2 SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceutical Works Private Limited **Code Name of Finished Product:** Balugrastim **Name of Active Ingredients:** Recombinant human albumin-human G-CSF	**Individual Study Table referring to of the Dossier** **Protocol No.: NEUGR-003**	**(For National Authority Use Only)**

Study Title A Randomized, Double-Blind, Active Comparator, Non-Inferiority Study of Subcutaneously Administered Neugranin (Recombinant Human Albumin-Human Granulocyte Colony Stimulating Factor) or Pegfilgrastim in Subjects with Breast Cancer Receiving Myelosuppressive Chemotherapy (Doxorubicin/Docetaxel), Followed by a Single-Arm, Open-Label Phase of Subcutaneously Administered Neugranin

Study Site Investigators and Respective Study Sites

Subjects were enrolled into the double-blind phase of the study by 59 investigators: 23 investigators in Russia, 16 investigators in Ukraine, 8 investigators in Romania, 8 investigators in Bulgaria, and 4 investigators in Serbia. Of these investigators, 28 investigators also enrolled subjects into the open-label phase: 5 investigators in Bulgaria, 15 investigators in Ukraine, 6 investigators in Romania and 2 investigators in Serbia.

Publication Based on Study Results

Not Applicable

Study Dates	First Subject Enrolled: 20 July 2010 Last Subject Completed the Treatment Phase: 5 May 2011	**Clinical Phase** III

Test Drug, Dose and Mode of Administration, Batch Number

Balugrastim 40 mg provided in prefilled syringes to be administered by subcutaneous injection, Batch no.: K43465 (3P) and K44342 (3P)

Reference Drug, Dose and Mode of Administration, Batch Number

Pegfilgrastim 6 mg provided in prefilled syringes to be administered by subcutaneous injection, Batch no.: 1016759 and 1019615

Objectives

Primary Objective

To evaluate the efficacy of balugrastim compared to pegfilgrastim in subjects receiving doxorubicin and docetaxel as evidenced by the duration of severe neutropenia (DSN) in Cycle 1.

To evaluate the safety and tolerability of balugrastim compared with pegfilgrastim in subjects receiving the combination of doxorubicin and docetaxel.

Secondary Objectives

To determine the incidence of febrile neutropenia and documented infections by cycle and across all

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cycles

To assess the incidence of severe neutropenia by cycle and across all cycles

To assess the DSN in Cycles 2-4.

To assess the time to absolute neutrophil count (ANC) recovery (ANC $\geq 1.5 \times 10^9$/L) in Cycles 1-4

Drug-Drug Interaction Sub-study Objective:

To investigate the effect of balugrastim and pegfilgrastim on the pharmacokinetics (PK) of doxorubicin.

ECG Sub-study Objectives:

To define the changes in electrocardiogram (ECG) intervals and morphology due to balugrastim and pegfilgrastim and to define the relationship of the change in QTcF duration with plasma concentration of balugrastim and pegfilgrastim over time.

Methodology

This study was a randomized, double-blind, active comparator, two phase (double-blind randomized phase and open-label safety cohort phase), multicenter trial conducted in subjects with breast cancer who were scheduled to receive up to four cycles of doxorubicin/docetaxel. The double-blind phase was powered to determine non-inferiority and planned to randomize approximately 300 subjects in a 1:1 ratio to balugrastim or pegfilgrastim. Subjects were assigned to treatment groups using a stratified randomization for balance among treatment groups based on weight (<50 kg, ≥50 kg and <80 kg, or ≥80 kg), prior chemotherapy exposure, and global location. Enrollment of new subjects into the open-label phase started after enrollment into the double-blind randomized phase was completed. The open-label phase planned to enroll 70 additional subjects to expand the safety database of subjects treated with balugrastim.

Eligibility was assessed during a screening period, which lasted up to 14 days. The eligibility criteria were the same for the double-blind and open-label phases. Only subjects with ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L at the conclusion of the screening period were eligible to enter the trial. Additional eligibility criteria are described below. The schedule of study procedures was the same for both phases of the study except that subjects enrolled into the open- label, safety cohort were not eligible to participate in the drug-drug interaction (DDI) sub-study or the ECG sub-study described below.

The chemotherapy regimen for this trial consisted of doxorubicin 60 mg/m^2, docetaxel 75 mg/m^2 administered sequentially by intravenous infusion on Day 1 of treatment for up to four 21-day cycles. Prior to receiving each cycle of therapy, subjects had to have an ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L. Treatment could be delayed up to two weeks for chemotherapy-related toxicity. A 25% dose reduction of both chemotherapies was allowed for Grade 3-4 non-hematologic toxicity or Grade 4

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thrombocytopenia in the previous cycle or if the subject experienced two prior Grade 3-4 infectious episodes.

Subjects experiencing severe hypersensitivity reactions or non-hematologic toxicities that precluded further cycles of chemotherapy were to be removed from study treatment and to complete follow-up.

In both phases of the study, the study drug was administered approximately 24 hours (±6 hours) after initiation of chemotherapy in up to four treatment cycles. For subjects participating in the DDI sub-study, the study drug was administered approximately 24 hours (±2 hours) after initiation of chemotherapy in Cycle 4 only.

Efficacy was assessed based primarily on complete blood counts obtained during each chemotherapy cycle on Day 1, Day 3, daily from Day 5 through Day 9 and continuing until ANC >2.0 x 10^9/L after the nadir, then twice weekly until the next cycle, and at the end of treatment.

Subjects were monitored for adverse events (AEs) and concomitant medications throughout the study. AEs were recorded from the time the subject signed informed consent until 30 days after the last dose of study drug. As part of a standard safety evaluation, subjects underwent serial ECG evaluations.

Tolerability was assessed based on the following criteria: proportion of subjects (%) who prematurely discontinued from the study, the proportion of subjects (%) who discontinued prematurely from the study due to AEs, and the time to withdrawal.

All subjects are being followed for 12 months from the start of treatment to assess overall survival, any adverse impact on the efficacy of the chemotherapy regimen in terms of time to progression and frequency of objective tumour remissions. Follow-up was scheduled for approximately 30 days after the last study dose of study drug and 6, 9, and 12 months after start of treatment. Immunogenicity was to be assessed prior to each administration of study drug, at the end of treatment period visit (approximately 30 days after the last dose of study drug), and during long-term follow-up at 6 and 12 months after the first study treatment.

Number of subjects (planned and analyzed)

The study planned to enroll 370 subjects (300 in the double-blind phase and 70 in the open-label phase) with an established diagnosis of breast cancer. A total of 304 subjects were randomized to treatment with balugrastim 40 mg (153 subjects) or pegfilgrastim 6 mg (151 subjects) in the double-blind phase, and 77 were enrolled into the open-label phase and were treated with balugrastim 40 mg. The intent-to-treat population was used for efficacy analyses and included 153 subjects randomized to treatment with balugrastim 40 mg and 151 subjects randomized to treatment with pegfilgrastim 6 mg during the double-blind phase and 77 subjects enrolled and treated with balugrastim 40 mg during the open-label phase. One subject randomized to pegfilgrastim received chemotherapy in Cycle 1 but withdrew consent before being treated with study drug. This subject did not contribute post-baseline data.

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Pharmacokinetic Assessments

A DDI sub-study was conducted by a subset of sites during the double-blind, randomized phase of the study. Samples for the determination of plasma levels of doxorubicin and its major metabolite, doxorubicinol, were obtained pre-dose, immediately post-infusion (approximately 0.25 hours), then at 0.5, 1, 3, 6, 24, 48, 72, 96, 120 and 168 hours (12 blood samples in total) following the start of the doxorubicin infusion in Cycle 4. Fifty subjects (25 per treatment arm) were planned to be enrolled into this sub-study.

In addition to blood samples obtained during the DDI sub-study, sparse serum samples to measure balugrastim concentrations were obtained during the study (prior to administration of study drug and 24, 72 and 144 hours post-dose in Cycles 1 and 4) to support interpretation of ECG data and to build a population PK database.

ECG Sub-Study

During the randomized, double-blind phase, 60 subjects in each treatment arm were assigned to more frequent ECG assessments. For these subjects, ECGs were recorded on Day 2, Day 3 and Day 5 in both Cycle 1 and Cycle 4. ECGs were recorded prior to study drug administration on Day 2 and prior to blood sampling on all three days. On-treatment ECGs were recorded in triplicate, and the tracings were sent to a central reading center (CRC) for measurement of intervals and interpretation.

Data Monitoring Committee

A Data Monitoring Committee (DMC) received blinded safety data periodically. DMC meetings were planned to occur after 60 subjects, 120 subjects, and 180 subjects completed Cycle 1 of chemotherapy. The DMC also could have met on an ad hoc basis if safety concerns arose. The DMC had the right to recommend discontinuation of the trial for safety reasons. Due to exceptionally rapid enrolment of subjects, data of 223, 301 and 379 subjects were reviewed at DMC meetings held in November 2010, January 2011, and April 2011, respectively.

Immunogenicity was to be assessed prior to each administration of study drug, at the end of treatment period visit (approximately 30 days after the last dose of study drug), and is being assessed during the long-term follow-up at 6 months and 1 year following initiation of study treatment.
All subjects are being followed over a 1-year period for disease progression and survival. Follow-up was scheduled at 30 days after the last dose of study drug administration and 6, 9, and 12 months after start of treatment.

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Main Inclusion Criteria

1. Patients with histologically or cytologically confirmed breast cancer scheduled to receive doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2
2. 18 years of age or older
3. Adequate hematologic function
   a. ANC $\geq$1.5 x 10^9/L
   b. Platelets $\geq$100 x 10^9/L
4. Adequate hepatic and renal function
   a. Serum creatinine <2.0 mg/dL
   b. Total bilirubin within normal limits
   c. Serum transaminases – alanine aminotransferase and aspartate transferase <1.5 x upper limit of normal
   d. Alkaline phosphatase <2.5 x upper limit of normal
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
6. Eligible to receive doxorubicin based on a left ventricular ejection fraction (LVEF) $\geq$ lower limit of normal
7. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study protocol procedures

Main Exclusion Criteria:

1. More than 1 prior chemotherapy regimen (including adjuvant and/or neoadjuvant therapy if given within the last 12 months prior to study chemotherapy)
2. Prior lifetime cumulative anthracycline dose exceeding 240 mg/m^2 doxorubicin or the equivalent dose of another anthracycline or anthracenedione
3. Prior chemotherapy/immunotherapy within 30 days prior to study chemotherapy (within 6 weeks of study chemotherapy for nitrosoureas (carmustine, lomustine) or mitomycin-C
4. Concomitant trastuzumab (Herceptin)
5. Received any investigational agent within 30 days prior to study chemotherapy
6. Myocardial infarction within 6 months prior to study chemotherapy, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or ECG abnormalities that may interfere with the accurate assessment of the QT interval, including intraventricular conduction delays (QRS >120 msec)

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7. Prior surgery within 2 weeks of study chemotherapy
8. Prior radiation therapy within 4 weeks of study chemotherapy (except spot irradiation for bone metastases)
9. Prior high-dose chemotherapy with hematopoietic stem cell transplant
10. Prior use of granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor or erythropoietin within 4 weeks of study chemotherapy
11. Received systemic antibiotics within 72 hours of study chemotherapy
12. History of myeloid malignancy or myelodysplasia

Duration of Treatment

Subjects received a single, subcutaneous injection of balugrastim or pegfilgrastim approximately 24 hours after chemotherapy in each of up to 4 chemotherapy cycles. The duration of treatment from the first dose of study drug to the end of study visit was 13 weeks. Subjects were followed for 12 months after the start of treatment.

Criteria for Evaluation

The primary efficacy endpoint was the DSN in Cycle 1. Secondary efficacy endpoints derived from ANC profiles included the DSN during Cycles 2, 3, and 4, time to ANC recovery, ANC nadir, and time to ANC nadir. Additional efficacy endpoints included the incidences of febrile neutropenia, severe neutropenia, and Grade 3/4 neutropenia, and various types of infection.

The safety of balugrastim was assessed by evaluation of the type, frequency, and severity of AEs, changes in clinical laboratory tests (hematology and clinical chemistry), immunogenicity, ECG evaluations, physical examinations and the monitoring of vital signs over time. All AEs and laboratory toxicities were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 4.02, September 15, 2009). The frequency and incidence of adverse events were tabulated for each treatment group according to the Medical Dictionary for Regulatory Activities (MedDRA, version 14).

PK parameters, including Cmax, AUC, AUC(0-inf), terminal elimination half-life, clearance, volume of distribution, were estimated for doxorubicin for both treatment groups (balugrastim and pegfilgrastim) using non-compartmental analysis. Relevant parameters were also calculated for doxorubicinol.

A table of individual as well as summary statistics for the plasma levels of doxorubicin and doxorubicinol with time was provided for each treatment. Plots of individual as well as mean plasma levels of doxorubicin and doxorubicinol with time also were provided.

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The primary ECG endpoint was the change from baseline in QTcF. Secondary endpoints included the change from baseline in QTcB; heart rate; PR, QRS, and uncorrected QT intervals; and ECG morphological patterns as well as the correlation between QTcF change from baseline and serum concentrations of balugrastim and pegfilgrastim.

Statistical Methods

The **all subjects** population included all subjects who gave their consent either in the double blind phase or the open-label phase of the study. The all subjects population was used for all listings.

For the double-blind phase, the **intent-to-treat (ITT)** population included all randomized subjects. In this population, treatment was assigned based upon the treatment to which subjects were randomized regardless of which treatment they actually received.

For the open-label cohort the ITT population included all enrolled subjects who satisfied eligibility criteria.

Efficacy analyses were performed on the ITT population of the double-blind cohort solely. Subjects enrolled in the open-label cohort were not included in the efficacy comparisons. The efficacy results for these subjects are displayed in the in-text and post-text tables, but are not included in the efficacy comparisons between balugrastim and pegfilgrastim as the open-label phase was not designed to demonstrate efficacy.

The **per protocol (PP)** population included all data from randomized subjects that were obtained prior to the occurrence of major protocol violations. Efficacy analyses, including the primary efficacy comparison, were performed on the per-protocol population of the double-blind cohort.

The **safety** population included all subjects who received at least one dose of study drug. In the double-blind cohort, treatment was assigned based upon the treatment subjects actually received regardless of the treatment to which they were randomized. Safety analyses were performed on the safety population in both study phases. One subject randomized to pegfilgrastim received chemotherapy but withdrew consent before being treated with study drug. As a result, the pegfilgrastim group has 151 subjects in the ITT population and 150 subjects in the safety population.

Demography, breast cancer history, and ECOG performance status were summarized using descriptive statistics.

Analysis of the Primary Efficacy Endpoint

The primary analysis assessed non-inferiority in the PP population with a procedure that provided an overall one-sided alpha of 0.025. The primary analysis consisted of hypothesis testing and corresponding confidence interval (CI) estimation of the difference in mean DSN in Cycle 1 between the balugrastim treatment group and the pegfilgrastim control group, defined as the mean DSN in the balugrastim group minus the mean DSN in the pegfilgrastim group. Non-inferiority to within 1 day was established if the upper bound of the 95% two-sided CI for the difference in mean DSN was <1

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day. If non-inferiority to within 1 day was established, the upper endpoint of the CI was to be compared to margins less than 1 day to establish the smallest treatment difference that can be excluded at a one-sided alpha of 0.025. This closed testing procedure controls overall one-sided alpha at 0.025. If the upper endpoint of the CI was less than or equal to 0.62, then non-inferiority to within a margin of 0.62 will have been demonstrated at a one-sided alpha of 0.025.

Analysis of Secondary Efficacy Endpoints

Mean time to ANC recovery (days) to $\geq 1.5 \times 10^9$/L, mean ANC nadir and mean time to nadir ANC (days) in all cycles were estimated and compared between treatment groups at each cycle. Treatment groups were compared using t-test.

Mean DSN was estimated and compared between treatment groups at Cycles 2-4 via one-way analysis of variance (ANOVA); 95% CI for the difference in mean DSN between treatment groups was presented as well. This analysis was repeated for the Grade 3/4 neutropenia at the Cycles 1-4.

Incidences of febrile neutropenia, severe neutropenia and Grade 3/4 neutropenia were estimated and compared between treatment groups at each cycle and across all cycles using Fisher Exact test.

Incidences of various types of infection treatment-emergent AEs (TEAEs) with primary or secondary system organ classes (SOC) of Infections and infestations were presented along with corresponding preferred terms and compared between treatment groups as described above for febrile neutropenia.

The effect of subject weight on difference in mean DSN in Cycle 1 was explored. The difference in mean DSN between the balugrastim group and the pegfilgrastim group was estimated within each weight stratum (<50 kg, ≥ 50 kg and < 80 kg, or ≥80 kg). Due to the relatively small sample sizes within strata, the differences in mean DSN were not expected to be statistically significant.

Confidence intervals and statistical tests on the secondary endpoints are exploratory in nature.

Safety Analyses

The frequency and rate of TEAEs were summarized by treatment (balugrastim and pegfilgrastim during the double-blind phase, balugrastim during the open-label phase, and all balugrastim), MedDRA SOC, high level term (HLT), and preferred term for all TEAEs, by relationship to study drug (related/not related), by relationship to chemotherapy and by NCI-CTCAE code. TEAEs without an NCI-CTCAE code were classified as mild, moderate, severe, life-threatening and death. Summaries of TEAEs by treatment cycle also were prepared. The potential influence of age and weight on the type and frequency of TEAEs was also evaluated.

TEAEs in the SOC of Infections and infestation (primary and secondary) were summarized by high level group term (HLGT) and preferred term for all TEAEs as well as for those TEAEs starting during a neutropenic state. AEs of special interest were summarized descriptively as were allergic TEAEs by four Standardised MedDRA Queries (SMQs) terms (angioedema, oropharnygeal allergic conditions, anaphylactic reaction, anaphylactic/anaphylactoid shock conditions).

Hematology and chemistry results were summarized for observed values and change from baseline by

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descriptive statistics, and the incidence of laboratory values with CTC grade ≥3 was summarized. Shift tables summarized the change from baseline to the worst post-baseline grade by CTC grade.

Observed values and changes from baseline were summarized by cycle and observation time for vital signs and ECG evaluations. The correlation between the change from baseline in QTcF and serum concentrations of balugrastim and pegfilgrastim also was determined.

SUMMARY-RESULTS

Subject Disposition

Of the 304 subjects (153 balugrastim, 151 pegfilgrastim) enrolled in the double-blind randomized phase, 21 subjects did not complete the study, 15 (9.8%) subjects treated with balugrastim and 6 (4.0%) subjects treated with pegfilgrastim. The most frequent reasons for early discontinuation were subject withdrew consent (5 balugrastim, 2 pegfilgrastim), treatment [chemotherapy] failure/disease progression (4 balugrastim), failed to return/lost to follow-up (3 balugrastim, 1 pegfilgrastim), and adverse events (2 balugrastim, 1 pegfilgrastim). The investigators considered all AEs leading to discontinuation to be not related to study drug.

Of the 77 subjects enrolled in the open-label safety cohort, 11 (14.3%) subjects did not complete the study. The most frequent reasons for early discontinuation were subject withdrew consent (6 subjects) and AEs (4 subjects). The investigators considered all AEs leading to discontinuation to be not related to study drug or chemotherapy.

During the Blinded Data Review Meeting (BDRM) prior to database lock, 3 subjects in each treatment group were excluded from the PP population. Three subjects in the balugrastim group and 2 subjects in the pegfilgrastim group were excluded because they had less than 5 ANC values between Day 1 and Day 9 of Cycle 1. After being randomized to pegfilgrastim, one subject withdrew consent after the first dose of chemotherapy treatment and was not treated with study drug. This subject was excluded from the PP and Safety Populations.

Clinical Effect Results

In the double-blind randomized phase, balugrastim and pegfilgrastim were comparable for DSN in Cycle 1 for both the PP and ITT populations. In the PP population, the mean DSN was 1.1 and 1.0 days in the balugrastim and pegfilgrastim groups, respectively. The difference (95% CI) between treatments was 0.1 (-0.13; 0.37) days. The upper endpoint of the CI was less than 0.62, which demonstrates non-inferiority to pegfilgrastim within a margin of 0.62 at a one-sided alpha of 0.025.

In the ITT population, the mean DSN during Cycle 1 was 1.1 and 1.0 days in the balugrastim and pegfilgrastim groups, respectively. The difference (95% CI) between treatments was 0.1 (-0.11; 0.38) days. The upper endpoint of the CI was less than 0.62, which demonstrates non-inferiority to pegfilgrastim within a margin of 0.62 at a one-sided alpha of 0.025.

For the PP and ITT populations, the mean DSN for each treatment group, the difference between treatments and its 95% CI were similar whether the ANC values were mixed, from the central

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laboratory only or from the local laboratory only.

The mean ANC nadir was 0.8 x 10^9/L and 1.0 x 10^9/L for the balugrastim and pegfilgrastim groups, respectively. The median ANC nadir was 0.3 x 10^9/L in each treatment group. The mean (6.7 days) and median (6.0 days) time to nadir was the same for both treatment groups. The mean time to recovery was 2.0 days in the balugrastim group and 2.1 days in the pegfilgrastim group. The median time to recovery was 2.0 days in both treatment groups.

Across treatment cycles, mean values were consistent with the results in Cycle 1. Within cycle, the treatments were similar, and treatment effect was not statistically significant for any parameter in Cycles 2-4.

During Cycle 1, febrile neutropenia was observed in 2 (1.3%) subjects in the balugrastim group and 4 (2.6%) subjects in the pegfilgrastim group. Febrile neutropenia was not observed in either treatment group during Cycles 2-4.Treatment effect was not statistically significant in any chemotherapy cycle.

Safety Results

More than 90% of subjects in each treatment group experienced at least one TEAE and at least one TEAE related to chemotherapy. In the double-blind phase, 19.6% and 18.7% of subjects in the balugrastim and pegfilgrastim groups, respectively, had TEAEs related to study drug, and 3.9% and 4.7%, respectively, had at least one serious AE (SAE).

TEAEs with a fatal outcome were observed for 2 (1.3%) subjects treated with balugrastim during the double-blind phase and 1 (1.3%) subject treated with balugrastim during the open-label phase. An additional subject treated with balugrastim during the open-label phase withdrew consent during Cycle 3 and subsequently died of progressive disease during the follow-up period. The investigators considered all four TEAEs with a fatal outcome to be unrelated to study drug or chemotherapy.

The incidence of SAEs was similar for the double-blind treatment groups (3.9% balugrastim, 4.7% pegfilgrastim), but was slightly higher for subjects treated with balugrastim during the open-label phase (7.8%). None of the SAEs were related to study drug. Chemotherapy-related SAEs were experienced by 4 (2.6%) balugrastim subjects and 4 (2.7%) pegfilgrastim subjects in the double-blind phase and 4 (5.2%) balugrastim subjects in the open-label phase.

The incidence of TEAEs leading to study discontinuation was slightly higher in the balugrastim (2.6%) group than in the pegfilgrastim group (0.7%); however, none of these TEAEs were considered by the investigator to be related to study drug.

During the double-blind phase, the incidence of TEAEs summarized by MedDRA high level term (HLT) differed between treatments by ≥5% for thrombocytopenia (15.0% balugrastim, 6.7% pegfilgrastim) and asthenic conditions (37.3% balugrastim, 32.0% pegfilgrastim). Thrombocytopenia was observed for 2.6% of subjects treated with balugrastim during the open-label phase and for 10.9% of all balugrastim subjects. For the remaining HLTs, the incidence was similar for the treatment groups in the double-blind phase. Except as noted for thrombocytopenia, the results for the open-label phase

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were consistent with the results in the double-blind phase.

Eleven categories of TEAEs of special interest were evaluated. TEAEs were observed in three categories: bone pain related symptoms, diarrhoea and diarrhoea haemorrhagic symptoms, and pulmonary adverse effects. Although the incidence was higher in the balugrastim group than in the pegfilgrastim group for bone pain related symptoms and diarrhoea like symptoms, the incidence of TEAEs of special interest considered by the investigators to be related to study drug was low and similar for balugrastim and pegfilgrastim during the double-blind phase.

The mean platelet count decreased from baseline in both treatment groups; however, the decrease from baseline tended to be larger in the balugrastim group than in the pegfilgrastim group from Day 6 to Day 11. The mean and median values were similar for the double-blind treatment groups at the beginning of each cycle.

The overall incidence of laboratory values with NCI-CTCAE Grade 3 or higher was similar for balugrastim, all balugrastim and pegfilgrastim for all parameters except platelet count and magnesium, which were higher in the balugrastim group than in the pegfilgrastim group.

Approximately half of the subjects in each treatment group had a non-clinically significant abnormality in the ECG at baseline. The only clinically significant abnormality at baseline was observed in one subject randomized to the balugrastim double-blind group. Of the subjects with a normal ECG at baseline, 20.5%, 29.9%, and 28.2% of the subjects in the balugrastim double-blind, pegfilgrastim double-blind, and balugrastim open-label groups, respectively, had non-clinically significant abnormalities post-baseline, and 1 (1.3%) subject in the balugrastim double-blind group had a clinically significant abnormality post-baseline. For heart rate and ECG intervals, the mean and median values for observed values and the change from baseline were similar across treatment groups. The percentage of outlier values for heart rate or ECG intervals generally was similar for the double-blind treatment groups. The percentage of subjects with a new QTcF >450 ms was higher for the balugrastim double-blind group than for the pegfilgrastim group (24.2% vs 19.3%) as was the percentage with a new QTcB>480 ms (13.1% vs 6.7%). There were no substantial differences between treatments for morphological analysis.

Pharmacokinetic Results

Population PK: Of the 380 subjects enrolled into the study, 348 subjects (211 balugrastim 137 pegfilgrastim) had at least one PK sample and were included in the Treatment Population. Mean balugrastim serum concentrations were, in general, greater in Cycle 1 than in Cycle 4. The variability, measured as percent coefficient of variation (CV%), of serum balugrastim concentrations was high. Mean pegfilgrastim serum concentrations were also greater in Cycle 1 compared to Cycle 4 with high variability as well, although the CV% for pegfilgrastim was slightly lower than balugrastim CV%. The mean pegfilgrastim serum concentrations were normalized to account for the difference in molecular weight with balugrastim.

Non-compartmental PK parameters for balugrastim and pegfilgrastim were determined from the

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concentration-time profiles. Maximum observed serum concentration (C_{MAX}), time of maximum concentration (T_{MAX}), and partial area under the serum concentration-time curve from time 0 to 144 hr (AUC0-144) were calculated from the PK Population.

In the PK Population, the mean 40 mg balugrastim C_{MAX} (CV%) was 847 ng/mL (90.4%) in Cycle 1 and 648 ng/mL (101.4%) in Cycle 4. T_{MAX} values for balugrastim ranged from 16.58 to 148.25 hours with a median T_{MAX} of 23.0 hours in Cycle 1. In Cycle 4, T_{MAX} ranged from 0.00 to 144.42 hours with a median of 22.75 hours. For balugrastim, mean AUC_{0-144} (CV%) values for Cycle 1 and Cycle 4 were 59236 hr•ng/mL (109.1%) and 31654 hr•ng/mL (110.0%), respectively. In the PK Population for pegfilgrastim (6 mg), the mean C_{MAX} (CV%) in Cycle 1 was 112 ng/mL (58.5%) while in Cycle 4 it was 113 ng/mL (67.7%). T_{MAX} values for pegfilgrastim ranged from 15.17 to 143.50 hours with a median T_{MAX} of 22.5 hours in Cycle 1 and in Cycle 4 T_{MAX} ranged from 16.85 to 143.42 hours with a median of 22.7 hours. The mean (CV%) AUC_{0-144} values for pegfilgrastim in Cycle 1 and Cycle 4 were 9556 hr•ng/mL (67.2%) and 6361 hr•ng/mL (65.4%), respectively. When adjusting for molecular weight, pegfilgrastim mean molecular weight normalized C_{MAX} in Cycle 1 was 666 ng/mL (58.5%) while in Cycle 4 it was 428 ng/mL (67.7%). The mean (CV%) molecular weight normalized AUC_{0-144} values for pegfilgrastim in Cycle 1 and Cycle 4 were 43002 hr•ng/mL (67.2%) and 28625 hr•ng/mL (65.4%), respectively.

It is important to note that estimates of half-life were compromised due to limitations on PK sampling that affected the ability to define the elimination phase in a number of patients with profiles that indicated a t½ value longer than the PK sampling window. For subjects who had definable elimination phase profiles (Complete PK population), the mean (CV%) t½ was 38.69 (40.0%) hours and 32.64 (37.4%) hours in Cycle 1 and Cycle 4, respectively, for balugrastim and 41.70 (24.8%) hours and 46.09 (26.3%) hours in Cycle 1 and Cycle 4, respectively, for pegfilgrastim.

While some relatively small differences in the PK between balugrastim and Pegfilgrastim adjusted molecular weight values were observed, these differences did not translate into a difference in pharmacodynamics as demonstrated by the fact that the effects of balugrastim and pegfilgrastim on ANC were similar when plotted over time.

DDI Sub-study: Of the 12 subjects (7 balugrastim, 5 pegfilgrastim) enrolled into the DDI sub-study, 11 subjects (7 balugrastim, 4 pegfilgrastim) had sufficient terminal slope concentrations to determine half-life.

Mean doxorubicin and doxorubicinol plasma concentrations were comparable when doxorubicin was administered with balugrastim or pegfilgrastim. The variability, measured as percent coefficient of variation, of plasma doxorubicin and doxorubicinol concentrations were moderate to high (range of 17.8% to 223.6% for doxorubicin; range of 17.3% to 264.6% for doxorubicinol).

Overall, the pharmacokinetic parameters for both doxorubicin and doxorubicinol were similar when doxorubicin was administered with either balugrastim or pegfilgrastim. The estimated terminal half-life of doxorubicin and doxorubicinol were also comparable between treatments. These results indicate

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that doxorubicin pharmacokinetics is comparable when co-administered with balugrastim or pegfilgrastim.

ECG Sub-study Results

The ECG sub-study evaluated the potential effects of balugrastim and pegfilgrastim in 61 subjects treated with balugrastim and 60 subjects treated with pegfilgrastim during the double-blind treatment period by assessing the mean change from baseline and the incidence of outliers in ECG parameters and morphological changes in the ECG.

The mean changes from baseline in heart rate and ECG intervals were comparable between treatments and were not clinically relevant.

No bradycardic outliers were observed, and the incidence of tachycardic outliers was lower for the balugrastim group (7%) than for pegfilgrastim group (12%). There were no outliers for the PR and QRS intervals in either treatment group. QTcF >480 ms was observed for 1 (2%) subject treated with balugrastim. QTcB >500 ms was observed for 1 (2%) subject treated with pegfilgrastim, and QTcB >480 ms were observed for 4 (7%) subjects in each treatment group.

The percentage of subjects with a QTcF increase from baseline of 30-60 ms was higher in the balugrastim group (15%) than in the pegfilgrastim group (7%) as was the percentage of subjects with a QTcB increase from baseline of 30-60 ms (18% vs 12%). Increases from baseline >60 ms were not observed for either QTcF or QTcB.

New ST depression or elevation was observed in 4 (7%) subjects treated with balugrastim and 3 (5%) subjects treated with pegfilgrastim, and new second or third degree heart block was observed for 1 (2%) subject treated with balugrastim and 5 (8%) subjects treated with pegfilgrastim. New atrial fibrillation was observed in 1 (2%) subject treated with pegfilgrastim. Other morphological changes were not observed in either treatment group.

A review of the QTcF intervals and the PK-PD relationships for balugrastim revealed that there was no significant effect of balugrastim on cardiac repolarization.

OVERALL CONCLUSIONS AND DISCUSSION

This study demonstrated non-inferiority of balugrastim to pegfilgrastim within a margin of 0.62 at a one-sided alpha of 0.025. The difference between treatments for DSN was 0.14, and the upper endpoint of the CI was less than 0.62.

In each chemotherapy cycle, the efficacy of balugrastim and pegfilgrastim was comparable based on results for the ANC nadir, time to ANC nadir, time to ANC recovery, the incidence and duration of Grade 3 or 4 neutropenia, and the incidence of febrile neutropenia.

Balugrastim was well tolerated when administered to breast cancer patients receiving myelosuppressive chemotherapy. The overall safety profile was similar for balugrastim and pegfilgrastim.

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