A PHASE 1-2 ASCENDING DOSE STUDY TO ASSESS THE PHARMACODYNAMICS, PHARMACOKINETICS, AND SAFETY OF PF-06881894 (HSP-130) IN SUBJECTS WITH NON-METASTATIC BREAST CANCER FOLLOWING SINGLE-DOSE AND MULTIPLE-DOSE ADMINISTRATION BY SUBCUTANEOUS INJECTION

Statistical Analysis Plan

Protocol C1221002 (ZIN-130-1504)

A PHASE 1-2 ASCENDING DOSE STUDY TO ASSESS THE PHARMACODYNAMICS, PHARMACOKINETICS, AND SAFETY OF PF-06881894 (HSP-130) IN SUBJECTS WITH NON-METASTATIC BREAST CANCER FOLLOWING SINGLE-DOSE AND MULTIPLE-DOSE ADMINISTRATION BY SUBCUTANEOUS INJECTION

Statistical Analysis Plan (SAP) Amendment 1

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C1221002 (ZIN-130-1504) is based on the protocol dated 22 December 2015.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
Amendment 1	Adding CTCAE grading. Additional PD parameters. Protein content adjusted PK parameters.	Responses to requests from regulatory agencies

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) will be provided for laboratory test results.

For Cycle 0, area under the effect curve for ANC from zero to infinity ($AUEC_{ANC\ 0\text{-}\infty}$), area under the effect curve from zero to infinity for $CD34^+$ ($AUEC_{CD34+\ 0\text{-}\infty}$) will be added as secondary endpoints.

The protein-content correction will be conducted for each individual's PK parameters, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, and C_{max}:

Protein-content corrected PK parameter = Nominal Protein-content PK parameter / (Actual protein concentration/10.0 mg/mL)

Where the actual protein concentrations are:

- 9.9 mg/mL for PF-06881894 (Lot 2052124),
- 10.0 mg/mL for PF-06881894 (Lot 2051124),
- 9.9 mg/mL for PF-06881894 (Lot 2459066).

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C1221002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Cycle 0

The primary objective of cycle 0 is to characterize the pharmacodynamic (PD) response of absolute neutrophil count (ANC) and $CD34^+$ count to PF-06881894 (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.

The secondary objectives are:

To characterize the pharmacokinetics (PK) of PF-06881894 (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 PF-06881894 (HSP-130) at doses of 3 mg and 6 mg when administered as a single SC dose without background chemotherapy.

Cycles 1-4

The primary objective of Cycles 1-4 is to characterize the PD response of duration of severe neutropenia (DSN) in Cycle 1 to PF-06881894 (HSP-130) over a range of doses when administered as single and multiple SC doses.

The secondary objectives are:

To characterize the PD response of ANC to PF-06881894 (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 PF-06881894 (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 PF-06881894 (HSP-130) over a range of doses when administered as single and multiple SC doses.

2.2. Study Design

This is an open-label, parallel group study characterizing the PD, PK, and safety of PF-06881894 (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 PF-06881894 (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 PF-06881894 (HSP-130) during the period between biopsy and definitive surgery.

The second group of subjects will receive up to 4 cycles of PF-06881894 (HSP-130), with concomitant background chemotherapy. Patients in Cycles 1-4 will receive PF-06881894 (HSP-130) after definitive surgery. Chemotherapy will consist of every 3 week taxane/cyclophosphamide-based regimen, ie, docetaxel, doxorubicin and cyclophosphamide (TAC).

Specifics of the study design are described in Figure 1.

Figure 1. Overall Study Design

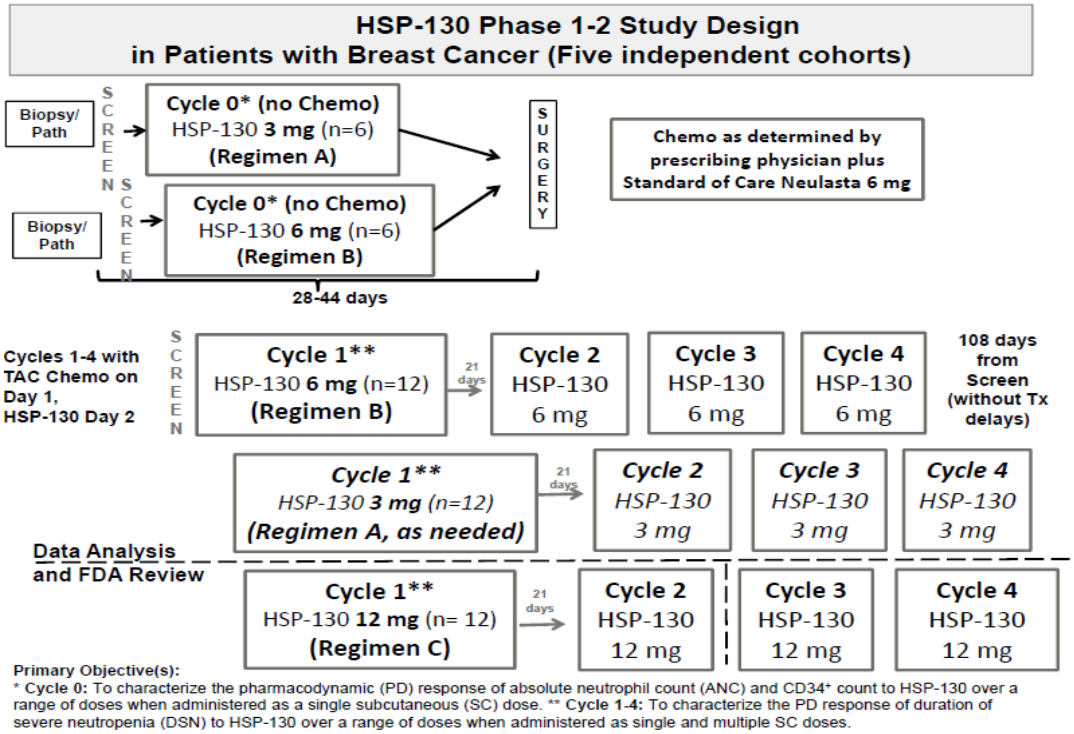

Table 2. Subject Cohorts/Cycles

Cohort	Cycle
(1) 3 mg/Cycle 0	0 (No chemotherapy)
(2) 6 mg/Cycle 0	0 (No chemotherapy)
(3) 6 mg/Cycles 1-4	1-4 (Chemotherapy)
(4) 3 mg/Cycles 1-4	1-4 (Chemotherapy)
(5) 12 mg/Cycles 1-4	1-4 (Chemotherapy)

Table 2 describes groups of subjects with planned regimens and they will be referred to as cohorts in this document. Note that Cohort 4 (3 mg/Cycles 1-4) and Cohort 5 (12 mg/ Cycles 1-4) were not administered in the study, and data for those cohorts will not be presented. Only those cohorts with data collected in the study (Cohorts 1-3) will be summarized and presented.

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 PF-06881894 (HSP-130) dose groups as follows:

Regimen A: PF-06881894 (HSP-130), 3 mg, single SC injection in the deltoid region (n = 6).

Regimen B: PF-06881894 (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 PF-06881894 (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 PF-06881894 (HSP-130) dosing.

After completion of Cycle 0, each of the subjects in these dosing groups will have completed their participation in assessment of PF-06881894 (HSP-130).

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 PF-06881894 (HSP-130) after definitive surgery. Eligible subjects will be enrolled sequentially to each of the PF-06881894 (HSP-130) dose groups as follows:

Regimen B: PF-06881894 (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 (Planned n = 12).

During Cycles 1-4, subjects will receive treatment with PF-06881894 (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 PF-06881894 (HSP-130) in Cycle 4.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Cycle 0

The primary pharmacodynamic variable is Area under the effect curve for ANC ($AUEC_{ANC}$). The primary pharmacokinetic variable is area under the serum PF-06881894 (HSP-130) versus time curve from the time of dose administration to time infinity ($AUC_{0-\infty}$) and the maximum observed serum PF-06881894 (HSP-130) concentration (C_{max}).

Cycles 1-4

The primary pharmacodynamics variable is duration of severe neutropenia (DSN). DSN is defined as days with grade 4 neutropenia (ANC < 0.5 x 10^9/L) in Cycle 1. The primary pharmacokinetic variables are AUC_{0-t} and C_{max} in Cycle 1 and Cycle 4.

3.2. Secondary Endpoint(s)

Cycle 0

The secondary pharmacodynamic variables are 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 ($CD34^+\ T_{max}$), area under the effect curve for ANC from zero to infinity ($AUEC_{ANC\ 0-\infty}$), area under the effect curve from zero to infinity for $CD34^+$ ($AUEC_{CD34+\ 0-\infty}$).

The secondary pharmacokinetic variables are area under the serum PF-06881894 (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 PF-06881894 (HSP-130) concentration (T_{max}), elimination half-life ($t_{1/2}$), elimination rate constant (λz), apparent clearance (CL). Protein-content corrected $AUC_{0-\infty}$, AUC_{0-t} , C_{max} will be calculated.

Cycle 1-4

The secondary pharmacodynamic variables are DSN in Cycle 4, ANC nadir, time of ANC nadir, area under the effect curve (AUEC), $AUEC_{ANC\ 0-\infty}$, incidence of febrile neutropenia (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 secondary pharmacokinetic variables are $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λz, and CL in Cycle 1 and Cycle 4. Protein-content corrected AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} will be calculated.

3.3. Other Endpoints

PF-06881894 (HSP-130) concentration for cohorts 1-3 and CD34+ for cohorts 1 and 2.

ANC_E_{max} and ANC T_{max} will also be provided as additional PD parameters for Cycle 1 and Cycle 4.

Safety endpoints are described in 3.5.

3.4. Baseline Variables

Baseline is defined as the last observation obtained prior to first dose of study medication.

Demographic variables such as age, gender, and race will be summarized by cohort.

3.5. Safety Endpoints

Safety endpoints include clinical adverse events (including AEs of Special Interest), SAEs, laboratory variables, vital signs, physical examination, ECGs, concomitant medication use, discontinuations from the study, exposure to study medication, and anti-pegfilgrastim (anti-drug) antibodies.

Adverse events, serious adverse events, concomitant medication use, discontinuations, and treatment exposure will be summarized by cohort. Selected cycle-specific data (quantitative laboratory parameters, vital signs) will be summarized by cycle within cohort.

3.5.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- The event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- The event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. The lag time in the study is 30 days after the last dose of study drug.

Definitions of Adverse Events of Special Interest

MedDRA version 17.1 or later will be employed in this study to code event terms. The methodology employed to medically group together similar medical constructs within MedDRA will be as follows: where a Standard MedDRA query (SMQ) in MedDRA 17.1 or later exists to summarize the AE of interest, the SMQ will be employed to medically group together the preferred terms. In order to ensure adequate specificity, the SMQ narrow in MedDRA 17.1 or later will be employed to offer a sensitive, but adequately specific approach to summarizing the AE of Special Interest. If an SMQ was not available in

MedDRA 17.1 or later to summarize the AE of interest, a selection of preferred terms will be identified by the sponsor to provide a medically comprehensive grouping of the medical concept. The AEs of Special Interest for PF-06881894 (HSP-130) are outlined below. AEs of Special Interest have been identified prospectively based on the safety information of the pegfilgrastim-US reference product, as described in the Neulasta (pegfilgrastim, Amgen) Package Insert, and grouped by similar medical constructs. The AEs of Special Interest were 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 PF-06881894 (HSP-130) and will be summarized by the medical concept (narrow SMQ and preferred term 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;
12. Glomerulonephritis (added as per the Safety Review Plan).

The identification of Adverse Events of Special Interests is included in the Safety Review Plan and may be adjusted according to Safety Review Plan.

3.5.2. Laboratory Data, Vital Signs, ECG and Immunogenicity

Quantitative laboratory test measurements and change from baseline will be summarized by cycle within cohorts. All laboratory values outside the normal range will be flagged in the data listing.

Quantitative vital sign variables will be listed and change from baseline will be summarized by cycle within cohorts.

ECG and physical exam data will be listed.

Immunogenicity data will be summarized and listed.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to database lock and releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

Full analysis set (FAS): All subjects who received at least 1 dose of study medication. In analysis of a particular parameter for a particular cohort, only those subjects who have sufficient data in the cycle 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. PD/PK parameters will be summarized for two populations: (1) FAS and (2) FAS excluding subjects who have confirmed positive anti-pegfilgrastim (anti-drug) antibody test result.

4.2. Per Protocol Analysis Set

Not applicable.

4.3. Safety Analysis Set

All subjects who received at least 1 dose of study medication.

Adverse events, serious adverse events, concomitant medication use, discontinuations, and treatment exposure will be summarized within the safety analysis set by cohort. Selected cycle-specific data (quantitative laboratory parameters, vital signs) will be summarized within the safety analysis set by cycle within cohort.

4.4. Other Analysis Sets

Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Not applicable. No statistical testing will be done. The primary and secondary endpoints will be summarized using descriptive statistics only.

5.2. General Methods

Pharmacodynamic/Pharmacokinetic variables and concentration data will be calculated using non-compartmental methods and summarized with descriptive statistics: number of subjects, mean, standard deviation (SD), coefficient of variation (CV), median, minimum and maximum.

For a particular parameter ($AUC_{0\text{-}t}$, C_{max} , ANC_E_{max}, ANC T_{max}, $AUEC_{CD34+}$, $AUEC_{CD34+\ 0\text{-}\infty}$ $CD34^{+}$_E_{max}, $CD34^{+}$ T_{max} $AUC_{0\text{-}\infty}$, $t_{1/2}$, λz, CL, $AUEC_{ANC}$, $AUEC_{ANC\ 0\text{-}\infty}$ and Protein-content corrected $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}) within a particular cohort/cycle, only those

subjects who have sufficient data in the cycle 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.

PD/PK variables will be listed with indicator variables for antibody test results (and anti-PEG, before and after dosing for each cycle). PD/PK variables will be summarized for FAS and FAS excluding subjects who have confirmed positive anti-pegfilgrastim (anti-drug) antibody tests. Data for subjects with positive anti-pegfilgrastim (anti-drug) antibody test results and positive anti-PEG antibody test results will be listed.

5.3. Methods to Manage Missing Data

Missing values will not be imputed.

5.4. Primary Endpoint(s)

Endpoints:

Cycle 0

PD: $AUEC_{ANC}$

PK: $AUC_{0-\infty}$ and C_{max}

Analysis population for PD/PK parameters**:** FAS and FAS excluding subjects with positive anti-pegfilgrastim (anti-drug) antibody test results.

These PD/PK parameters will be summarized by cohort (Cohort 1 and 2) using descriptive statistics.

Cycles 1-4

PD: DSN in Cycle 1.

PK: AUC_{0-t} and C_{max} in Cycle 1 and Cycle 4.

Analysis population for PD/PK parameters**:** FAS and FAS excluding subjects with positive anti-pegfilgrastim (anti-drug) antibody test results.

These PD/PK parameters will be summarized by cycle within Cohort 3 using descriptive statistics.

5.5. Secondary Endpoint

Endpoints:

Cycle 0

PD:

- ANC_E_{max}, ANC T_{max}, $AUEC_{ANC\ 0-\infty}$.

- $AUEC_{CD34+\ 0\text{-}t}$, $CD34^+\_E_{max}$, $CD34^+\ T_{max}$, $AUEC_{CD34+\ 0\text{-}\infty}$.

PK: $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, λz, CL, protein-content corrected $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}.

Analysis population for PD/PK parameters**:** FAS and FAS excluding subjects with positive anti-pegfilgrastim (anti-drug) antibody test results.

These PD/PK parameters will be summarized by cohort (Cohorts 1 and 2) using descriptive statistics.

Cycle 1-4

PD:

- DSN in Cycle 4.
- ANC nadir, time of ANC nadir, $AUEC_{ANC}$, incidence of FN, incidence of severe neutropenia , time to ANC recovery, and $AUEC_{ANC\ 0\text{-}\infty}$ in Cycle 1 and Cycle 4.

PK: $AUC_{0\text{-}\infty}$, T_{max}, $t_{1/2}$, λz, CL, protein-content corrected $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} in Cycle 1 and Cycle 4.

Analysis population for PD/PK parameters**:** FAS and FAS excluding subjects with positive anti-pegfilgrastim (anti-drug) antibody test results.

These PD/PK parameters will be summarized by cycle within Cohort 3 using descriptive statistics.

5.6. Other Endpoint(s)

PF-06881894 (HSP-130) concentration and $CD34^+$ values will be summarized by cycle within cohorts using descriptive statistics.

Analysis population**:** FAS and FAS excluding subjects with positive anti-pegfilgrastim (anti-drug) antibody test results

5.7. Subset Analyses

Not planned.

5.8. Baseline Summaries

Summaries of baseline characteristics (demography, medical history, previous medication use) will follow Pfizer's implementation of CDISC standards; these will be presented by cohort.

5.9. Safety Summaries and Analyses

Safety (adverse events, serious adverse events, discontinuations from study, vital signs, ECGs, concomitant medication use) and treatment exposure will be summarized by cohort according to Pfizer's implementation of CDISC standards for safety reporting.

Adverse events for subjects with positive anti-pegfilgrastim and positive anti-PEG antibody test results will be listed together with antibody test information.

Quantitative laboratory test measurements and change from baseline will be summarized by cycle within cohorts. All laboratory values outside the normal range will be flagged in the data listing. NCI CTCAE information will be listed.

Quantitative vital sign variables will be listed and change from baseline will be summarized by cycle within cohorts.

ECG, physical exam, immunogenicity, WHO Performance Status, Clinical Index of Stable Febrile Neutropenia (CISNE), and quality of life assessment FACT-N data will be listed.

Immunogenicity data will be summarized and listed.

6. INTERIM ANALYSES

Not applicable.