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AN ASSESSOR-BLIND, BALANCED, RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, SINGLE-DOSE, TWO-WAY, CROSSOVER, COMPARATIVE, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF SUBCUTANEOUS INJECTIONS OF INTP5 OF INTAS PHARMACEUTICALS LTD., INDIA AGAINST NEULASTA OF AMGEN INC., USA IN HEALTHY, ADULT HUMAN SUBJECTS UNDER FED CONDITION.

SAP VERSION : 01
SAP DATE : 9th May 2018
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SPONSOR : Intas Pharmaceuticals Ltd.,
[redacted]

PREPARED BY : [redacted]

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ABBREVIATIONS & DEFINITIONS

λ_Z	:	First order rate constant associated with the terminal (log-linear) portion of the curve
ADA	:	Anti-Drug Antibody
AE	:	Adverse Event
ANC	:	Absolute Neutrophil Count
ANOVA	:	Analysis of Variance
AUC	:	Area Under Curve
AUC_{0-t}	:	Area under the serum concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method
$AUC_{0-\infty}$	:	Area under the serum concentration versus time curve from time zero to infinity
AUC_%Extrap_obs	:	% of the Area Under the Curve That has been Derived After Extrapolation Or % Residual Area
$AUEC_{0-t}$	:	Area under the ANC versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method
BMI	:	Body Mass Index
Ct	:	Last measurable serum concentration
C_{max}	:	Maximum Measured Serum Concentration
CV	:	Coefficient of Variation
CRO	:	Contract Research Organization
ECG	:	Electrocardiogram
E_{max}	:	Maximum measured ANC.
G-CSF	:	Granulocyte -Colony Stimulating Factor
IMP		Investigational medicinal product
K_2EDTA	:	Dipotassium ethylenediaminetetraacetic acid
Ln	:	Logarithmic value to the base ‘e’
mg	:	Milligram
mL/ml	:	Milliliter
NSAIDs	:	Non-Steroidal Anti-Inflammatory Drugs
PK	:	Pharmacokinetic
PD	:	Pharmacodynamic
R^2 adjusted	:	Goodness of fit statistic for the terminal phase, adjusted for the number of points used in the estimation of λ_Z
SAS	:	Statistical Analysis System
$t_{1/2}$	:	Terminal half-life

T_{max} : Time to reach the maximum measured serum concentration

1 INTRODUCTION

The following analysis plan provides the framework for the analysis and summarization of the data generated from the study conducted to compare the pharmacokinetic and pharmacodynamics profiles of INTP5 of Intas Pharmaceuticals Ltd and Neulasta® of Amgen Inc, USA. The analysis plan may change due to unforeseen circumstances. Any changes made after unblinding will be documented in the clinical study report.

2 OBJECTIVES

Primary Objective: To assess and compare PK and PD profiles of INTP5 and Neulasta® in healthy, adult, human subjects.

Secondary Objective: To assess and compare the safety and tolerability of INTP5 and Neulasta® in healthy, adult, human subjects.

If there are any concerns for PK/PD, immunogenicity would be evaluated for that subject.

3 ENDPOINTS

Primary PK Endpoints: Pegfilgrastim C_{max} and $AUC_{0-\infty}$.

Secondary PK Endpoints: Pegfilgrastim AUC_{0-t}, $AUC_{\_\%Extrap\_Obs}$, T_{max}, λ_z, R^2 adjusted, and $t_{1/2}$.

Primary PD Endpoints: E_{max} and $AUEC_{0-t}$ for baseline non-adjusted absolute neutrophil counts (ANC).

Secondary PD Endpoints: T_{max} for baseline non-adjusted ANC. E_{max}, $AUEC_{0-t}$, T_{max}, λ_z and $t_{1/2}$ for baseline-adjusted ANC.

4 STUDY DESIGN

Study Design

This is an assessor-blind, balanced, randomized, two-treatment, two-period, single-dose, two-way crossover, comparative, PK and PD study of subcutaneous pegfilgrastim injection (6 mg/0.6 ml) in healthy adult human subjects under fed condition.

Investigational Medicinal Products

Test Product-T

- INTP5
- Active content: Pegfilgrastim, Strength: 6 mg/0.6 ml
- Dose for administration: 6 mg/0.6 ml
- Marketing Authorization Holder: Intas Pharmaceuticals Ltd., India
- Pharmaceutical form: Pre-filled syringe
- Route of administration: Subcutaneous
- Storage: 2ºC - 8ºC

Reference Product-R

- Neulasta® (US Licensed product)
- Active content: Pegfilgrastim, Strength: 6 mg/0.6 ml
- Dose for administration: 6 mg/0.6 ml

- Marketing Authorization Holder: Amgen Inc., Thousand Oaks, California, USA
- Pharmaceutical form: Pre-filled syringe
- Route of administration: Subcutaneous
- Storage: 2ºC - 8ºC

Sample Size

Based on the in-house study data, maximum intra-subject variability observed for primary PK parameter $AUC_{0-\infty}$ of Pegfilgrastim was ~32%. The sample size was determined using SAS software considering the following assumptions:

a. T/R ratio = 90.0-110.0%
b. Intra-Subject CV (%) ~ 32%
c. Significance Level = 5%
d. Power ≥ 90%
e. Bioequivalence Limits: 80.00-125.00%

Based on the above estimates, **122 completers** will be sufficient to establish bioequivalence between formulations with adequate power for a two-way crossover study. Considering ~15% dropouts/withdrawals, **144* subjects** will be enrolled. Efforts will be made to recruit equal number of healthy male and female subjects.

Above sample size will also be sufficient to prove bioequivalence of baseline non-adjusted data of ANC as intra-subject variability for baseline non-adjusted data of ANC has been observed as low compared to PK data.

* Study may be conducted in multiple groups.

Randomization

The order of receiving test (T) and reference (R) products for each subject during both the periods will be determined according to a balanced randomization schedule. The randomization schedule will be generated using SAS® Version 9.3 or higher (SAS Institute Inc., USA) by the biostatistician.

The sequence of administration of treatments, i.e. “TR” or “RT”, to the subjects will be determined according to the randomization schedule.

The personnel involved in dispensing of study drugs and verification of dispensed study drugs will be accountable for ensuring compliance to the randomization schedule.

This is an assessor-blind study so coded treatment blinding is not required.

Blinding

The study staff taking care of subject’s safety during the clinical study conduct and the laboratory personnel doing the sample analysis of PK, PD and immunogenicity will be blinded to the study treatment assigned. The pharmacokinetic and statistical team that handle the trial analysis will be provided the Bioanalytical data (PK, PD and Immunogenicity raw data) only after the clinical database lock and blinded data review document is finalized. This will ensure blinding of the pharmacokinetic and statistical team until clinical database lock and blinded data review activity is completed.

Sampling Schedule

A total of 29 blood samples will be collected for PK evaluation and 20 blood samples for PD evaluation.

The blood samples will be kept at room temperature during sample collection activity.

For PK evaluation:

The venous blood samples will be withdrawn at Pre-dose (collected within 60 minutes prior to dosing) and at 2.000, 4.000, 6.000, 8.000, 10.000, 12.000, 14.000, 16.000, 18.000, 20.000, 22.000, 24.000 (Day 2), 26.000, 30.000, 36.000, 42.000, 48.000 (Day 3), 60.000, 72.000 (Day 4), 96.000 (Day 5), 120.000 (Day 6), 144.000 (Day 7), 168.000 (Day 8), 192.000 (Day 9), 240.000 (Day 11), 288.000 (Day 13), 336.000 (Day 15) and 504.000 (Day 22) hours following drug administration in each period.

For PD evaluation:

The venous blood samples will be withdrawn at pre-dose (collected within 60 minutes prior to dosing) and at 6.000, 12.000, 24.000 (Day 2), 36.000, 48.000 (Day 3), 60.000, 72.000 (Day 4), 96.000 (Day 5), 120.000 (Day 6), 144.000 (Day 7), 168.000 (Day 8), 192.000 (Day 9), 216.000 (Day 10), 240.000 (Day 11), 288.000 (Day 13), 312.000 (Day 14), 336.000 (Day 15), 360.000 (Day 16) and 504.000 (Day 22) hours following drug administration in each period.

For immunogenicity evaluation:

For immunogenicity evaluation, venous blood samples (06 ml each) will be withdrawn at screening, pre-dose of period-I (Day 1), at 2 weeks (day 15) and at 4 weeks (day 29) after the first dose, at pre-dose of period-II (Day 43) and at 2 weeks (Day 57) and 4 weeks (Day 71) after the second dose.

5 ANALYSIS POPULATIONS

The analysis populations will be defined as follows:

PK Population: This population will include all subjects who have received at least one dose of study medication and have their blood pegfilgrastim concentration measured.

A subject may be excluded from the PK population due to the following reasons:

- Any subject with at least 3 consecutive Missing (M)/Non-reportable (NR) samples during the absorption phase in a given period will be excluded from the PK population in that period.
- Any subjects with at least 3 consecutive M/NR samples in the elimination phase in a given period will be excluded from the PK analysis of AUC_{0-t} and other elimination phase parameters (i.e. $AUC_{0-\infty}$, AUC%extrap, λ_z, and $t_{1/2}$) for that period.

PK parameters of all subjects included in the PK population will be presented in the PK parameter tables.

PK Evaluable Population: This population will include subjects in the PK population that

- Complete both study periods and

- Have a pre-dose concentration which is ≤ 5% of his/her C_{max} value (The subject's data without any adjustments will be included in all PK measurements and calculations; no baseline correction will be performed).

In addition, a subject may be excluded from the PK evaluable population due to the following reasons:

- Subjects who have events or protocol deviations that would be judged to compromise the integrity of the PK results (e.g. AE's like infection, co-medications that may affect PK, interferences with PK lab parameters assessments). The main summary statistics and statistical comparisons will be performed/presented excluding these subjects. Bioequivalence will be based on these main statistical comparisons. Additional summary statistics and statistical comparisons that include these excluded subjects will be presented separately as sensitivity analysis and will be used for supportive information. Data of these excluded subjects will be presented in both the PK concentration and PK parameter tables.

PD Population: This population will include all subjects who have received at least one dose of study medication and have their PD parameters measured.

A subject may be excluded from the PD population due to the following reasons:

- Subjects excluded from the PK population, which impact the interpretation of PD parameter.
- Any subject with at least 3 consecutive M/NR samples early before T_{max} in the profile will be excluded from the PD population.
- Any subjects with at least 3 consecutive M/NR samples in the latter phase of the PD profile will be excluded from the analysis of $AUEC_{0-t}$.

PD parameters of all subjects included in the PD population will be presented in the PD parameter tables.

PD Evaluable Population: This population will include subjects in the PD population that complete both the study periods and who do not have events or protocol deviations that would be judged to compromise the integrity of the PD results (e.g. AE's like infection, co-medications that may affect PD, interferences with PD lab parameter assessments). The main summary statistics and statistical comparisons will be performed/presented excluding these subjects. Bioequivalence will be based on PD evaluable population statistical comparisons.

Additional summary statistics and statistical comparisons that include the 'PD evaluable population excluded subjects' will be presented separately as sensitivity analysis and will be used for supportive information. Data of these excluded subjects will be presented both in the PD concentration and PD parameter tables.

Immunogenicity Population: This population includes all subjects whose immunogenicity sample has been analyzed based on the immunogenicity analysis plan.

Additionally, following criteria will be used to identify subjects for immunogenicity testing:

- Clinical criteria: Subjects with treatment-related adverse events with a plausible immune mediated pathology will be analyzed for immunogenicity. These may include (but not limited) to the following items:
  - Skin rash
  - Fever not due to infection / could not be concluded as due to infection
  - Injection site reaction
  - Signs and symptoms related to immune complex mediated pathology, such as glomerulonephritis.

PK and PD parameters based criteria: After the PK and PD analysis, Lund's outlier test (i.e. studentized residual test) will be performed for ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ for baseline non-adjusted ANC. If any subject is identified as outlier for ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ for baseline non-adjusted ANC, then further immunogenicity analysis of that subject will be suggested.

Safety Population: This population includes all randomized subjects who received at least one dose of study medication. All subjects included in the trial and dosed will be evaluated for safety.

6 BLINDED DATA REVIEW

All subjects included in the trial and dosed will be considered for data review. Data review will be performed on the basis of clinical phase of the study without consideration of respective treatment arms. Those subjects having concerns (e.g. Infections needing antibiotic usage, used comedications or are identified to have any valid concerns or protocol deviations that may affect the pharmacokinetic or pharmacodynamic endpoints) will be excluded from the PK / PD analysis after providing justification. A sensitivity analysis will be performed including these excluded subjects and results would be presented as supportive information.

The decision to exclude the subjects from data sets for analysis will be determined by the bio-statistician, pharmacokineticist, medical reviewer in consultation with sponsor and/or investigator.

Person involved in this data review process will be blinded to the bioanalytical data (PK/PD/immunogenicity).

Based on above defined data review process, subjects identified for exclusion during pharmacokinetic or pharmacodynamic data analysis would be documented and provided in the Clinical Study Report.

There may be further revisions beyond the protocol / SAP defined criteria for deciding population suitability for inclusion in statistical analysis of pharmacokinetic, pharmacodynamic and immunogenicity parameters; however, these will be pre-defined before unblinding and documented in writing in the blinding-unblinding document.

7 PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

Pharmacokinetic Parameters

The following PK parameters will be computed for Pegfilgrastim using non-compartmental model of Phoenix® WinNonlin® Version 6.4 or higher (Certara L.P.):

Primary PK parameters:

C_{max}	:	Maximum measured serum concentration.
$AUC_{0-\infty}$	:	Area under the serum concentration versus time curve from time zero to infinity. Where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable concentration and λ_z is the terminal rate constant.

Secondary PK parameters:

AUC_{0-t}	:	Area under the serum concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
T_{max}	:	Time to reach the maximum measured serum concentration.
λ_z	:	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least squares regression analysis using at least last 3 or more non-zero serum concentration values.
$t_{1/2}$	:	The terminal half-life will be calculated as $0.693/\lambda_z$.
AUC_%Extrap_obs	:	The residual area in percentage will be determined by the formula, $[(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}] \times 100$.
R^2 adjusted	:	Goodness of fit statistic for the terminal phase, adjusted for the number of points used in the estimation of λ_z.

For all the above computations, actual time points of the sample collection will be used. All concentration values below the lower limit of quantification will be set to zero for the PK and statistical calculations. No value of λ_z, $AUC_{0-\infty}$, AUC_% Extrap_obs, R^2adjusted and $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Pharmacodynamic Parameters

Using the measured ANC, the following variables will be calculated based on baseline non-adjusted and baseline-adjusted data using non-compartmental model of Phoenix® WinNonlin® Version 6.4 or higher (Certara L.P.):

For ANC [baseline non-adjusted data]:

Primary PD Parameters: E_{max} and $AUEC_{0-t}$

Secondary PD Parameter: T_{max}

For ANC [baseline-adjusted data]:

PD parameters: E_{max}, $AUEC_{0-t}$, T_{max}, λ_z and $t_{½}$

E_{max}	:	Maximum measured ANC.
$AUEC_{0-t}$	:	Area under the ANC versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
T_{max}	:	Time to reach the maximum measured ANC.
λ_z	:	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least squares regression analysis using at least last three or more non-zero values.
$t_{1/2}$	:	The terminal half-life will be calculated as $0.693/\lambda_z$.

For all the above computations, actual time points of the sample collection will be used. All concentration values below the lower limit of quantification will be set to zero for the PD and statistical calculations. No value of λ_z or $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

The pre-dose levels will be used for the baseline adjustment of the post-dose levels for ANC. Baseline adjustment will be done by subtracting the baseline value (i.e. pre-dose value) from all the pre- and post-dose values. If, after adjustment, any negative concentration values are obtained, they will be set to zero. Baseline values of the 2nd period will be used for calculating the baseline corrected values of the 2nd period.

8 SAFETY ASSESSMENT

Safety and tolerability to the test product will be evaluated through the assessment of adverse events (i.e., seriousness, severity, relationship to the study drug), vital signs, serum pregnancy test (for female subjects) and clinical laboratory parameters. Adverse events will be tabulated. Changes from baseline values in vital signs and clinical laboratory parameters will be evaluated.

Assessment of Eligibility/Safety

The following assessments will be conducted before the entry of the subjects into the study:

i. Demographic data: Age, height, weight and BMI.

ii. Vital signs: Blood pressure, radial pulse, respiratory rate, oral body temperature.

iii. Medical history and current status: The subject's status as a healthy volunteer will be confirmed.

iv. Medication and therapy history: Current medication and use of any concomitant therapy or ingestion of any prescription drugs (i.e. medication other than paracetamol or NSAIDS for pain) for previous 1 month of dosing. Also, no over-the-counter (OTC) medicines will be allowed during the study until the last sample collection of trial, except vitamins, minerals and nutritional supplements that may be taken at the discretion of the Investigator.

v. Clinical examination: A standard clinical examination will be conducted, including 12-lead ECG and chest X-ray (P/A view, if not done within the last 6 months), abdominal ultrasonography and clinical significant finding will be recorded if any.

vi. Clinical laboratory screening: Blood and urine will be tested for standard parameters. Following laboratory test will be performed.

Screening: hematology, biochemistry, urine analysis, immunological tests, sickling test and serum pregnancy test in case of females.

Prior to check-in of each period: Serum pregnancy test in case of females.

Pre-check-in: Estimation of hematology (except sickling test), biochemistry and urine analysis will be done within 3 working days prior check in of Period-II.

End of the study: (after the last ambulatory sample of Period-II): Hematology (except sickling test), biochemistry, urine analysis and serum pregnancy test (for female subjects).

Biochemistry: Biochemistry will be performed at screening and at the end of the study (i.e. after last ambulatory sample of period-II). The following will be assessed: Total protein, albumin, serum globulin, A/G ratio, bilirubin total, GGT, total cholesterol, blood urea, SGOT (AST), SGPT (ALT), creatinine, random glucose, alkaline phosphatase, sodium, potassium, chloride, calcium and triglycerides.

Immunology: Anti HIV AB (I & II), anti HCV, HBsAg and IgM HBc will be performed at screening.

Hematology: Hematology will be performed at screening and the end of the study (i.e. after last ambulatory sample of period-II). The following will be assessed: CBC. Sickling test will be done only at screening.

Urinalysis: Urinalysis will be performed at screening, and the end of the study (i.e. after last ambulatory sample of period-II). The following will be assessed: specific gravity, pH, glucose, protein, bilirubin, ketones, urobilinogen, erythrocytes, leucocytes, nitrite, and if necessary, microscopic examination will be performed on abnormal findings.

Trial assessments: The following will be recorded during the study:

- Clinical Examination and recording of vital signs at regular intervals
- Concomitant therapy
- Adverse event monitoring and reporting

9 STATISTICAL METHODS AND ANALYSIS

All the statistical and safety analyses will be performed using SAS® Version 9.3 or higher (SAS Institute Inc., USA).

Statistical analysis will be performed on the PK evaluable population and PD evaluable population.

Descriptive statistics will be calculated for PK parameters of Pegfilgrastim and for PD parameters of ANC (baseline non-adjusted and baseline-adjusted data).

PD assessment will be based on the baseline non-adjusted data of ANC only. The baseline adjusted data of ANC will be presented for supportive information only.

i. **Analysis of Variance**

The ln-transformed PK parameters C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and ln-transformed PD parameters E_{max} and $AUEC_{0-t}$ for baseline non-adjusted and baseline adjusted data of ANC will be subjected to ANOVA.

ANOVA model will include group, sequence, sequence*group, formulation, group*formulation, and period (group) as fixed effects and subject (sequence*group) as a random effect. Group, sequence and sequence*group effects will be tested using subject (sequence*group) as an error term.

If group*formulation effect is found to be statistically insignificant at 5% level, this interaction term (group*formulation) will be dropped from the model and statistical analyses will be re-performed excluding this interaction term.

Each ANOVA will include calculation of least-squares means, the difference between adjusted formulation means, and the standard error associated with this difference. The above statistical analyses will be done using the appropriate SAS® procedure.

An F-test will be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05).

ii. **Power**

The power of the study will be computed and reported for ln-transformed C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and E_{max} and $AUEC_{0-t}$ for baseline non-adjusted and baseline adjusted ANC.

iii. **Ratio Analysis**

Ratio of geometric least squares means of test and reference formulations will be computed and reported for ln-transformed C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and E_{max} and $AUEC_{0-t}$ for baseline non-adjusted and baseline adjusted ANC.

iv. **Inter and Intra-Subject Variability**

Inter and intra-subject variability will be computed and reported for ln-transformed C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and E_{max} and $AUEC_{0-t}$ for baseline non-adjusted and baseline adjusted ANC.

v. **Missing and Non-Reportable Values**

Any missing samples (M) or non-reportable (NR) concentration value will be disregarded in PK, PD and statistical analysis.

vi. **Two One-Sided Tests for Bioequivalence**

Using two one-sided tests for bioequivalence, 90% confidence intervals for the test to reference ratio of geometric least squares means will be calculated for ln-transformed C_{max} and $AUC_{0-\infty}$ for Pegfilgrastim and 90 and 95% confidence intervals for the test to reference ratio of geometric least squares means will be calculated for ln-transformed E_{max} and $AUEC_{0-t}$ for baseline adjusted and non-adjusted ANC.

vii. **Pharmacokinetic Bioequivalence Criteria**

Bioequivalence of the test product with that of the reference product will be concluded if 90% confidence interval for the test to reference ratio of the geometric least squares means

for ln-transformed PK parameters (PK evaluable population) C_{max} and $AUC_{0-\infty}$ of Pegfilgrastim falls within the acceptance range of 80.00% to 125.00%.

viii. **Pharmacodynamic Bioequivalence Criteria**

Bioequivalence of the test product with that of the reference product will be concluded if 90% confidence interval for the test to reference ratio of the geometric least squares means for ln-transformed PD parameters E_{max} and $AUEC_{0-t}$ of baseline non-adjusted ANC (PD evaluable population) falls within the acceptance range of 80.00% to 125.00%.

ix. **Immunogenicity Data Analysis**

Immunogenicity (anti-drug antibody - ADA) data will be presented and evaluated, if required for individual subjects. PK, PD and immunogenicity will be presented across both the periods in the identified subjects.

10 SAFETY STATISTICAL ANALYSIS

Demographic parameters will be summarized descriptively.

Safety analysis will be performed using the safety population (see Section 5). Safety variables include AEs, clinical laboratory parameters, vital signs, and physical examinations. Safety variables will be listed and summarized with descriptive statistics as appropriate. Continuous variables will be summarized by treatment/sequence group using summary statistics (number of observations, mean, standard deviation, median, minimum and maximum etc.) as applicable. Categorical values will be summarized by treatment group using frequencies and percentages.

Result obtained when evaluating safety (adverse events, vital signs, clinical laboratory tests etc.) will be listed and evaluated descriptively.

Disposition of Subjects

Number (percent) of subjects who discontinued will be summarized by reason for discontinuation.

Adverse Events

All adverse events reported during the study must be included in the safety analysis. AEs will be classified by system organ class, by preferred term from the MedDRA version 20.1 or higher and p-values will be presented using chi-square test or fisher exact test. They will be presented in individual listings and summary tables, and evaluated descriptively and in terms of frequencies, by treatment. AEs will be summarized for all subjects in safety population across two treatment groups by System Organ Class (SOC) and Preferred Term (PT). A subject will only be counted once per SOC and once per PT within a treatment.

If a subject has two AEs in the same SOC or PT, but intensity is different, then the subject will be counted for the highest intensity outcome. Similarly, if a subject has two AEs in the same SOC or PT, but the relationship is different, then the subject will be counted in worst category.

Clinical Laboratory Values

Clinical laboratory values will be compared to their reference ranges. Values outside the normal ranges will be highlighted. The Investigator has to comment, whether the abnormality is clinically

relevant. Shift tables (cross-tabulations of low, normal, high) at start and end of dosing visit will be used to summarize laboratory test results.

Other Safety Parameters

All results of vital sign measurements will be presented in individual listings by sequence. Where appropriate, results and possible changes in parameters will be evaluated descriptively or by descriptive statistics (mean, SD, median, range), separate for each sequence. Shift tables will be provided as appropriate.

Demographic data will be shown in tables as mean values, SD and ranges (min, max).

Clinical laboratory data will be shown in tables as mean values, SD and ranges (min, max). Shift tables will be provided (Normal, Low and High).

Physical examination and concomitant medication will be presented in tables and data listings.

Shift table for physical examination will be provided (Normal, Abnormal).

Protocol Deviations

Protocol deviations will be presented in listing. Number of subjects with minor and major deviations will be provided.

If a subject has more than one minor / one major protocol deviations, then the count of the subject will be considered as one and commented in the more severe category.

11 CHANGE FROM PROTOCOL

In this SAP, T_{max} for baseline non-adjusted ANC has been added in the secondary PD endpoints.

ANOVA, 90% confidence interval using two one-sided tests and ratio analysis, power for ln-transformed PD parameters E_{max} and $AUEC_{0-t}$ will be computed and reported for baseline adjusted ANC as supportive information.

95% confidence interval using two one-sided tests for ln-transformed PD parameters E_{max} and $AUEC_{0-t}$ will be computed and reported for baseline adjusted and non-adjusted ANC as supportive information in addition to 90% confidence interval data.

12 SOFTWARE FOR ANALYSIS

Phoenix® WinNonlin® Version 6.4 or higher (Certara L.P.) will be used for PK and PD analysis.

SAS® software Version 9.3 or higher (SAS Institute Inc., USA) will be used for safety, statistical and immunogenicity analysis.

13 FORMAT SPECIFICATIONS AND GENERAL PROGRAMMING NOTES FOR OUTPUTS

1. Output files like (statistical analyses, summary tables, individual data listings, etc.) will be produced as PDF files (using SAS).
2. Each individual PDF file will contain the statistical analysis output, i.e. a summary table, or data listing grouped by treatment or/and visit, for one analysis set, and for a single type of analysis.
3. The rules for grouping may vary according to the type of data (study outcome, safety), individual data listings, listings of derived variables, etc. and the type of output file which is

produced (statistical analyses, summary tables, graphs).

4. Page format will be Letter
5. Each listing will be numbered in the format Page X of Y (where Y denotes total number of pages in that particular table or listing). Page number will appear in the bottom right part of the listing.
6. For each output, [redacted] will appear in the Top left corner of the Header, 'Confidential' and 'Title' of the output will appear in the Center of the Header and towards the Top right corner the 'project number' will be presented.
7. The font and font size for header/footer, body will be Courier New size 9 pt for tables and listings generated from SAS.
8. Treatment information and description should be part of footer for each tables & listings. Following text should be displayed in each output as applicable.
   Treatment T: Subcutaneous Dose of INTP5 Administered at 6 mg/0.6 mL
   Treatment R: Subcutaneous Dose of Neulasta® (Pegfilgrastim) Administered at 6 mg/0.6 mL
9. For each output, appropriate footnote representing D, N, n and e should be added as applicable.
   D = Number of doses of drug administered to the enrolled subjects.
   N = Number of enrolled subjects in respective treatment population.
   n = Number of subjects in respective categories.
   e = Number of events.
10 Listings generated before treatment decoding will not include column of treatment/sequence. Table generated before treatment decoding will be include dummy treatment/sequence.

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14.3.7	Summary of vital signs (Safety population)
14.3.8	Summary of vital signs and time point absolute change from check-in values (Safety population)
14.3.9	Summary of overall status from check in status of vital sign assessments (Safety population)
14.3.10	Summary of quantitative safety laboratory variables (Safety population)
14.3.11	Summary of qualitative safety laboratory variables (Safety population)
14.3.12	Summary of quantitative safety laboratory variables absolute change from screening values at assessment visit (Safety population)
14.3.13	Summary of reference range shift from baseline for laboratory parameters (Safety population)
14.3.14	Summary of assessment shift from check-in for physical and systemic examination (Safety population)
14.3.15	Summary of overall assessment shift from period-1 for ECG examination (Safety population)
14.3.16	Summary of concomitant medication (Safety population)
14.3.17	Summary of serious adverse events by system organ class and preferred term (Safety population)
14.3.18	Summary of adverse events by system organ class and preferred term which leading to discontinuation (Safety population)

Statistical Outputs:

16.1.9	Documentation of statistical methods
16.1.9.1	SAS output of group effect for Pegfilgrastim (PK evaluable population)
16.1.9.2	SAS output of ANOVA and BE for Pegfilgrastim (PK evaluable population)
16.1.9.3	SAS output of group effect for Pegfilgrastim (Sensitivity Analysis)
16.1.9.4	SAS output of ANOVA and BE for Pegfilgrastim (Sensitivity Analysis)
16.1.9.5	SAS output of group effect for baseline non-adjusted ANC (PD evaluable population)
16.1.9.6	SAS output of ANOVA and BE for baseline non-adjusted ANC (PD evaluable population)
16.1.9.7	SAS output of group effect for baseline non-adjusted ANC (Sensitivity Analysis)
16.1.9.8	SAS output of ANOVA and BE for baseline non-adjusted ANC (Sensitivity Analysis)
16.1.9.9	SAS output of group effect for baseline adjusted ANC (PD evaluable population)
16.1.9.10	SAS output of ANOVA and BE for baseline adjusted ANC (PD evaluable population)
16.1.9.11	SAS output of group effect for baseline adjusted ANC (Sensitivity Analysis)
16.1.9.12	SAS output of ANOVA and BE for baseline adjusted ANC (Sensitivity Analysis)

16.1.9.13 Statistical Analysis Plan

16.2.5 Compliance and/or drug concentration data

16.2.5.1 Pharmacokinetic summary table of Pegfilgrastim

16.2.5.2 Pharmacokinetic final parameters of Pegfilgrastim

16.2.5.3 Pharmacokinetic summary table of baseline non-adjusted ANC

16.2.5.4 Pharmacokinetic final parameters of baseline non-adjusted ANC

16.2.5.5 Pharmacokinetic summary table of baseline adjusted ANC

16.2.5.6 Pharmacokinetic final parameters of baseline adjusted ANC

Individual Plot

16.2.6 Individual pharmacokinetic and pharmacodynamic response data

16.2.6.1 Individual serum concentration vs. time curve for Pegfilgrastim

16.2.6.2 Individual concentration vs. time curve for baseline non-adjusted ANC

16.2.6.3 Individual concentration vs. time curve for baseline adjusted ANC

Note: Numbering in outputs may change depending on the inclusion/exclusion of the subjects considered for statistical analysis.

List of Listings

16.2.1 Discontinued subjects

16.2.1.1 Study completion status

16.2.1.2 Inclusion criteria

16.2.1.3 Inclusion criteria description

16.2.1.4 Exclusion criteria

16.2.1.5 Exclusion criteria description

16.2.1.6 Subject distribution in analysis

16.2.2 Protocol deviations

16.2.3 Subjects excluded from the PK and PD evaluable population

16.2.3.1 Subjects excluded from the PK evaluable population

16.2.3.2 Subjects excluded from the PD evaluable population

16.2.4 Demographic data

16.2.4.1 Demographic data

16.2.4.2 Systemic examination

16.2.4.3 Physical examination

16.2.4.4 Personal history

16.2.4.5 Medical history

16.2.5 Compliance and/or drug concentration data
16.2.5.7 IMP administration
16.2.5.8 Study drug administration-compliance
16.2.5.9 Pharmacokinetic blood samples
16.2.5.10 Pharmacodynamic samples
16.2.5.11 Immunogenicity samples
16.2.5.12 Compliance and well being at the time of ambulatory sample
16.2.7 Adverse event listings (each subject)
16.2.7.1 Adverse events by severity and relationship to the study drug
16.2.7.2 Adverse events by system organ class and preferred term
16.2.7.3 Serious adverse events (if applicable)
16.2.8 Listing of individual laboratory measurements (by subject)
16.2.8.1 Laboratory parameters
16.2.8.2 Pregnancy test
16.2.8.3 Data of Immunogenicity (if applicable)
16.2.8.4 Summary of Immunogenicity Results for ADA-Confirmed Positive Subjects (if applicable)
16.2.9 Individual subject data listings
16.2.9.1 Vital sign and well-being record
16.2.9.2 Breath test for alcohol consumption
16.2.9.3 Urine scan for drugs of abuse
16.2.9.4 Clinical examination
16.2.9.5 ECG
16.2.9.6 X-ray
16.2.9.7 Injection site assessment
16.2.9.8 Meal distribution records
16.2.10 Concomitant medications

15 REFERENCES

1. ICH Harmonized Tripartite Guideline – Statistical Principles for Clinical Trials (E9). Step 4, 5 February 1998.
2. ICH Harmonized Tripartite Guideline – Structure and Content of Clinical Study Reports (E3). Step 4, 30 November 1995.