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AN ASSESSOR-BLIND, BALANCED, PARALLEL, RANDOMIZED, TWO-TREATMENT, COMPARATIVE IMMUNOGENICITY STUDY OF MULTIPLE DOSES OF INTP5 OF INTAS PHARMACEUTICALS LIMITED, INDIA AGAINST NEULASTA® OF AMGEN INC., USA ADMINISTERED SUBCUTANEOUSLY IN HEALTHY, ADULT, HUMAN SUBJECTS UNDER FED CONDITION

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TABLE OF CONTENTS

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
CL	:	Confidence Limit
Ct	:	Last measurable serum concentration
C_{max}	:	Maximum Measured Serum Concentration
CRO	:	Contract Research Organization
CV	:	Coefficient of Variation
ECG	:	Electrocardiogram
E_{max}	:	Maximum measured ANC
G-CSF	:	Granulocyte -Colony Stimulating Factor
K_2EDTA	:	Dipotassium Ethylene Diamine Tetraacetic acid
Mg	:	Milligram
mL/ml	:	Milliliter
NAB	:	Neutralizing Antibody
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 multiple-dose immunogenicity 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; Any changes made from the protocol will be detailed in this analysis plan.

2 OBJECTIVES

Primary Objective: To assess and compare multiple-dose immunogenicity 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 any subject develops immunogenicity, impact of immunogenicity on pharmacokinetic (PK) and pharmacodynamic (PD) would be evaluated for that subject.

3 STUDY DESIGN

Study Design

This is an assessor-blind, balanced, parallel, randomized, two-treatment, comparative immunogenicity study of multiple doses of INTP5 of Intas Pharmaceuticals Limited, India against Neulasta® of Amgen Inc., USA administered subcutaneously in healthy, adult, human subjects under fed condition.

Investigational Medicinal Products

Test Product-T

- INTP5 (INTP5 is an internal code assigned to Pegfilgrastim manufactured by Intas Pharmaceuticals Limited)
- 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® (Pegfilgrastim) (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

As per the data from prescribing information, 6% patients develop antibodies to Pegfilgrastim. Hence, we hypothesize that 94% patients will not develop antibodies, and based on this assumption, the sample size has been calculated. For a comparison of two independent binomial proportions using Pearson's Chi-square statistic with a Chi-square approximation with a two-sided significance level of 5%, 89 completers per group achieves a power of at least 80% when the proportions are 94% for both test and reference and the null proportion difference is assumed as 10%.

Considering dropouts/withdrawals, approximately 100 subjects per treatment group (approximately 200 subjects for two treatment groups)* will be required.

Subsequent dropouts if any after first dosing will not be replaced.

*Study will be conducted in multiple groups.

Randomization

The allocation to test (T) or reference (R) product for each subject during the study 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.

Equal allocation of subjects in each treatment arm (i.e. 'T' or 'R') will be ensured.

The personnel involved in dispensing of study drug 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 data 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 is finalized. This will ensure blinding of the pharmacokinetic and statistical team until, clinical database lock and blinded data review activity are completed.

Sampling Schedule

A total of 8 blood samples will be collected for immunogenicity analysis, including the sample at screening.

<u>For Immunogenicity evaluation:</u>

Venous blood samples will be withdrawn at screening, pre-dose (0) and at 336 (Day 15, week 2), 504 (Day 22, week 3, within 60 minutes before 2nd dose), 840 (Day 36, week 5), 1176 (Day 50, week 7), 1680 (Day 71, week 10) and 2016 (Day 85, week 12) hours after the first dose.

Note: Pre-dose sample will be collected within 60 minutes before the scheduled time. Post-dose in-house blood samples will be collected within ±2 minutes and ambulatory blood samples will be collected within ±1 hour from the scheduled time.

Samples for immunogenicity evaluation at 336 (Day 15, week 2), 504 (Day 22, week 3, within 60 minutes before 2nd dose), 840 (Day 36, week 5), 1176 (Day 50, week 7), 1680 (Day 71, week 10) and 2016 (Day 85, week 12) hours after the first dose will be collected on an ambulatory basis.

A total of 23 blood samples will be collected for PK and PD evaluations. (Note: The last sample of the previous dose and the pre-dose sample of the following dose will be the same).

For Pharmacokinetic evaluation:
1st and 2nd dose: Venous blood samples will be withdrawn at pre-dose (0) and at 8, 16, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 240 (Day 11), 336 (Day 15) and 504 (Day 22) hours following 1st and 2nd dose administration.

[Note: Post-dose sample of 1st dose at 504 (Day 22) hours will be considered as pre-dose sample of 2nd dose, which should be collected within 5 minutes prior to 2nd dose].

Note: Samples for PK at and after 96 hours after each dose will be collected on an ambulatory basis.

For Pharmacodynamic evaluation:
1st and 2nd dose: Venous blood samples will be withdrawn at pre-dose (0) and at 8, 16, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 240 (Day 11), 336 (Day 15) and 504 (Day 22) hours following 1st and 2nd dose administration.

(Note: Post-dose sample of 1st dose at 504 (Day 22) hours will be considered as pre-dose sample of 2nd dose, which should be collected within 5 minutes prior to 2nd dose).

Note: Samples for PD at and after 96 hours after each dose will be collected on an ambulatory basis.

4 ANALYSIS POPULATIONS

The analysis population will be defined as follows:

Immunogenicity Population: This population includes all subjects who were administered at least one dose of the study drug (either INTP5 or Neulasta) and have at least one pre-dose or post-dose immunogenicity sample.

PK Population: This population includes all subjects who received at least one dose of the study drug (either INTP5 or Neulasta) and have at least one confirmatory ADA positive sample and sufficient data to estimate PK parameters.

PD Population: This population includes subjects who received at least one dose of the study drug (either INTP5 or Neulasta). PD population will be further divided into the following subgroups:

> **ADA-Positive PD population**: Subjects in PD population who have at least one confirmatory ADA test positive.

ADA-Negative PD population: Subjects in PD population who are ADA-negative (includes screening negative plus confirmatory negative results). Subjects may be excluded from the ADA-negative PD population for the following reasons:

- Any subject with at least 3 consecutive M/NR samples before T_{max} in the profile.
- 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 $AUEC_{0-t}$.
- Any protocol deviation that would be judged to impact the PK and PD parameter interpretation, such as AE's like infection, co-medications that may affect PD, and interferences with PD lab parameter assessments.

Note: The decision to exclude a subject from PK and PD parameter estimation will be based on appropriate scientific rational and will be determined by the clinician, pharmacokinetician, biostatistician and the bioanalytical team in consultation with the sponsor and/or investigator. The rationale will be documented.

Safety Population : This population includes all randomized subjects who received at least one dose of study medication.

5 DATA REVIEW

No subjects from the immunogenicity population will be excluded from the immunogenicity analysis.

No blinded review will be performed.

6 IMMUNOGENICITY DATA ANALYSIS

Immunogenicity (anti-drug antibody; ADA) data will be presented for all subjects' samples collected.

Descriptive analysis will be provided for immunogenicity (ADA) data.

Risk difference between the test and the reference will be estimated using 90% CI. Percentage incidence within +10% of expected ADA positivity incidence of Test (6% ADA for Test is anticipated from literature) would not be considered clinically significant.

7 PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

Pharmacokinetic Parameters

For the PK Population, following PK parameters will be computed for Pegfilgrastim for the samples collected after the first dose and second dose, separately using non-compartmental model of Phoenix® WinNonlin® Version 6.4 or higher (Certara L.P.):

C_{max}	:	Maximum measured serum concentration.
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. 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.
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 pharmacokinetic and statistical calculations. No value of λ_z, $AUC_{0-\infty}$, AUC_% Extrap_obs, R^2 adjusted 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

For the PD Population, following PD parameters will be computed for baseline non-adjusted and baseline-adjusted ANC for the samples collected after the first dose and second dose, separately using non-compartmental model of Phoenix® WinNonlin® Version 6.4 or higher (Certara L.P.):

For baseline non-adjusted ANC: E_{max}, $AUEC_{0-t}$ and T_{max}

For baseline-adjusted ANC: E_{max}, $AUEC_{0-t}$, T_{max}, λ_z and $t_{1/2}$

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 baseline adjustment of the post-dose levels for ANC. Baseline adjustment will be done for both the treatments for the dosing-related values, by subtracting the baseline value (i.e. pre-dose value) from all the pre- and post-dose values. If, after adjustment, any negative concentrations values are obtained, they will be set to zero.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

If any subject develops positive immunogenicity (confirmed ADA positive test result), impact of immunogenicity on PK and PD will be evaluated for that subject. Impact of immunogenicity on PK will be assessed by comparing individual PK parameters of first dose and second dose. Individual subject-wise PK parameters will be presented for dose 1 and dose 2, separately for the two treatment groups, along with the descriptive statistics.

Individual PD parameters will be compared between dose 1 and dose 2, treatment wise, for the ADA-positive PD population. Additionally, these parameters will be compared with the pooled data of the ADA-negative PD population, separately for the two treatments.

Descriptive statistical analysis of PD parameters of ADA-positive PD population and ADA-negative PD population will be done separately for the two treatments.

All PK and PD parameters will be presented using descriptive statistics (including variability data).

No statistical inferential methods will be used to assess the impact of immunogenicity on PK and PD.

9 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), ECG, 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 done 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 was confirmed.

iv. Medication 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 were 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: 12-lead ECG and chest X-ray (P-A view if not done within the last 6 months), abdominal ultrasonography and clinical significant finding.

vi. Clinical laboratory screening: Blood and urine tests for standard parameters, listed below:

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

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

Pre- check in (within three working days prior to receiving dose 2): Hematology (except sickling test), biochemistry and urine analysis.

End of the study (after the last ambulatory sample after dose 2): Hematology (except sickling test), biochemistry (except sodium, potassium, calcium, and chloride), urine analysis and serum pregnancy test (for females).

Biochemistry: A/G ratio, total protein, albumin, serum globulin, bilirubin total, GGT, SGOT (AST), SGPT (ALT), random glucose, alkaline phosphatase, blood urea, creatinine and electrolytes (sodium, potassium, calcium, and chloride).

Immunology: Anti HIV AB (I & II), Anti HCV and HBsAg at screening.

Hematology: CBC (including RBC count, platelet count) ANC, and sickling test.

Urinalysis: Specific gravity, pH, glucose, protein, bilirubin, ketones, urobilinogen, erythrocytes, leucocytes, nitrite and, if necessary, microscopic examination on abnormal findings.

Assessments during Study

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

10 SAFETY STATISTICAL ANALYSIS

The safety analysis will be performed on the safety population. 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 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. No statistical hypothesis will be tested.

Considering study objective as a comparative immunogenicity study, safety data analysis will not be adjusted for factors, such as gender, BMI, etc.

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 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. Where appropriate, results and possible changes in parameters will be evaluated descriptively or by descriptive statistics (mean, SD, median, range), separate for each treatment. Shift tables (cross-tabulations of Normal, Abnormal) at start and end of dosing visit will be presented.

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 THE PROTOCOL

In this SAP, T_{max} for baseline non-adjusted ANC has been added.

12 SOFTWARE INFORMATION FOR ANALYSIS

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

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

13 FORMAT SPECIFICATIONS 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 (US Licensed product)
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 set.
   n = Number of subjects in respective categories.
   e = Number of events.
10 Listings generated before treatment decoding will not include column of treatment. Table generated before treatment decoding will be include dummy treatment.

14 SUMMARY TABLES AND FIGURES

14.1 SUBJECT DISPOSITION AND DEMOGRAPHIC DATA

14.1.1 Demographic data and baseline characteristics (Safety population)

Positive PD Population)

14.2.4.20 Concentration of data excluded from ADA-Positive PD Population for baseline adjusted ANC (if applicable)

14.2.5 Deviations used for Pharmacokinetic and Pharmacodynamic Evaluation

14.2.5.1 Actual time points used for pharmacokinetic evaluation

14.2.5.2 Actual time points used for pharmacodynamic evaluation

14.2.6 Figures of Pharmacokinetic and Pharmacodynamic Data

14.2.6.1 Mean plot of Pegfilgrastim concentration vs time curve for Dose 1 and Dose 2 of Test Product-T

14.2.6.2 Mean plot of Pegfilgrastim concentration vs time curve for Dose 1 and Dose 2 of Reference Product-R

14.2.6.3 Mean plot of ANC concentration (baseline non-adjusted) vs time curve for Dose 1 and Dose 2 of Test Product-T (ADA-Positive population)

14.2.6.4 Mean plot of ANC concentration (baseline non-adjusted) vs time curve for Dose 1 and Dose 2 of Reference Product-R (ADA-Positive population)

14.2.6.5 Mean plot of ANC concentration (baseline non-adjusted) vs time curve for Dose 1 and Dose 2 of Test Product-T (ADA-Negative population)

14.2.6.6 Mean plot of ANC concentration (baseline non-adjusted) vs time curve for Dose 1 and Dose 2 of Reference Product-R (ADA- Negative population)

14.2.6.7 Mean plot of ANC concentration (baseline adjusted) vs time curve for Dose 1 and Dose 2 of Test Product-T (ADA-Positive population)

14.2.6.8 Mean plot of ANC concentration (baseline adjusted) vs time curve for Dose 1 and Dose 2 of Reference Product-R (ADA-Positive population)

14.2.6.9 Mean plot of ANC concentration (baseline adjusted) vs time curve for Dose 1 and Dose 2 of Test Product-T (ADA-Negative population)

14.2.6.10 Mean plot of ANC concentration (baseline adjusted) vs time curve for Dose 1 and Dose 2 of Reference Product-R (ADA- Negative population)

14.2.6.11 Plot of individual data points for PK parameter C_{max} with a mean value for Dose 1 and Dose 2 of Test Product-T

14.2.6.12 Plot of individual data points for PK parameter C_{max} with a mean value for Dose 1 and Dose 2 of Reference Product-R

14.2.6.13 Plot of individual data points for PK parameter $AUC_{0-\infty}$ with a mean value for Dose 1 and Dose 2 of Test Product-T

14.2.6.14 Plot of individual data points for PK parameter $AUC_{0-\infty}$ with a mean value for Dose

1 and Dose 2 of Reference Product-R

14.2.6.15 Plot of individual data points for PD parameter E_{max} (ADA positive and negative subjects) for baseline adjusted data for Dose 1 and Dose 2 of Test Product-T

14.2.6.16 Plot of individual data points for PD parameter E_{max} (ADA positive and negative subjects) for baseline adjusted data for Dose 1 and Dose 2 of Reference Product-R

14.2.6.17 Plot of individual data points for PD parameter $AUEC_{0-t}$ (ADA positive and negative subjects) for baseline adjusted data for Dose 1 and Dose 2 of Test Product-T

14.2.6.18 Plot of individual data points for PD parameter $AUEC_{0-t}$ (ADA positive and negative subjects) for baseline adjusted data for Dose 1 and Dose 2 of Reference Product-R

14.3 SAFETY DATA

14.3.1 Overall summary of adverse events (Safety population)

14.3.2 Summary of adverse events by system organ class and preferred term (Safety population)

14.3.3 Summary of adverse events by relationship to study drug and system organ class and preferred term (Safety population)

14.3.4 Summary of adverse events by severity and system organ class and preferred term (Safety population)

14.3.5 Summary of adverse events by toxicity grade and system organ class and preferred term (Safety population)

14.3.6 Summary of subject disposition

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 screening 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)

15 STATISTICAL OUTPUTS

16.1.9 Documentation of statistical methods

16.1.9.1 Statistical Analysis Plan

16.2.5 Compliance and/or drug concentration data

16.2.5.1 Pharmacokinetic summary table for Pegfilgrastim (Dose 1) (PK Population)

16.2.5.2 Pharmacokinetic final parameters for Pegfilgrastim (Dose 1) (PK Population)

16.2.5.3 Pharmacokinetic summary table for Pegfilgrastim (Dose 2) (PK Population)

16.2.5.4 Pharmacokinetic final parameters for Pegfilgrastim (Dose 2) (PK Population)

16.2.5.5 Pharmacodynamic summary table for baseline non-adjusted ANC (Dose 1) (ADA-Positive PD Population)

16.2.5.6 Pharmacodynamic final parameters for baseline non-adjusted ANC (Dose 1) (ADA- Positive PD Population)

16.2.5.7 Pharmacodynamic summary table for baseline non-adjusted ANC (Dose 2) (ADA-Positive PD Population)

16.2.5.8 Pharmacodynamic final parameters for baseline non-adjusted ANC (Dose 2) (ADA- Positive PD Population)

16.2.5.9 Pharmacodynamic summary table for baseline non-adjusted ANC (Dose 1) (ADA-Negative PD Population)

16.2.5.10 Pharmacodynamic final parameters for baseline non-adjusted ANC (Dose 1) (ADA-Negative PD Population)

16.2.5.11 Pharmacodynamic summary table for baseline non-adjusted ANC (Dose 2) (ADA-Negative PD Population)

16.2.5.12 Pharmacodynamic final parameters for baseline non-adjusted ANC (Dose 2) (ADA-Negative PD Population)

16.2.5.13 Pharmacodynamic summary table for baseline adjusted ANC (Dose 1) (ADA-Positive PD Population)

16.2.5.14 Pharmacodynamic final parameters for baseline adjusted ANC (Dose 1) (ADA-Positive PD Population)

16.2.5.15 Pharmacodynamic summary table for baseline adjusted ANC (Dose 2) (ADA-Positive PD Population)

16.2.5.16 Pharmacodynamic final parameters for baseline adjusted ANC (Dose 2) (ADA-Positive PD Population)

16.2.5.17 Pharmacodynamic summary table for baseline adjusted ANC (Dose 1) (ADA-Negative PD Population)

16.2.5.18 Pharmacodynamic final parameters for baseline adjusted ANC (Dose 1) (ADA-Negative PD Population)

16.2.5.19 Pharmacodynamic summary table for baseline adjusted ANC (Dose 2) (ADA-Negative PD Population)

16.2.5.20 Pharmacodynamic final parameters for baseline adjusted ANC (Dose 2) (ADA-Negative PD Population)

Individual Plot

16.2.6 Individual Pharmacokinetic/Pharmacodynamic response data

16.2.6.1 Individual serum concentration vs. time curve for Pegfilgrastim (Dose 1)

16.2.6.2 Individual serum concentration vs. time curve for Pegfilgrastim (Dose 2)

16.2.6.3 Individual concentration vs. time curve for baseline non-adjusted ANC (Dose 1)

16.2.6.3.1 Individual concentration vs. time curve for baseline non-adjusted ANC (Dose 1) (ADA-Negative PD Population)

16.2.6.3.2 Individual concentration vs. time curve for baseline non-adjusted ANC (Dose 1) (ADA-Positive PD Population)

16.2.6.4 Individual concentration vs. time curve for baseline non-adjusted ANC (Dose 2)

16.2.6.4.1 Individual concentration vs. time curve for baseline non-adjusted ANC (Dose 2) (ADA-Negative PD Population)

16.2.6.4.2 Individual concentration vs. time curve for baseline non-adjusted ANC (Dose 2) (ADA-Positive PD Population)

16.2.6.5 Individual concentration vs. time curve for baseline adjusted ANC (Dose 1)

16.2.6.5.1 Individual concentration vs. time curve for baseline adjusted ANC (Dose 1) (ADA-Negative PD Population)

16.2.6.5.2 Individual concentration vs. time curve for baseline adjusted ANC (Dose 1) (ADA-Positive PD Population)

16.2.6.6 Individual concentration vs. time curve for baseline adjusted ANC (Dose 2)

16.2.6.6.1 Individual concentration vs. time curve for baseline adjusted ANC (Dose 2) (ADA-Negative PD Population)

16.2.6.6.2 Individual concentration vs. time curve for baseline adjusted ANC (Dose 2) (ADA-Positive PD Population)

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

16 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 analysis
16.2.3.1 Subjects excluded from the PK analysis
16.2.3.2 Subjects excluded from the PD analysis
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
16.2.5.13 IMP administration
16.2.5.14 Study drug administration-compliance
16.2.5.15 Pharmacokinetic blood samples
16.2.5.16 Pharmacodynamic samples
16.2.5.17 Immunogenicity evaluation
16.2.5.18 Compliance and well being at the time of ambulatory sample
16.2.6 Individual immunogenicity response data
16.2.6.1 Immunogenicity Data
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

16.2.8.4 Immunogenicity Results for ADA-Confirmed Positive Subjects

16.2.9 Individual subject data listing

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 examination

16.2.9.8 Meal distribution records

16.2.10 Concomitant medications

17 REFERENCES

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2. ICH Harmonized Tripartite Guideline – Structure and Content of Clinical Study Reports (E3). Step 4, 30 November 1995.