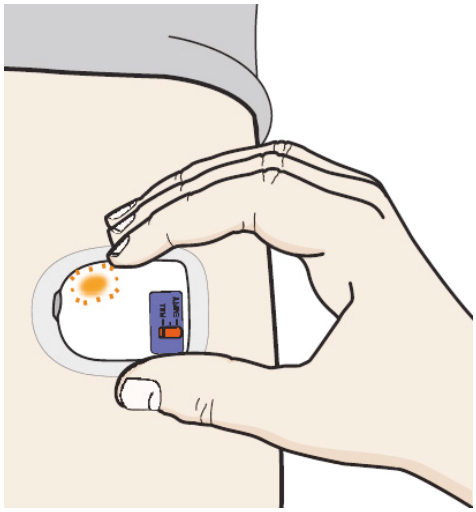
Back of Upper Arm



Vertical with light facing down toward elbow

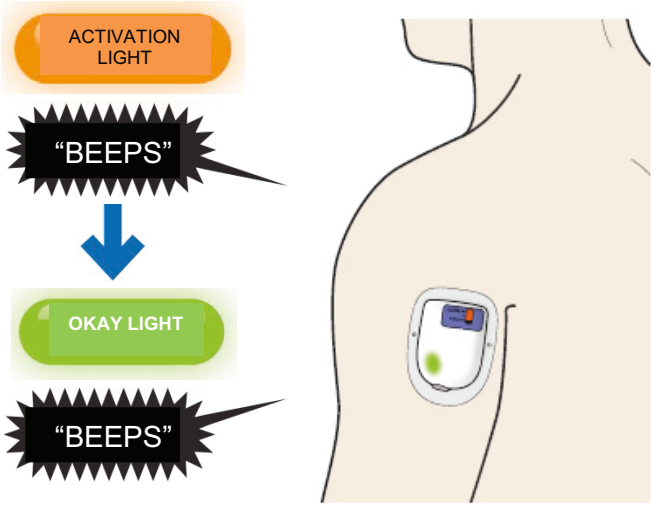
Abdomen

Horizontal with light facing navel



STOP! Do not worry if On-body Injector is quiet. When 3 minutes are up, On-body Injector will beep.

D **Beeping will tell you the cannula is about to insert. You may hear a series of clicks. This is okay.**
A long beep will sound, and the status light will turn to green. This means the cannula insertion is complete.



! If the adhesive folds over near the cannula window or there are folds anywhere that prevent the On-body Injector from securely adhering, remove the On-body Injector. Start again with a new Neulasta Onpro kit and call Amgen at 1-800-772-6436.

Step 4: Finish

A Fill in the Dose Delivery Information section in the patient instructions. Be sure to include when the On-body Injector was applied, when the dose will begin, and your contact information. Review this information with the patient.

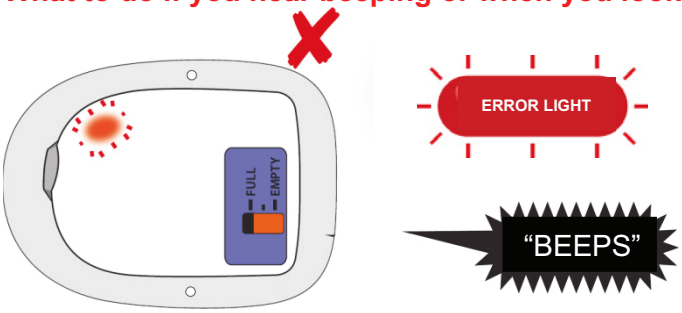
Review each step in the patient instructions with your patient. Give your patient the instructions, and reference guide to take home.

Before your patient goes home, make sure your patient understands:

- The On-body Injector will always flash a slow green light to let them know it is working properly.
- **After approximately 27 hours, beeps will signal that the dose delivery will begin in 2 minutes.**
- **When the dose delivery starts it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.**
- The patient should remain in a place where they can monitor the On-body Injector for the entire dose delivery. The patient should avoid activities and settings that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector (this includes the approximately 45-minute delivery period plus an hour post-delivery).
- If the patient has an allergic reaction during the delivery of Neulasta, the patient should remove the On-body Injector and call his or her healthcare provider or seek emergency care right away.
- If placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector.
- When the dose delivery is complete, the patient or caregiver will hear a beep and see a solid green light.
- Always dispose of the empty On-body Injector in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Attention!

What to do if you hear beeping or when you look at status light and it is flashing red.

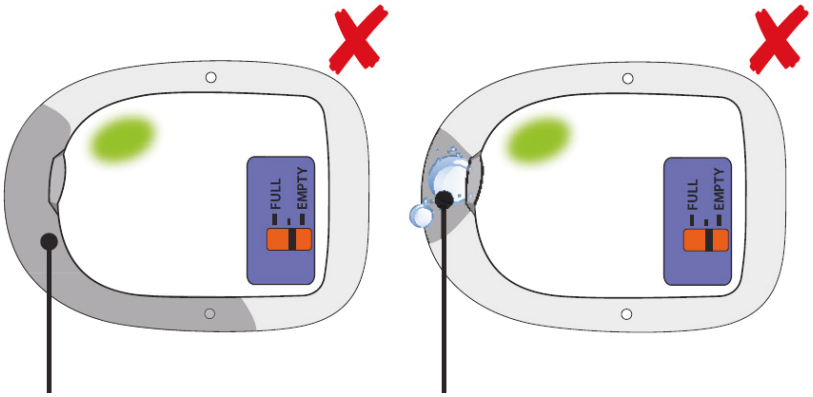


If at any time the On-body Injector beeps continuously for 5 minutes, and the status light is flashing red, take the On-body Injector off of the patient.

- DO NOT apply On-body Injector to patient if red error light is on.
- DO NOT leave On-body Injector on patient if red error light is on.

In all cases, do not use. Start over with a new Neulasta Onpro kit, and call Amgen at 1-800-772-6436.

What to do if the adhesive becomes saturated with fluid or the On-body Injector is dripping.



Saturated adhesive Dripping fluid from On-body Injector

If patient reports an On-body Injector leak, they might not have received full dose. Schedule a follow-up appointment, and report the incident to Amgen at 1-800-772-6436.

Neulasta® (pegfilgrastim)
Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

www.neulasta.com 1-800-772-6436 (1-800-77-AMGEN)

Issued: 09/2015
v3

Do not expose the On-body Injector for Neulasta to the following environments as the On-body Injector may be damaged and the patient could be injured:
• MRI
• X-ray
• CT-Scan
• Ultrasound
• Oxygen rich environments such as hyperbaric chambers

Symbol	Meaning
	Do not reuse this On-body Injector. Single-use only
	Refer to Instructions for Use
	Do not use if packaging is damaged.
	Temperature Limitation
	Humidity Limitation
	Expiration Date (use by date)
REF	Reference/model number
LOT	Lot Number
	Type BF medical device (protection from electrical shock)
STERILE EO	Sterilized by ethylene oxide
IPX8	Waterproof up to 8 feet for 1 hour
℞ Only	Prescription use only
	Not MRI-safe
	On-body Injector for Neulasta® (pegfilgrastim)
	Neulasta® (pegfilgrastim) Prefilled Syringe

Electromagnetic Compatibility
The information contained in this section (such as separation distances) is, in general, specifically written in regard to the On-body Injector for Neulasta. The numbers provided will not guarantee faultless operation but should provide reasonable assurance of such. This information may not be applicable to other medical electrical equipment; older equipment may be particularly susceptible to interference.

General Notes:
Medical electrical equipment requires special precautions regarding electromagnetic compatibility (EMC), and needs to be installed and put into service according to the EMC information provided in this document.

Portable and mobile RF communications equipment can affect medical electrical equipment.

Cables and accessories not specified within the instructions for use are not authorized. Using cables and/or accessories may adversely impact safety, performance, and electromagnetic compatibility (increased emission and decreased immunity).

Care should be taken if the On-body Injector for Neulasta is used adjacent to other electrical equipment; if adjacent use is inevitable, the On-body Injector for Neulasta should be observed to verify normal operation in this setting.

Electromagnetic Emissions		
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of the On-body Injector for Neulasta should ensure that it is used in such an environment.		
Emissions	Compliance according to	Electromagnetic environment
RF Emissions (CISPR 11)	Group 1	The On-body Injector for Neulasta uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby equipment.
CISPR B Emissions Classification	Class B	

Electromagnetic Immunity			
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of this equipment should ensure that it is used in such an environment.			
Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment – Guidance
ESD IEC 610000-4-2	±6kV Contact ±8kV Air	6kV Contact ±8kV Air	Floors should be wood, concrete or ceramic tile. If floors are synthetic, the r/h should be at least 30%.
Power Frequency 50/60 Hz Magnetic Field IEC 61000-4-8	3A/m	3A/m	Power frequency magnetic fields should be that of typical commercial or hospital environment.
Radiated RF Fields 61000-4-3	3 V/m 80 MHz to 2.5 GHz	(E1)=3V/m	Portable and mobile communications equipment should be separated from the On-body Injector for Neulasta by no less than the distances calculated/listed below: D=(3.5/V1)(√P)150 kHz to 80 MHz D=(3.5/E1)(√P)80 to 800 MHz D=(7/E1)(√P)800 MHz to 2.5 GHz Where P is the max power in watts and D is the recommended separation distance in meters. Field strengths from fixed transmitters, as determined by an electromagnetic site survey, should be less than the compliance levels (V1 and E1). Interference may occur in the vicinity of equipment containing a transmitter.

Recommended separation distances between portable and mobile RF communications equipment and the On-body Injector for Neulasta			
You can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the On-body Injector for Neulasta, as recommended below, according to the maximum power of the communication equipment.			
Rated maximum output power of transmitter, in watts	Separation distance according to frequency of transmitter, in meters		
	150 kHz to 80 MHz D=(3.5/V1)(√P)	80 to 800 MHz D=(3.5/E1)(√P)	800 MHz to 2.5 GHz D=(7/E1)(√P)
0.01	0.11667	0.11667	0.23333
0.1	0.36894	0.36894	0.73785
1	1.1667	1.1667	2.3333
10	3.6894	3.6894	7.3785
100	11.667	11.667	23.333

{SIDE 1 Information}

Patient Instructions for Use

On-body Injector for Neulasta Description

The On-body Injector for Neulasta is intended for delivery of Neulasta. The On-body Injector is small, for one-time use, lightweight, battery-powered, and waterproof up to 8 feet for 1 hour. Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The prefilled syringe with Neulasta and the On-body Injector are provided to your healthcare provider as part of Neulasta Onpro™ kit. The On-body Injector is applied directly to your skin using a self-adhesive backing. The On-body Injector informs you of its status with sounds and lights.

The On-body Injector contains electronic components as well as: a plastic housing, acrylic adhesive, batteries, a cannula introducer (needle) and a cannula. The On-body Injector is approximately: 2.4 in long, 1.6 in wide, 0.7 in height (62 mm long, 41 mm wide, 17 mm height).

Warnings

- **Before** you receive Neulasta, tell your healthcare provider if you:
  - Have sickle cell trait or sickle cell disease
  - Have problems with your kidneys
  - Have any other medical problems
  - Are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.
  - Are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breastmilk.
- **DO NOT** take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta®) or to filgrastim (Neupogen®).
- Tell your healthcare provider if you are allergic to latex. A prefilled syringe is used to fill the On-body Injector by your healthcare provider prior to applying the On-body Injector. The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex. Latex may be transferred to your skin.
- Tell your healthcare provider if you have had severe skin reactions to acrylic adhesives.
- The On-body Injector is for adult patients only.
- Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, **AVOID** traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute dose delivery period plus an hour post-delivery).
  If you must travel by airplane **before** the approximately 45-minute dose delivery period with the On-body Injector, avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector from being accidentally removed. For more information go to
  http://www.tsa.gov/traveler-information/travelers-disabilities-and-medical-conditions
  If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
- Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.

- Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of acute respiratory distress syndrome (ARDS): fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- Call your healthcare provider right away if you experience any of these symptoms of kidney injury (glomerulonephritis): puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.
- Keep children away from the used On-body Injector.
- You should only receive a dose of Neulasta on the day your healthcare provider tells you.
- You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy. The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector on your skin.
- **DO NOT** expose the On-body Injector to the following because the On-body Injector may be damaged and you could be injured:
    - MRI
    - X-ray
    - CT-Scan
    - Ultrasound
    - Oxygen rich environments, such as hyperbaric chambers
- **DO NOT** use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
- **DO NOT** expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
- **DO NOT** sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect the On-body Injector performance.
- **DO NOT** peel off or disturb the On-body Injector's adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

Precautions

Environmental:
- Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
- Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C-40°C).
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Activity Related:
- Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
- Be careful not to bump the On-body Injector or knock the On-body Injector off your body.

Biohazard:
Properly dispose of the On-body Injector:

- The On-body Injector contains batteries, electronics, and a needle. The On-body Injector should be placed in a sharps disposal container, with an appropriate sized opening, regardless of whether or not the needle is exposed. Follow instructions provided by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com to enroll.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: http://www.fda.gov/safesharpsdisposal.

Risks

You can avoid most risks related to using the On-body Injector for Neulasta by following the Patient Instructions for Use. Immediately call your healthcare provider if any of the following occur:

- The adhesive becomes noticeably wet (saturated) with fluid, or you see dripping
- If the On-body Injector fill indicator is not at the empty position after On-body Injector removal (You should see a black line next to the EMPTY indicator.)
- The On-body Injector comes off from the skin before or during a dose delivery (**DO NOT re-apply it.**)
- Status light is flashing red
- Allergic reaction
- Persistent or worsening redness or tenderness at the application site (may be a sign of infection)
- Severe pain or skin discomfort around your On-body Injector
- Any concern about your medication
- If the needle is exposed after On-body Injector removal

{SIDE 2 Information}

On-body Injector for Neulasta® (nu-las-tah) (pegfilgrastim) Injection
Patient Instructions for Use

Dose Delivery Information

Your On-body Injector was applied:

_____

Day Time AM / PM

Your dose delivery will start around:

_____

Day Time AM / PM

Name of Healthcare Provider:

_____

Last, First

Healthcare Provider contact number:

_____

On-body Injector lot number:

_____

Important Information

- This On-body Injector delivers Neulasta with an under-the-skin (subcutaneous) injection. See Patient Information for medicine information.
- If you have concerns about your medication, call your healthcare provider immediately. Serious allergic reactions can happen with Neulasta. Ask your caregiver to be nearby for the first use.
- Plan to be in a place where you or your caregiver can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery.
- Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector (hours 26-29).

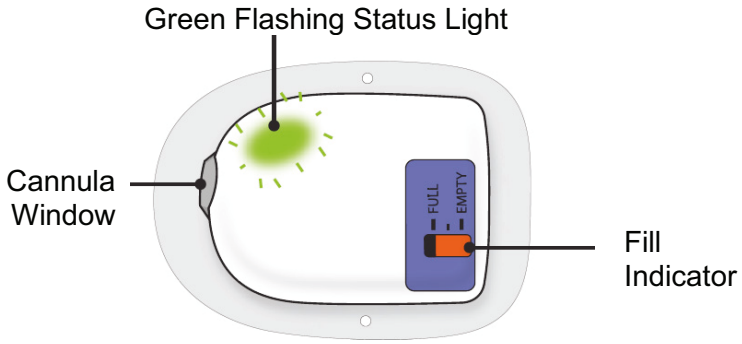
- If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
- The On-body Injector should be applied to intact, non-irritated skin on the stomach area (abdomen) or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
- Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.
- Be careful not to bump the On-body Injector or knock the On-body Injector off your body.
- Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
- Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
- Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C and 40°C).
- After On-body Injector removal, properly dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

DO NOT:

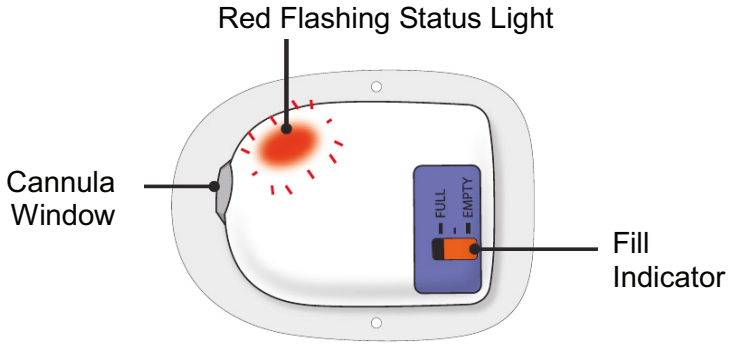
- use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
- expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
- sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect On-body Injector performance.
- peel off or disturb the On-body Injector adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

A healthcare provider who is familiar with Neulasta should answer your questions. For general questions or support call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com.

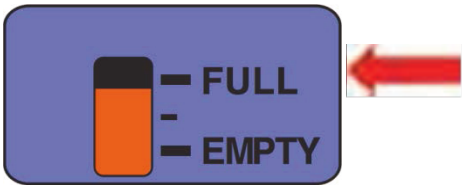
Guide to Parts for On-body Injector for Neulasta



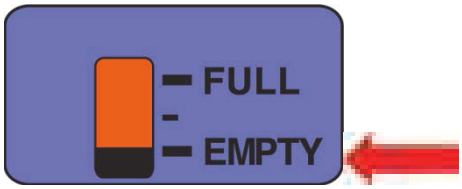
The On-body Injector is working properly.



If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.



FULL

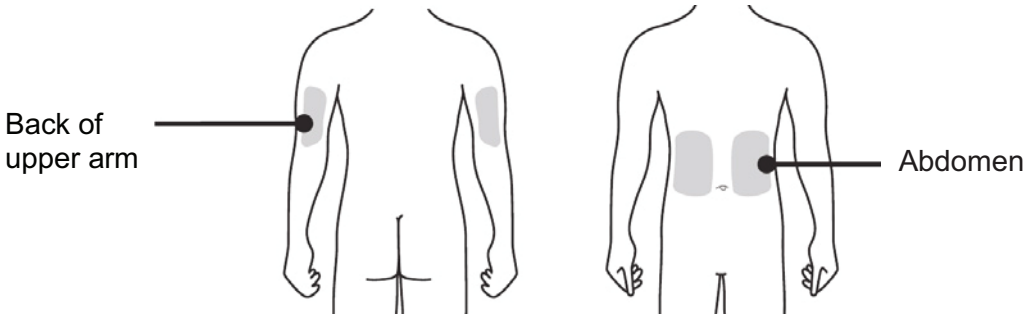


EMPTY

Fill indicator

After your dose delivery is complete, check to see if the black line on your On-body Injector fill indicator is at empty.

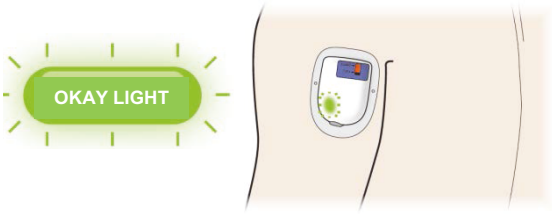
On-body Injector Placement



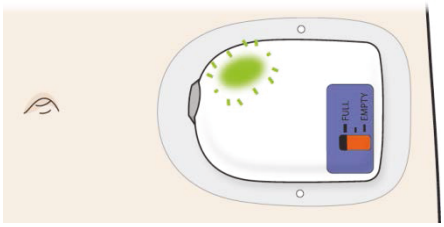
Step 1: Monitor On-body Injector

A **Check your status light occasionally for approximately 27 hours. Since it flashes slowly, watch for at least 10 seconds. If the status light is flashing green, it is okay.**

If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

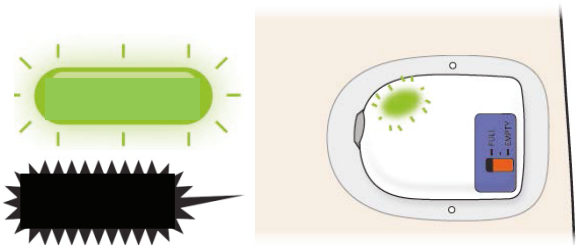


If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the status of the On-body Injector.



B **After approximately 27 hours, your On-body Injector will beep to let you know your dose delivery will begin in 2 minutes. When the dose delivery starts, it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.**

! If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

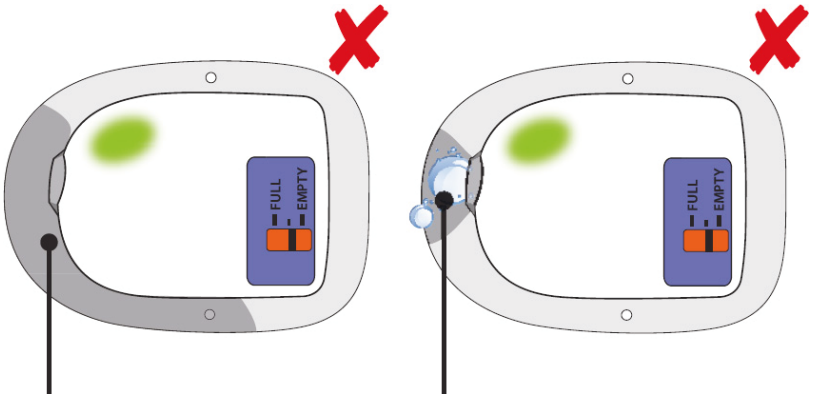


⊘ **DO NOT remove the On-body Injector before the dose delivery is complete.**

Step 2: Monitor Dose Delivery

STOP

For the next 45 minutes, monitor your On-body Injector frequently for leaks during dose delivery. If the On-body Injector was placed on the back of your arm, a caregiver must be available to monitor your On-body Injector.



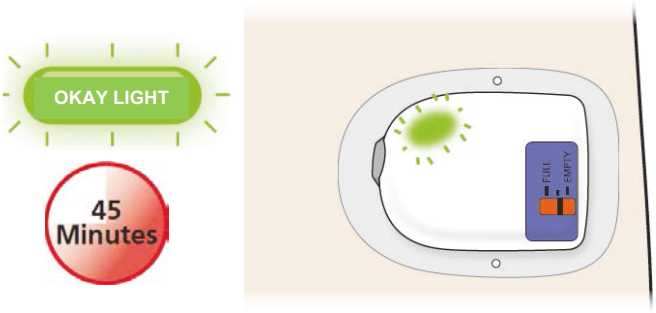
Noticeably wet (saturated) adhesive

Dripping fluid from On-body Injector

If the adhesive becomes noticeably wet (saturated) with fluid, or you see dripping, call your healthcare provider immediately.

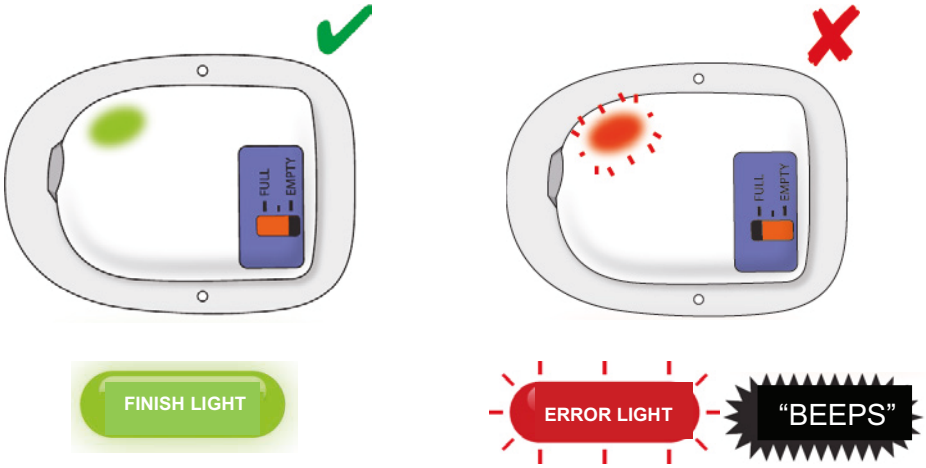
A Your dose delivery will take around 45 minutes to complete.

- You may hear a series of clicks. This is okay.
- A beep will sound when the dose delivery is complete.



Step 3: Remove On-body Injector When Dose Delivery Is Complete

A When beeping starts, check to see the color of the status light.

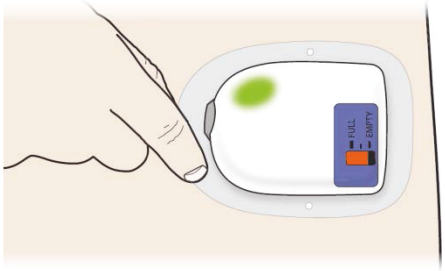


Check to see if the status light is SOLID GREEN or has switched off. This means the dose is complete. Remember, **any time you see a leak, call your healthcare provider immediately.** If the dose is complete, go to the next step.

If you see the status light is flashing red, your On-body Injector is not functioning properly. Call your healthcare provider immediately, as you may not have received a full dose.

B Grab the edge of the adhesive pad. Slowly peel off the On-body Injector.

- If medicine has leaked or the adhesive is noticeably wet (saturated), call your healthcare provider immediately as you may not have received your full dose.
- Remove any extra adhesive using soap and water.

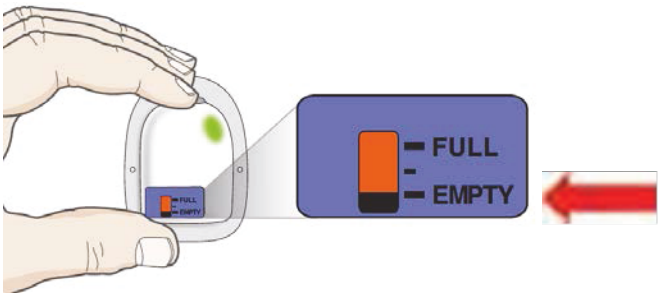


⊘ **DO NOT** grasp the On-body Injector itself to try to pull it off of your body.

Step 4: Finish

STOP **Check to see if your On-body Injector is empty.**

- You should see a black line next to the EMPTY indicator. If the On-body Injector is not empty, call your healthcare provider immediately.



- Check your status light again. Watch for at least 10 seconds. If the status light is solid green or it has switched off, it is okay.
- If you hear beeping, or when you check the status light and it is flashing red, call your healthcare provider immediately.

! After On-body Injector removal, place the On-body Injector in a sharps disposal container whether the needle is exposed or not. If the needle is exposed, call your healthcare provider immediately.

A Record the end state of your On-body Injector.

- Mark the box of the description that represents your On-body Injector after it has been used.

☐ **Status light is solid green or the status light has switched off. This means that the delivery is complete.**

☐ **On-body Injector leaked, call your healthcare provider immediately.**

☐ **Status light is red, call your healthcare provider immediately.**

B Properly dispose of the On-body Injector.

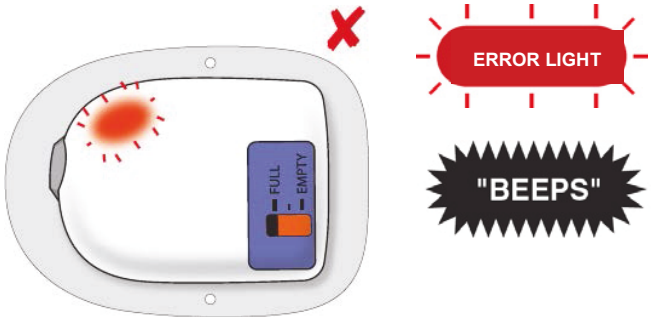
- The On-body Injector contains batteries, electronics, and a needle. Dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit www.neulasta.com to enroll.
  For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: http://www.fda.gov/safesharpsdisposal.

! Keep children away from the used On-body Injector.

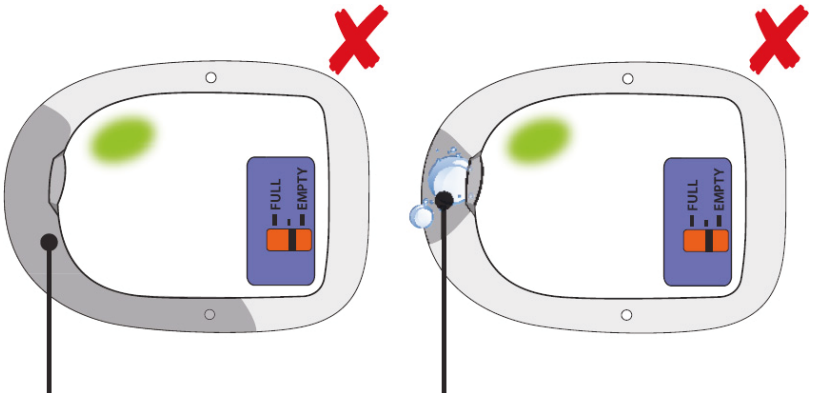
Attention!

What to do if you hear beeping or when you look at the status light and it is flashing red.

! If the status light is flashing red, you may not have received your full dose. Call your healthcare provider immediately.



What to do if the On-body Injector adhesive becomes noticeably wet (saturated) with fluid, or you see dripping.



Noticeably wet (saturated) adhesive

Dripping fluid from On-body Injector

- ! If the adhesive becomes saturated with fluid, or you see dripping, your medicine may have leaked out.
- ! Even with a leak, the status light may remain green and the fill indicator may be at EMPTY.
- ! Call your healthcare provider immediately as you may not have received your full dose.

Note: It is normal to see a few drops of fluid at the application site, but not normal to see a noticeably wet (saturated) adhesive.

What do I do if the On-body Injector comes off before the full dose is delivered?

Call your healthcare provider immediately if the On-body Injector at any time comes away from your skin before your full dose delivery, **DO NOT** reapply it.

What if there is blood at my application site after the On-body Injector has been removed?

If there is blood, press a clean cotton ball or gauze pad on the application site. Apply an adhesive bandage if needed.

What if my application site is red or tender after On-body Injector removal?

Call your healthcare provider immediately if you experience persistent or worsening redness or tenderness at the application site, as this can be a sign of infection.

Neulasta® (pegfilgrastim)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License No. 1080

Patent: http://pat.amgen.com/neulasta/

www.neulasta.com

1-844-MYNEULASTA (1-844-696-3852) Issued: 11/2015 vX

Patient Information

Neulasta® (nu-las-tah)
(pegfilgrastim)
injection

On-body Injector for Neulasta

Read this Patient Information before you receive Neulasta and each time you receive Neulasta with the On-body Injector for Neulasta. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?

- **See the Instructions for Use for the On-body Injector for Neulasta for detailed information about the On-body Injector for Neulasta and important information about your dose delivery that has been written by your healthcare provider.**
  - Know the time that delivery of your dose of Neulasta is expected to start.
  - Avoid traveling, driving, or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied. Avoid activities and places that may interfere with monitoring during the **45-minute** period that Neulasta is expected to be delivered by the On-body Injector for Neulasta, and for 1 hour after delivery.
- A caregiver should be with you the first time that you receive Neulasta with the On-body Injector for Neulasta.
- **If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.**
- **You should only receive a dose of Neulasta on the day your healthcare provider tells you**.
- **You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy.** The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- **Do not** expose the On-body Injector for Neulasta to the following because the On-body Injector for Neulasta may be damaged and you could be injured:
  - MRI
  - X-ray
  - CT-Scan
  - Ultrasound
  - Oxygen rich environments, such as hyperbaric chambers

- Avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector for Neulasta from being accidentally removed.
- **Keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances.** If the On-body Injector for Neulasta is too close to electrical equipment, it may not work correctly and can lead to a missed or incomplete dose of Neulasta.
- The On-body Injector is for adult patients only.
- **Call your healthcare provider right away if the**:
  - On-body Injector for Neulasta comes off before or during a dose delivery. **Do not re-apply it**.
  - On-body Injector for Neulasta is leaking.
  - adhesive on your On-body Injector for Neulasta becomes noticeably wet (saturated) with fluid, or there is dripping. This may mean that Neulasta is leaking out of your On-body Injector for Neulasta. If this happens you may only receive some of your dose of Neulasta, or you may not receive a dose at all.
  - On-body Injector for Neulasta status light is flashing red.

What is Neulasta?

Neulasta is a prescription medicine used to help reduce the chance of infection due to a low white blood cell count, in people with certain types of cancer (non-myeloid), who receive anti-cancer medicines (chemotherapy) that can cause fever and low blood cell count.

Who should not take Neulasta?

Do not take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta®) or to filgrastim (Neupogen®).

What should I tell my healthcare provider before receiving Neulasta?

Before you receive Neulasta, tell your healthcare provider if you:

- have sickle cell trait or sickle cell disease
- have had severe skin reactions to acrylic adhesives
- are allergic to latex
- have problems with your kidneys
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who become pregnant during treatment with Neulasta. The purpose of this registry is to collect information about the health of you and your baby. You are encouraged to enroll in this registry. Your healthcare provider may enroll you, or you may enroll by calling 1-800-AMGEN (1-800-772-6436).

- are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive Neulasta?

See the Instructions for Use for detailed information about how you will receive a dose of Neulasta with the On-body Injector for Neulasta, and how to remove and dispose of the On-body Injector for Neulasta.

- **See the section "What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?"**
- Neulasta is given as an injection under the skin (subcutaneous). Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The prefilled syringe with Neulasta and the On-body Injector are provided to your healthcare provider as part of Neulasta Onpro™ kit. The On-body Injector for Neulasta will be applied to the stomach area (abdomen) or back of your arm by your healthcare provider. If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the On-body Injector for Neulasta.
- Your healthcare provider should place the On-body Injector for Neulasta on an area of your skin that does not have swelling, redness, cuts, wounds, or abrasions. Tell your healthcare provider about any skin reactions that happen in the On-body Injector for Neulasta application area after it has been applied.
- The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- The dose of Neulasta will be delivered over about 45 minutes. During dose delivery and for 1 hour after delivery, it is best to stay in a place where you or a caregiver can monitor the On-body Injector for Neulasta to make sure you receive your full dose of Neulasta and watch for symptoms of an allergic reaction.
- Keep the On-body Injector for Neulasta dry for about the last 3 hours before the dose delivery is expected to start. This will help you to better detect possible leaking from the On-body Injector for Neulasta.
- Only expose the On-body Injector for Neulasta to temperatures between 41°F to 104°F (5°C to 40°C).

What should I avoid while the On-body Injector for Neulasta is in place?

While the On-body Injector for Neulasta is in place you should avoid:

- traveling, driving or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied.

- sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta. The On-body Injector for Neulasta may not work properly.
- bumping the On-body Injector for Neulasta or knocking it off your body.
- getting body lotion, creams, oils, and skin cleansing products near the On-body Injector for Neulasta. These products may loosen the adhesive that holds the On-body Injector for Neulasta onto your body.
- using hot tubs, whirlpools, or saunas, and direct sunlight. These may affect Neulasta.
- peeling off or disturbing the On-body Injector for Neulasta adhesive before you receive your full dose of Neulasta.

What are possible side effects of Neulasta?

Neulasta can cause serious side effects, including:

- **Spleen rupture**. Your spleen may become enlarged or may rupture during treatment with Neulasta. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.

- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS)**. Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of ARDS: fever, shortness of breath, trouble breathing, or a fast rate of breathing.

- **Serious allergic reactions**. Get emergency medical help right away if you get any of these symptoms of a serious allergic reaction with Neulasta: shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives.

  If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.

- **Sickle cell crises**. Severe sickle cell crises, and sometimes death, can happen in people with sickle cell trait or disease who receive filgrastim, a medicine similar to Neulasta (pegfilgrastim).

- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received Neulasta. You should notify your healthcare provider right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.

- **Increased white blood cell count (leukocytosis)**. Your doctor will check your blood during treatment with Neulasta.

- **Capillary Leak Syndrome**. Neulasta can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
    - swelling or puffiness and are urinating less often
    - trouble breathing
    - swelling of your stomach-area (abdomen) and feeling of fullness
    - dizziness or feeling faint
    - a general feeling of tiredness

The most common side effect of Neulasta is pain in the bones and in your arms and legs.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Neulasta. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Neulasta

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you would like more information about Neulasta, talk with your healthcare provider or pharmacist. You can ask your pharmacist for information about Neulasta that is written for health professionals.

For more information, go to www.neulasta.com or call 1-844-696-3852 (1-844-MYNEULASTA).

What are the ingredients in Neulasta?

Active ingredient: pegfilgrastim
Inactive ingredients: acetate, polysorbate 20, and sodium, sorbitol in Water for Injection.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Neulasta® (pegfilgrastim)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License No. 1080

Patent: http://pat.amgen.com/neulasta/

www.neulasta.com

1-844-MYNEULASTA (1-844-696-3852)
Issued: 11/2015
vX

Neulasta®

Pegfilgrastim

Information for Patients and Caregivers

This patient package insert provides information and instructions for people who will be receiving Neulasta or their caregivers. This patient package insert does not tell you everything about Neulasta. You should discuss any questions you have about treatment with Neulasta with your doctor.

What is Neulasta?

Neulasta is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *Escherichia coli*. G-CSF is a substance produced by the body. It stimulates the growth of neutrophils (**nu**-tro-fils), a type of white blood cell important in the body's fight against infection.

Who <u>should not take</u> Neulasta?

Do not take Neulasta if you have had:

- A serious allergic reaction to Neulasta® (pegfilgrastim) or to Neupogen® (filgrastim).

What important information do I need to know about receiving Neulasta?

Occasionally, pain and redness may occur at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to the doctor.

Neulasta should only be injected on the day the doctor has determined and should not be injected until approximately 24 hours after receiving chemotherapy.

If your child weighs less than 45 kg, do not use the prefilled syringe for direct administration of Neulasta. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 6 mg.

The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

What should I tell my healthcare provider before taking Neulasta?

If you have a sickle cell disorder, make sure that your doctor knows about it before you start using Neulasta. If you have a sickle cell crisis after getting Neulasta, tell your doctor right away.

If you have a problem with your kidneys, make sure that your doctor knows about it before you start using Neulasta as you may need more frequent urine tests.

If you have any questions, talk to your doctor.

Why am I given Neulasta if I was exposed to radiation?

Exposure to high levels of radiation damages bone marrow. Damage to the bone marrow can be deadly. Neulasta increases your chance of survival.

Effectiveness of Neulasta in increasing survival after radiation exposure was only studied in animals. Neulasta given after deadly radiation levels could not be studied in people.

What are possible serious side effects of Neulasta?

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking Neulasta. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.

- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your doctor or seek emergency care right away if you have shortness of breath, trouble breathing, or a fast rate of breathing.

- **Serious Allergic Reactions.** Neulasta can cause serious allergic reactions. These reactions can cause shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives. If you start to have any of these symptoms, call your doctor or seek emergency care right away. If you have an allergic reaction during the injection of Neulasta, stop the injection. Call your doctor right away.

- **Sickle Cell Crises.** You may have a serious sickle cell crisis if you have a sickle cell disorder and take Neulasta. Serious and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, a medicine similar to Neulasta (pegfilgrastim). Call your doctor right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.

- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received Neulasta. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.

- **Increased white blood cell count (leukocytosis)**. Your doctor will check your blood during treatment with Neulasta.

- **Capillary Leak Syndrome**. Neulasta can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
    - swelling or puffiness and are urinating less often
    - trouble breathing
    - swelling of your stomach-area (abdomen) and feeling of fullness
    - dizziness or feeling faint
    - a general feeling of tiredness

What are the most common side effects of Neulasta?

The most common side effect you may experience is aching in the bones and muscles. If this happens, it can usually be relieved with a non-aspirin pain reliever, such as acetaminophen.

What about pregnancy or breastfeeding?

Neulasta has not been studied in pregnant women, and its effects on unborn babies are not known. If you take Neulasta while you are pregnant, it is possible that small amounts of it may get into your baby's blood. It is not known if Neulasta can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breastfeeding, you should tell your doctor before using Neulasta. If you become pregnant during Neulasta treatment, you are encouraged to enroll in Amgen's Pregnancy Surveillance Program. You should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

HOW TO PREPARE AND GIVE A NEULASTA INJECTION

If your child weighs less than 45 kg, do not use the prefilled syringe for direct administration of Neulasta. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 6 mg.

Neulasta is provided in a prefilled syringe. **Neulasta should be stored in its carton to protect from light until use.** If you are giving someone else Neulasta injections, it is important that you know how to inject Neulasta. Before getting your Neulasta injection, always check to see that:

- The name Neulasta appears on the carton and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed. **You should not use a prefilled syringe after the date on the label.**
- The Neulasta liquid should always be clear and colorless. Do not use Neulasta if the contents of the prefilled syringe appear discolored or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

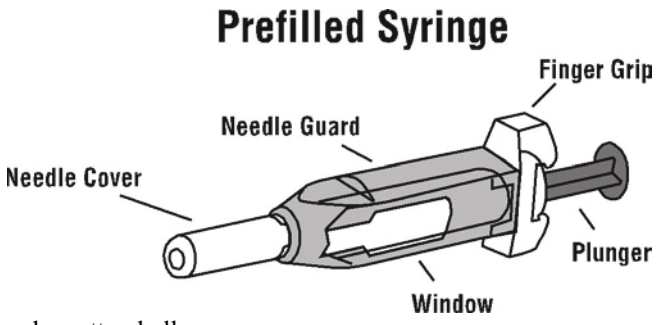
Setting up for an injection

Note: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

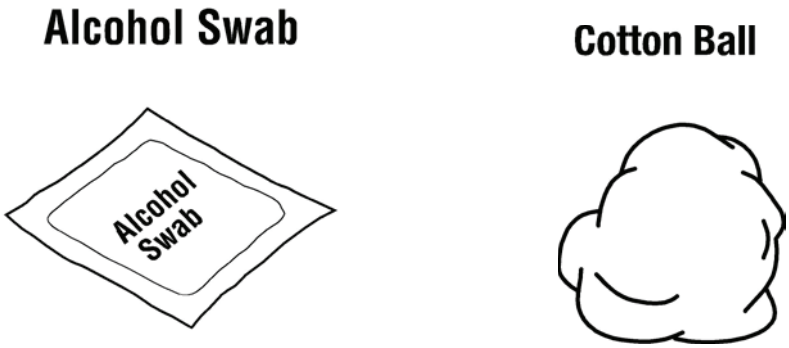
1. Find a clean, flat working surface, such as a table.

2. Remove the carton containing the prefilled syringe of Neulasta from the refrigerator. Allow Neulasta to reach room temperature (this takes about 30 minutes). Remove the syringe from the carton before injection. Each prefilled syringe should be used only once. DO NOT SHAKE THE PREFILLED SYRINGE. Shaking may damage Neulasta. If the prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.

3. Assemble the supplies you will need for an injection:
   - Neulasta prefilled syringe with transparent (clear) plastic blue needle guard attached



   - An alcohol swab and a cotton ball or gauze



   - Puncture-proof disposal container

4. Wash your hands with soap and warm water.

HOW TO PREPARE FOR INJECTION OF NEULASTA

5. Remove the prefilled syringe from the package and the tray. Check to see that the plastic blue needle guard is covering the barrel of the glass syringe. DO NOT push the blue needle guard over the needle cover before injection. This may activate or lock the needle guard. If the blue needle guard is covering the needle that means it has been activated. DO NOT use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new prefilled syringe. **Do not activate the needle guard prior to injection.**

6. Hold the syringe barrel through the needle guard windows with the needle pointing up. Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cover straight off.

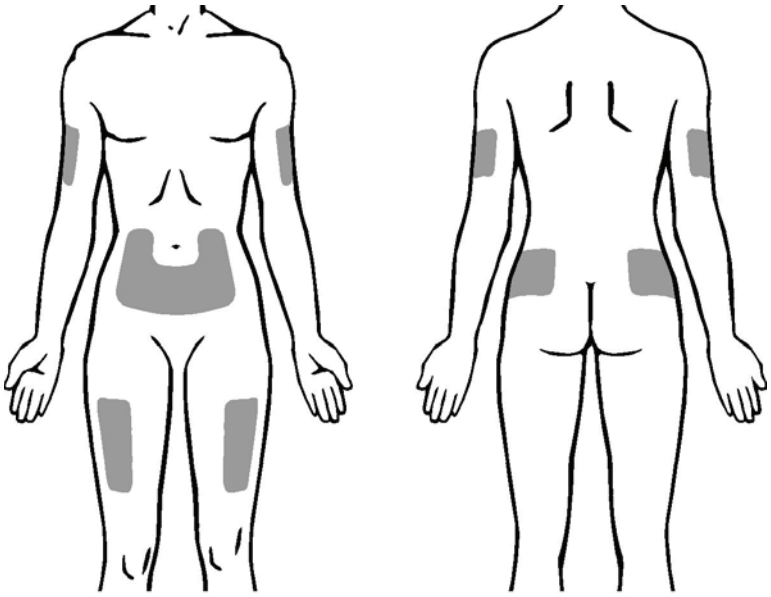
7. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

8. Gently place the prefilled syringe with the window flat on your clean working surface so that the needle does not touch anything.

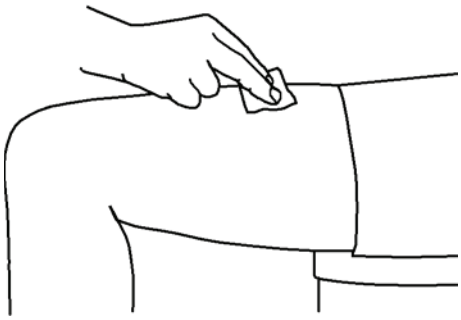
Selecting and preparing the injection site

9. Choose an injection site. Four recommended injection sites for Neulasta are:

    - The outer area of the upper arms
    - The abdomen, except for the two-inch area around the navel
    - The front of the middle thighs
    - The upper outer areas of the buttocks



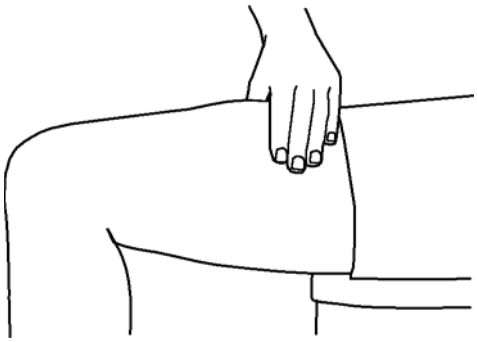
10. Clean the injection site with an alcohol swab.



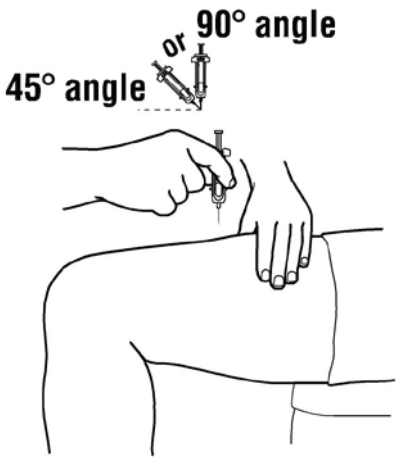
Injecting the dose of Neulasta

11. Pick up the prefilled syringe from your clean, flat working surface by grabbing the sides of the needle guard with your thumb and forefinger.

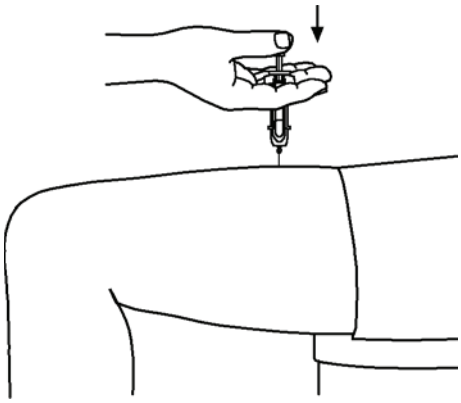
12. Hold the syringe in the hand you will use to inject Neulasta. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: Hold the syringe barrel through the needle guard windows when giving the injection.



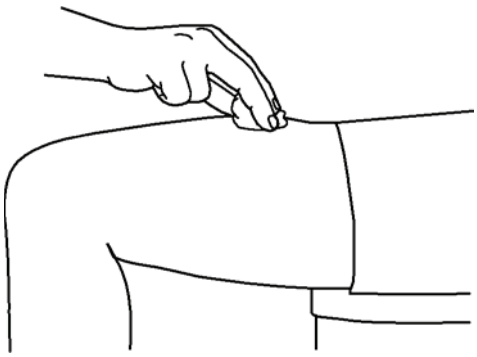
13. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



14. Inject the prescribed dose subcutaneously as directed by your doctor, nurse, or pharmacist.



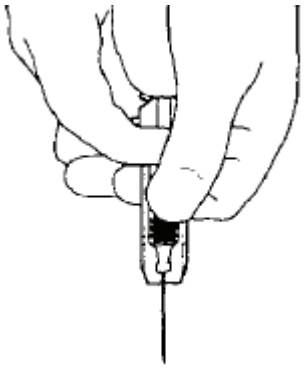
15. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.

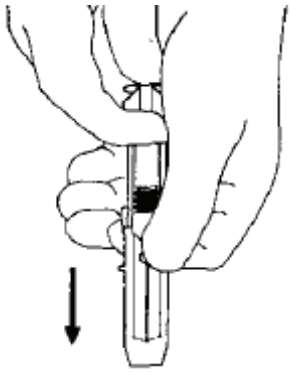


16. Use a prefilled syringe with the needle guard only once.

Activating the Needle Guard after the injection has been given

17. After injecting Neulasta from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. While holding the clear plastic finger grip of the syringe with one hand, grasp the blue needle guard with your free hand and slide the blue needle guard over the needle until the needle is completely covered and the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**





18. Place the prefilled syringe with the activated needle guard into a puncture-proof container for proper disposal as described below.

Disposal of prefilled syringes and needle guards

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes and needle guards. There may be special state and local laws for disposal of used needles and syringes.

- Do not throw the container in the household trash. Do not recycle.
- DO NOT put the needle cover (the cap) back on the needle.
- Place all used needle covers and syringes in a hard plastic container with a screw-on cap or in a metal container with a plastic lid such as a coffee can labeled "used syringes." If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.

How should Neulasta be stored?

Neulasta should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Neulasta should be protected from light, so you should keep it in its carton until you are ready to use it. Avoid shaking Neulasta. If Neulasta is accidentally frozen, allow it to thaw in the refrigerator before injecting. However, if it is frozen a second time, do not use. Neulasta can be left out at room temperature for up to 48 hours. Do not leave Neulasta in direct sunlight. For all questions about storage, contact your doctor, nurse, or pharmacist.

What are the ingredients in Neulasta?

Each syringe contains pegfilgrastim in a sterile, clear, colorless, preservative-free solution containing acetate, sorbitol, polysorbate 20, and sodium.

AMGEN®

Neulasta® (pegfilgrastim)

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Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/neulasta/

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Revised: 11/2015

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