SYNOPSIS

NAME OF COMPANY Hospira - A Pfizer Company **NAME OF FINISHED PRODUCT** Filgrastim **NAME OF ACTIVE INGREDIENT(S)** Granulocyte-colony stimulating factor	**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of study	A Phase III randomised, multicentre, double-blind, therapeutic equivalence study of biosimilar G-CSF (PLIVA/Mayne filgrastim) versus Neupogen® (filgrastim - Amgen) in subjects receiving doxorubicin and docetaxel as combination therapy for breast cancer		
Study centre(s)	Subjects were enrolled at 37 investigational sites in 10 countries (UK, Bulgaria, Germany, Hungary, Latvia, Poland, Romania, Russia, Serbia and Czech Republic).		
Publication (reference)	N/A		
Study period	First subject screened: 30 August 2007 First subject randomised: 04 September 2007 Last follow-up assessment: 30 September 2008	Clinical phase	III
Objectives	Primary: To demonstrate the therapeutic equivalence of PLIVA/Mayne filgrastim and Neupogen®. Secondary: • To compare the efficacy, safety and tolerability of PLIVA/Mayne filgrastim and Neupogen®. • To compare the immunogenicity of PLIVA/Mayne filgrastim and Neupogen®.		
Methodology	A randomised, multicentre, double-blind, therapeutic equivalence study. Subjects were randomised (2:1) to one of two treatment arms (5 µg/kg PLIVA/Mayne filgrastim or 5 µg/kg Neupogen®). Subjects were stratified according to country and treatment setting: neoadjuvant/adjuvant versus metastatic. Up to 6 cycles of PLIVA/Mayne filgrastim or Neupogen® were administered at three-weekly intervals. Subjects were followed up 28 days after the last dose of PLIVA/Mayne filgrastim or Neupogen®, and at 6 months.		
Number of subjects	Planned: Up to 279 subjects (186 in the 5 µg/kg PLIVA/Mayne filgrastim treatment group, and 93 in the 5 µg/kg Neupogen® treatment group). Studied: 279 subjects were randomised; 184 subjects to PLIVA/Mayne filgrastim and 95 to Neupogen®. Completed: 253 subjects completed the study; 169 randomized to PLIVA/Mayne filgrastim and 84 randomized to Neupogen®.		

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Diagnosis and criteria for inclusion	The main criteria for inclusion were: • Female subjects, aged ≥ 18 and ≤ 70 years. • Subjects with invasive breast cancer appropriate for treatment with doxorubicin and docetaxel combination therapy in the neoadjuvant/adjuvant or first line metastatic treatment setting, who had not previously received treatment with anthracyclines or taxanes. • Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. • Estimated life-expectancy > 6 months. • Adequate bone marrow function as indicated by Hb ≥ 10 g/dL (transfusion permitted); absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; and platelets ≥ 100 x 10^9/L. • Adequate renal and hepatic function as indicated by: 1) creatinine < 1.5 x ULN; 2) total bilirubin within normal reference range (unless elevation is known to be due to Gilbert's disease); and 3) either alkaline phosphatase within normal reference range and both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 x ULN; or alkaline phosphatase < 2.5 x ULN and both AST and ALT < 1.5 x ULN; or c) alkaline phosphatase < 5 x ULN and both AST and ALT within normal reference range. • No previous treatment with G-CSFs.
Test product, dose, mode of administration and batch number(s)	Granulocyte-colony stimulating factor (G-CSF) (PLIVA/Mayne filgrastim) administered at doses of 5 µg/kg via a subcutaneous (sc) injection Batch numbers: 6636017, 6635017 and 6633047
Duration of treatment	Subjects received up to 6 cycles of doxorubicin (60 mg/m^2 bolus injection) in combination with docetaxel (75 mg/m^2 1-hour infusion) supported by PLIVA/Mayne filgrastim or Neupogen®. Subjects did not have to be enrolled with the intention of receiving all 6 cycles (e.g., if the standard care was to treat with fewer cycles). Treatment with Investigational Product (IP), i.e., PLIVA/Mayne filgrastim or Neupogen®, was to be initiated the day after the administration of chemotherapy. In each cycle, 5 µg/kg PLIVA/Mayne filgrastim or 5 µg/kg Neupogen® was to be administered by daily sc injection at approximately the same time each day until: EITHER the documented ANC nadir had passed and ANC was > 3 x 10^9/L, OR for a maximum of 14 days, whichever occurred first. During the study patients could receive a maximum of 84 doses of IP.
Reference therapy, dose, mode of administration and batch number(s)	Neupogen® (filgrastim - Amgen) administered at doses of 5 µg/kg via a sc injection. Batch numbers: N1275AD, N1288AD, 1000643 and 1003779

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Criteria for evaluation	The primary endpoint was duration of severe neutropenia (DSN) (in days) (ANC $< 0.5 \times 10^9$/L) in Cycle 1. Secondary efficacy endpoints were: • DSN (ANC $< 0.5 \times 10^9$/L) in Cycles 2 to 3; • Time to ANC recovery (ANC $> 3 \times 10^9$/L) in Cycles 1 to 3; • Incidence of febrile neutropenia (ANC $< 0.5 \times 10^9$/L and body temperature of $\geq$ 38.5ºC) in Cycles 1 to 3; • Incidence of documented infection in Cycles 1 to 3; • Cumulative dose of PLIVA/Mayne filgrastim or Neupogen®. Secondary safety endpoints were: • Incidence and duration of hospitalisation of subjects with febrile neutropenia, • Incidence of adverse events (AEs), • Changes in safety laboratory parameters, • G-CSF antibody formation.

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Statistical methods	Subject characteristics at the start of the study and treatment efficacy and safety data during the study were summarised. The primary efficacy endpoint of DSN (in days) (ANC < 0.5 x 10^9/L) in Cycle 1 was derived as follows: The time taken in days from the date when the ANC was < 0.5 x 10^9/L (post-first dose of study medication) to the date when the ANC was ≥ 0.5 x 10^9/L in Cycle 1. The primary efficacy analysis was based on the Per Protocol (PP) population and was an equivalence analysis performed by calculating a 2-sided 95% confidence interval for the difference of the adjusted DSN means (i.e. ANOVA least square means) in the two treatment groups. Secondary efficacy analyses were based on both the PP and the ITT populations and included analyses for DSN in Cycles 1 to 3 (ITT Cycle 1, PP & ITT Cycles 2 to 3), the incidence of febrile neutropenia, the incidence of documented infections, and the cumulative dose of G-CSF. The incidence and duration of hospitalization for subjects with febrile neutropenia (ANC <0.5 x 10^9/L and body temperature of ≥38.5°C) were summarised for each cycle and over all cycles by treatment group. AEs and serious adverse events (SAEs) were summarised by the total number of subjects experiencing any event by system organ class and preferred term of each treatment group. Frequency of treatment-emergent AEs was calculated for each body system, by preferred term, by treatment, for number of subjects and percentage reporting the event. The severity of the AEs and the relationship to the IP was summarised for each body system and preferred term by treatment group. Incidence of AEs was summarised by treatment group and CTCAE grade. The CTCAE grades as recorded on the CRF were used. All laboratory values outside the normal range were coded to CTCAE grade, and the maximum grade (within each cycle) observed by a subject for that laboratory parameter was summarised by cycle and treatment group. A further summary of maximum CTCAE grade during the entire study period, showing the number and percentage of subjects at each grade, was also presented by treatment group. These summaries were only produced for laboratory parameters that had a CTCAE classification defined within the NCI CTCAE version 3.0 (August 9, 2006) guideline.

SUMMARY - CONCLUSIONS

SUBJECT DISPOSITION

Of the 184 subjects randomised to PLIVA/Mayne filgrastim, 15 did not complete the study due to withdrawal of consent (n=7), Investigator decision (n=2), AE (n=1), lack of efficacy of chemotherapy regimen (n=4), and 'other'[one subject,maximum cumulative dose of anthracycline was reached] (n=1).

Of the 95 subjects randomised to Neupogen®, 11 did not complete the study due to withdrawal of consent (n=5), Investigator decision (n=1), AE (n=2), lack of efficacy of chemotherapy regimen (n=1), death (n=1) and 'other' [one subject, Sponsor decision] (n=1).

Subjects did not have to complete all 6 cycles of chemotherapy in order to complete the study.

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EXPOSURE TO STUDY MEDICATION

A total of 183 subjects were given PLIVA/Mayne filgrastim (the mean number of injections over Cycles 1-6 was 42.0; range 8 to 64 injections) and 95 subjects were given Neupogen® (the mean number of injections over Cycles 1-6 was 41.9; range 4 to 63 injections).

EFFICACY

- Analysis of the primary efficacy endpoint, DSN in Cycle 1, gave adjusted means (adjusted for treatment setting - neoadjuvant/adjuvant vs metastatic) of 1.85 and 1.47 days for PLIVA/Mayne filgrastim and Neupogen®, respectively, with a difference between the two treatment group means of 0.38 (CI 0.08, 0.68). The CI for the difference of the treatment means lay entirely within the pre-defined range -1 to +1 day. Therefore, equivalence between PLIVA/Mayne filgrastim and Neupogen® has been demonstrated. This conclusion was supported by analysis of the ITT population and the secondary efficacy endpoints, which revealed no marked differences between the two treatment groups.
- Mean DSN in Cycle 1 was 1.6 days (SD 1.20) in the PLIVA/Mayne filgrastim group and 1.3 days (SD 1.08) in the Neupogen® group. Median survival time estimates for DSN in Cycle 1 (95% CI) were 2.0 (1.0, 2.0) and 1.0 (1.0, 2.0) in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively.
- In Cycle 1, 128/165 (77.6%) PLIVA/Mayne filgrastim subjects experienced severe neutropenia compared with 58/85 (68.2%) Neupogen® subjects. In subjects with severe neutropenia, DSN was 1-3 days in the 91.4% of cases in the PLIVA/Mayne filgrastim group and 100% in the Neupogen® group. Ten (7.8%) and one (0.8%) subjects in the PLIVA/Mayne filgrastim group had a DSN of 4 and 5 days, respectively. Three of the 11 subjects with DSN of $\geq$ 4 days in Cycle 1 had febrile neutropenia during that cycle, but the incidence of the clinically relevant associated endpoints of protocol-defined febrile neutropenia and documented infection were similar in the two treatment arms during Cycle 1 and Cycles 1-3 combined. In addition, there was no evidence of a delay in time to ANC recovery in PLIVA/Mayne filgrastim subjects.
- Similar results were seen in Cycle 2 with 48.7% subjects with severe neutropenia in the PLIVA/Mayne filgrastim group and 34.9% in the Neupogen® group. However, in Cycle 3 there was a lower proportion of subjects with severe neutropenia in the PLIVA/Mayne filgrastim group (39%) compared with the Neupogen® group (42.3%). Severe neutropenia lasting $\geq$ 4 days during Cycle 2 was seen in 0.6% of subjects in the PLIVA/Mayne filgrastim group and 2.4% of subjects in the Neupogen® group. During Cycle 3, DSN was $\geq$ 4 days in 1.3% of subjects in the PLIVA/Mayne filgrastim group and 0.0% of subjects in the Neupogen® group.
- In Cycles 1-3 ANC was not always measured daily post-nadir until it had recovered to > 3 x10^9/L, as was required by protocol; therefore, calculation of the time to ANC > 3 x10^9/L was, in some cases, unreliable and in other cases subjects may have been excluded from the PP analysis (depending on the extent of the deviation) following the blinded data review meeting. Despite this limitation, the mean time to ANC recovery in Cycles 1, 2 and 3 were similar in the two treatment groups: In Cycle 1 mean time to ANC recovery was 7.8 days for both treatment groups; in Cycles 2 and 3, the mean time to ANC recovery was 7.4 days and 7.5 days for the PLIVA/Mayne filgrastim group and 7.6 days in both cycles for the Neupogen® group.
- There were few subjects with protocol-defined febrile neutropenia (ANC <0.5 x 10^9/L and body temperature of $\geq$ 38.5^{o}C) with no difference in incidence between the two treatment groups: 2.4% over Cycles 1 to 3 in both treatment groups. Use of prophylactic antibiotics was noted in both treatment groups which may have reduced the overall incidence of febrile neutropenia in this study but use was balanced between the two treatment groups: 9.3% of subjects in the PLIVA/Mayne filgrastim group and 8.4% in the Neupogen® group

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over Cycles 1 – 3.

- The incidence of documented infection was low and was similar between the two treatment groups. The proportion of subjects experiencing one or more infections in Cycles 1-3 was 3.0% in the PLIVA/Mayne filgrastim compared with 3.5% in the Neupogen® group.
- The mean number of injections given to subjects in Cycles 1-3 and Cycles 4-6 were similar between the two treatment groups. Over Cycles 1-6 a mean of 42.4 injections (range 8-64 injections) were administered to PLIVA/Mayne filgrastim subjects compared with 43.0 injections (range 12-63) in the Neupogen® group.
- When the effects on DSN in Cycles 1 – 3 of age (< 50 vs ≥ 50), race (Caucasian and Asian) and delayed chemotherapy (excluding subjects with delay of > 1 week) were examined there were no marked differences in DSN between the sub-categories or between treatment groups.
- The results for the ITT population were similar to the PP population for all primary and secondary efficacy analyses.

SAFETY

- A similar proportion of subjects experienced treatment-emergent AEs in the two treatment groups: 159 (86.9%) and 80 (84.2%) in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively. The proportion of subjects experiencing treatment-related AEs was also similar in both treatment groups: 45 (24.6%) and 22 (23.2%) subjects in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively.
- Few subjects in either treatment group experienced injection site-related AEs (3 [1.6%] subjects on PLIVA/Mayne filgrastim and 3 [3.2%] subjects on Neupogen®) showing both treatments to be well tolerated and provoking no marked immunogenic reaction.
- The majority of subjects in each treatment group experienced only CTCAE Grade 1 or 2 (mild or moderate) AEs during the study. CTCAE Grade 3 or 4 (severe or life-threatening/disabling) AEs were experienced by identical proportions of patients in the two treatment groups: 23 (12.6%) in the PLIVA/Mayne filgrastim group and 12 (12.6%) in the Neupogen® group. One (1.1%) subject died in the Neupogen® group (CTCAE Grade 5).
- Treatment-emergent AEs were most frequently reported in the System Organ Class of Gastrointestinal disorders: 105 (57.4%) and 52 (54.7%) subjects in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively. Treatment-related AEs were most frequently reported in the System Organ Class of Musculoskeletal and connective tissue disorders: 35 (19.1%) and 18 (18.9%) subjects in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively.
- The most common treatment-emergent AE was nausea, seen in 94 (51.4%) and 47 (49.5%) subjects in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively. The most common treatment-related AE was bone pain, seen in 26 (14.2%) and 9 (9.5%) subjects in the PLIVA/Mayne filgrastim and Neupogen® groups, respectively.
- There were higher incidences (≥ 5% difference) of treatment-emergent fatigue (41.0% and 35.8%) and bone pain (26.2% and 16.8%) in the PLIVA/Mayne filgrastim group than in the Neupogen® group, respectively. However, when relationship to treatment was taken into consideration, very few differences in the incidences of treatment-related AEs emerged between the two groups. More subjects experienced treatment-related fatigue in the PLIVA/Mayne filgrastim group (9, 4.9%) than in the Neupogen® group (2, 2.1%), but the numbers with this symptom were too low for reliable attribution to the two treatments in subjects with breast cancer on treatment with chemotherapy. The incidences of treatment-related bone pain appeared to differ (26 [14.2%] in the PLIVA/Mayne filgrastim group and 9 [9.5%] in the Neupogen® group), but this difference largely disappeared when all descriptions/locations of treatment-related skeletal pain (bone pain, back pain, arthralgia, musculoskeletal pain and pain in the extremity) were summed (19.7% for

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PLIVA/Mayne filgrastim and 18.0% for Neupogen®).

- A low proportion of subjects in each group experienced SAEs. Although the proportion of subjects experiencing SAEs was slightly higher in the PLIVA/Mayne filgrastim group than the Neupogen® group (6.6% and 4.2%, respectively) no SAEs were considered related to study treatment. The small difference in SAE incidence appeared to be accounted for by events of neutropenia or infection (5.5% on PLIVA/Mayne filgrastim and 2.1% on Neupogen®) which the investigators considered to be probably or certainly related to chemotherapy.
- The incidence of hospitalisation due to protocol-defined febrile neutropenia (ANC $<0.5 \times 10^9$/L and body temperature $\geq 38.5^{o}$C) was low at 2.1% in the two treatment groups.
- Approximately 2% of subjects in each treatment group withdrew due to AEs; none of the events were considered related to study treatment. One subject in the PLIVA/Mayne filgrastim group withdrew due to febrile neutropenia and one subject in the Neupogen® group withdrew due to appendicitis. One subject in the Neupogen® group died during the study due to unknown causes; the event was considered unrelated to treatment.
- No clinically significant differences between treatment groups were observed for the majority of laboratory parameters. CTCAE Grade 4 neutropenia occurred more frequently in the PLIVA/Mayne filgrastim group than the Neupogen® group in all cycles except Cycle 3. However, the incidence of the clinically relevant associated endpoints of protocol-defined febrile neutropenia and documented infection were similar in the two treatment arms during Cycle 1 and Cycles 1-3 combined. An increase in AST from within to above the normal range was observed in a higher proportion of subjects in the Neupogen® group (15 [9.9%] on PLIVA/Mayne filgrastim group and 11 [15%] subjects on Neupogen®) but this appeared to be an isolated finding which was not observed in any other markers of liver function.
- The incidence of detectable G-CSF antibodies was low 1.64% (3/183) of subjects on PLIVA/Mayne filgrastim and 0% (0/95) of subjects on Neupogen® had one or more samples with borderline positive results in the highly sensitive radioimmunoprecipitation assay (RIP). All of the samples from the three subjects with borderline positive results in the RIP assay were found to be negative when tested in a cell-based neutralising antibody assay. Furthermore, there was no evidence of a negative impact on the pharmacodynamic (ANC) response in these subjects which might suggest a potential anti-GCSF antibody response.
- No clinically significant differences were seen between the treatment groups in vital signs, tympanic temperature, ECG and weight.

CONCLUSION

Analysis of the primary efficacy endpoint, DSN in Cycle 1, showed that the 95% CI for difference of the treatment means lay within the range -1 to +1 day. Therefore, equivalence between PLIVA/Mayne filgrastim and Neupogen® has been demonstrated. This conclusion is supported by analysis of the ITT population and the secondary efficacy endpoints.

PLIVA/Mayne filgrastim and Neupogen® had similar safety profiles which were manageable in the setting of breast cancer treatment. There was no evidence of a clinically relevant anti-GCSF antibody response to PLIVA/Mayne filgrastim or Neupogen during this study.

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