11.2 Phase II/III studies of paclitaxel in combination with cisplatin

The GOG, on the basis of the Phase I data, performed trial GOG 111, the pivotal trial in this application. Following the completion of the GOG 111 study and its presentation at ASCO and subsequent publication, several confirmatory studies have opened; none are complete. Preliminary information from these trials is important, however, in verifying the benefit observed in GOG 111.

The **European-Canadian Study group** performed a "confirmatory" trial of cisplatin and paclitaxel (CP) as first-line therapy of Stage IIB-IV ovarian cancer compared with a control arm of cisplatin-cyclophosphamide (CC). This trial was published in abstract form only (Piccart MJ, Bertelsen K, Stuart G, et al. Proc. Amer. Soc. Clin. Onc. 16: page 352a, abstract 1258, 1997) and included toxicity data alone. The authors updated their data in their oral presentation (Oncology News International 6 [7] Suppl 2: 22, 1997) and copies of the slides, a transcript of the presentation, the statistical report, and the original protocol document were supplied by BMS in this NDA. No primary data have been submitted to or reviewed by FDA. The treatment regimens were cyclophosphamide 750 mg/m^2 IV followed by cisplatin 75 mg/m^2 (PC) or paclitaxel 175 mg/m^2 IV over 3 hours followed by the same dose of cisplatin (PT). The primary objective of the trial was to detect a difference in progression-free survival. Six hundred eighty patients were randomized on study, of which 668 were considered eligible. Reasons for ineligibility included incorrect histology (6), second non-ovarian malignancy (4), incorrect stage of disease (1), and poor medical condition (1). The PT arm contained 338 eligible patients, and the PC arm contained 330 eligible patients. The treatment arms were well-balanced for age, PS, cell type, tumor grade, FIGO stage, residual disease after staging laparotomy, and measurability. Less than 10% of patients were Stage II, a stage of disease excluded from the GOG trial. Two hundred thirty-nine patients, balanced between the two arms, had optimally debulked Stage III disease, a second group excluded from GOG 111. Patients could undergo interval debulking after 3 cycles of chemotherapy; this surgery was performed in 8% (28 patients) of PC patients and 9% (31) of PT patients. Although up to 9 cycles of chemotherapy were allowed, the median number was 6 in each arm. The protocol permitted substitution of carboplatin for cisplatin for toxicity; this option was exercised in 12% (43) of patients on PT and in 9% (30) of patients on PC. Paclitaxel doses were escalated in 233 (70%) of patients on PT. In terms of delivered dose, 17% (58) of PT patients required cisplatin dose reductions and 23% (77) experienced dosing delays. In the PC arm, these figures were 15% (49) and 42% (137) respectively. The delivered dose-intensity (DI; dose per unit time) of cisplatin was 24.4 mg/m^2/week in the PT arm and 22.3 mg/m^2/week in the PC arm ($p<0.001$).

Three hundred patients had measurable disease at baseline and were evaluated for response. The response rate was 57% in the PT arm and 43% in the PC arm ($p=0.02$) for patients who had the required confirmatory evaluation one month later. If the investigators included all patients with a response, with or without confirmation, these figures were 77% and 66% ($p=0.03$). One hundred twenty-five patients underwent a second-look laparotomy (70 PT; 55 PC). The pathologic CR rate was 33/70 or 47% for PT and was 13/55 or 24% for PC. Pathologic response rates for pCR plus microscopic residual disease were 46/70 (66%) and 23/55 (42%) respectively.

At a follow-up time of 20 months for the 675 patients with available data (intent-to-treat, regardless of eligibility), the progression-free survival was 16.6 months for CP patients compared to 12 months for the CC patients (p=0.0001). The risk ratio was 0.66 (95% CI: 0.65-0.80). An analysis adjusted for prognostic factors for ovarian cancer was performed. The factors included age, PS, FIGO stage, histologic subtype, cytology, measurability, and amount of residual disease. The difference in PFS remained significant after adjustment. In order to assess PFS in a group comparable to that included in GOG 111, this endpoint was evaluated in the subset of patients with suboptimally debulked Stage III disease (428 patients). In this subset, PFS was approximately 14 months for PT and 10 months for PC. The values for the optimally debulked patients were 24 months and 18 months respectively.

Paclitaxel-based therapy was associated with a higher incidence of neurotoxicity (14% grade 3-4 neurosensory toxicity on PT; 1% on PC), arthralgia/myalgia (9% grade 3 toxicity on PT; 1% on PC), alopecia (48% grade 3-4 toxicity on PT; 20% PC), and hypersensitivity (5% grade 3-4 toxicity on PT; 2% PC), but less emesis (23% PT; 35% PC). Hematologic toxicity was similar in both arms.

BMS sent a copy of the abstract of this study submitted to the 1998 Proceedings of the ASCO. An updated analysis with a median follow-up of 28 months confirmed the difference in progression-free survival: 131 of 342 patients (38.3%) treated with cisplatin and paclitaxel had progressed, compared to 168 of 337 (49.9%) on the cisplatin/cyclophosphamide arm. At this time point, a significant difference in overall survival was observed. The median survival on PT was 35 months, compared to 25 months on PC (p<0.001).

There are several differences between this study and GOG 111, the pivotal study in this application (Ozols RF, Semin. Oncol. 24[1]Suppl 2: S2-1--S2-9, 1997) that may limit their comparability.

- *First*, patients with Stages IIB through IV disease were entered in the Intergroup trial; only patients with suboptimal stage III-IV were entered on the GOG study.

  The first issue should not significantly influence the results of the studies. Although the Intergroup trial included patients with a better prognosis (IIB and optimally debulked III), they were randomly distributed between the study arms. Thus, a survival difference between the 2 arms should still be apparent if present.

- *Second*, paclitaxel was given at a dose of 175-200 mg/m^2 as a 3-hour infusion in the Intergroup study; the GOG study gave paclitaxel at a dose of 135 mg/m^2 over 24 hours.

  The second issue raises an unresolved question about the relative importance of the dose and/or the infusion duration for paclitaxel. Paclitaxel exhibits non-linear pharmacokinetics with increasing dose, and studies of 135 mg/m^2 in breast cancer patients have reported results that are inferior to those obtained with doses of 175 mg/m^2 or greater. Trials in several different malignancies have shown a trend toward higher response rates with increasing doses, but whether the increased response rate translates into a meaningful clinical benefit for the patient,

particularly with the increased toxicity seen with higher doses, is unknown. The infusion length may affect efficacy, also. Preclinical data suggest that prolonged exposure to paclitaxel results in greater tumor cell death. A comparison of 3- and 24-hour infusions in previously treated ovarian cancer patients showed no difference in response rates, but less toxicity with the 3 hour infusion. However, in untreated patients, the duration of exposure may be important, and current studies are exploring the utility of 96-hour paclitaxel infusions. It is unclear in the untreated ovarian cancer population whether the optimal administration of paclitaxel is achieved by increasing the dose, prolonging its infusion, or using a combination of these factors.

- *Third,* the EORTC study permitted 9 cycles of chemotherapy, compared to 6 in the GOG study.

  Six cycles of chemotherapy has been the standard of care for first-line therapy of ovarian cancer; additional cycles add toxicity, but do not clearly add benefit. The median number of cycles administered was 6, suggesting that few patients received additional treatment.

- *Fourth*, patients treated with CC in the Intergroup trial could receive paclitaxel as salvage therapy; patients treated with CC in the GOG study did not have this option available to them, as paclitaxel was not approved for use as second-line therapy in ovarian cancer.

  With regard to the third point, Ozols noted that patients who failed CC and received paclitaxel may live longer than patients who failed CC and received other salvage drugs. Therefore, a survival difference might not be observed in the European-Canadian study because of improved salvage therapy on the CC arm. Patients in the PC arm were prohibited from receiving paclitaxel until there was objective evidence of progressive disease. Therefore, the large sample size (680 patients) and its well-defined time to progression endpoint (rather than survival) should allow a statistically meaningful comparison of the two arms. However, although paclitaxel was approved as second-line therapy for ovarian cancer, the data do not clearly indicate a survival benefit in this situation. It is unlikely that crossover therapy will change a survival endpoint. This hypothesis is supported by the latest results from the Intergroup study, which demonstrate a survival benefit with initial paclitaxel therapy.

- *Fifth*, second-look laparotomy was not required in the EORTC study, which also permitted interim debulking.

  The 5th difference (requirement for second-look laparotomy) is important in confirming response, but will not affect time to progression or survival endpoints.

The authors concluded that the results of this trial confirmed the results obtained in GOG 111. The higher incidence of neurotoxicity in this trial compared to GOG 111 was ascribed to the 3 hour infusion schedule of paclitaxel, the higher dose of paclitaxel, and an increased number of cycles.

Several ancillary studies were performed in conjunction with the EORTC study. A prospective study of quality of life was conducted in 2 of the 4 cooperative groups involved in this trial (the Gynecological Cancer Cooperative Group [GCCG] of the EORTC and the NCI-C). The GCCG also performed a cost-effectiveness study. All groups evaluated CA-125 as a marker of clinical outcome. Results of these ancillary studies are not available at present.

Other published material from this trial includes a toxicity report from Cavaletti and colleagues (Cavaletti G, Bogliun G, Crespi V, et al. J. Clin. Oncol. 15[1]: 199-206, 1997). This report comprises results of extended neurologic and otologic testing on a subset of patients enrolled in the larger European-Canadian study, the 51 patients entered at the authors' affiliated institution. Forty-six patients consented to additional testing. Baseline neurologic status was similar in both treatment groups. Comparisons between the baseline examination (exam 1) and examination 2 as well as between examinations 1 and 3 and examinations 1 and 4 were performed. Both groups showed statistically significant differences in sensory-neurologic status between the first and third examinations; however, both treatments produced the same degree of sensory impairment. No evidence of motor dysfunction was found in either group. Similarly, both groups showed progressive impairment by audiometry, but there was no significant difference in the degree of impairment induced by the two treatments. Ten of 22 patients (45%) on the PC arm had an objective response to therapy compared to 16/24 (67%) on the PT arm. Because this patient group represents a subset analysis, the efficacy data cannot be considered definitive. However, the detailed safety testing provides important information about the relative toxicity and tolerability of the two regimens.

This large multicenter prospective randomized trial, despite differences in trial design, supports the conclusions of GOG 111. A significant difference in TTP and OS was observed with first-line paclitaxel therapy; these data are comparable to those obtained in GOG 111. Exploratory subset analysis indicates that the benefit is observed in both suboptimally and optimally debulked disease, suggesting clinical utility in patients with Stage IIB through Stage IV disease.

The **GOG 132** study randomized suboptimal Stage III and Stage IV ovarian cancer patients to receive cisplatin 100 mg/m^2 IV every 21 days x 6 versus paclitaxel 200 mg/m^2 over 24 hours every 21 days x 6 versus cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2 over 24 hours every 21 days x 6 (Ozols RF, Semin.Oncol. 22[5] Suppl 12: 61-6, 1995; Ozols RF, Semin.Oncol. 22[6] Suppl 15: 1-6, 1995). Patients were stratified by measurable versus non-measurable disease. Filgrastim was not used prophylactically, but could be added for patients with febrile neutropenia or delayed recovery of neutrophil counts. A second-look laparotomy was required for patients with a clinical complete response after 6 cycles of treatment. The GOG 132 trial was presented in abstract form at the 1997 ASCO meeting. Copies of the slides, transcript, statistical report, and original protocol document were included in the sponsor's application. No primary data have been submitted to or reviewed by FDA. Six hundred forty-eight patients were randomized; 615 were eligible. For cisplatin alone, 209 were randomized, and 200 were evaluable. For

paclitaxel alone, 224 were randomized and 213 were evaluable. For the combination, 215 were randomized and 201 were evaluable. Reasons for ineligibility included wrong primary (17), incorrect disease stage (5), wrong cytology (4), second non-ovarian malignancy (4), improper prior therapy (2), and poor PS (2). Data was analyzed for the eligible patients:

The patient groups were well-balanced for baseline prognostic factors. The median number of cycles given in each arm was 6. However, a greater percentage of patients completed PT therapy (83%) compared to P (69%) or T (71%). Eighteen percent of patients on P discontinued therapy because of toxicity or refusal, compared to 5% on PT and 4% on T. Discontinuation because of progressive disease occurred in 19% of patients treated with taxol alone, compared to 8% on cisplatin and 6% on PT. Discontinuations for other reasons or due to death on study were comparable between the 3 arms.

Clinical response was evaluated in patients with measurable disease (PT). The response rates were 75% for cisplatin alone, 46% for paclitaxel alone, and 72% for the PT combination; the paclitaxel alone arm was statistically significantly inferior to the other two ($p<0.05$), which did not differ significantly from each other.

Pathologic response was evaluated in the 614 eligible patients with available data. The incidence of pathologic CR was 15% (29/200) P, 6% (12/213) T, and 22% (44/201) PT. Response in the P and PT arms was statistically significantly better than in the T arm. The difference between P and PT was not significantly different ($p=0.07$). If residual microscopic disease was included, the rates were 25%, 12%, and 33% respectively. The same statistical relationships exist as for pathologic CR.

The median progression-free survivals were 16.4 months for P, 11.4 months for T, and 14.1 months for PT. At the time of analysis, 524 or 85% of patients had progressed. Treatment with paclitaxel as a single agent was a negative prognostic sign, with a relative risk of 1.39 (95% CI 1.12, 1.71). The times to progression observed with P compared to PT were not significantly different. Cox multivariate analysis demonstrated that the presence of measurable disease, clear cell/mucinous histology, and treatment with paclitaxel alone were significant poor prognostic factors.

Median survivals were 30.2, 26.0, and 26.6 months respectively. At the time of analysis, 408 or 66% of the patients had died. A Cox multivariate analysis for survival identified clear cell/mucinous histology as the only significant negative prognostic factor. There were no significant differences in survival between the 3 arms.

In the analysis of this trial, the sponsor notes that salvage therapy was used frequently and affected TTP and OS. Patients who discontinued therapy due to toxicity or refusal began salvage therapy prior to documentation of progression. Of the 209 patients randomized to P, 54% crossed over to paclitaxel; of the 224 patients randomized to T, 71% crossed over to cisplatin or carboplatin regimens; and of the 215 patients randomized to PT, 24% received subsequent paclitaxel and 39% received additional cisplatin or carboplatin. The authors hypothesize that because patients assigned to paclitaxel generally received cisplatin for salvage and patients assigned to cisplatin generally received paclitaxel for survival, the survival advantage conveyed by the cisplatin/paclitaxel combination was masked.

In terms of toxicity, paclitaxel alone or in combination with cisplatin induced grade 3-4 neutropenia/leukopenia in 97% and 95% of patients respectively, compared with 49% with

cisplatin alone. Anemia (grade 3-4) was more common with cisplatin alone (12%) compared to T (6%) and PT (9%). Thrombocytopenia (grade 3-4) was comparable between the 3 arms, as was grade 3-4 fever. Grade 3-4 gastrointestinal toxicity was more common in the cisplatin arm (33%) than in T (10%) or PT (18%), as was renal toxicity (5%, 1%, 0 respectively). Any grade of neurologic toxicity was observed in 41% of patients treated with P, 32% of those treated with T, and 40% treated with PT. Grade 3-4 neurotoxicity was observed in 12%, 2%, and 5% respectively.

The investigators concluded that cisplatin and cisplatin-paclitaxel had comparable efficacy, but the combination therapy required fewer dose reductions and treatment delays. Both gave results superior to paclitaxel alone. However, they noted that sequential therapies should be further evaluated.

This trial, in contrast to GOG 111 and the Intergroup trial, showed no survival advantage for the combination of paclitaxel and cisplatin over cisplatin alone and demonstrated comparable results between single agent cisplatin and the PT combination. The PFS and OS values for cisplatin alone and for PT in this study are comparable to those observed for the PT arm in GOG 111. This study raises the question of whether paclitaxel adds any efficacy to dose-intense delivery of cisplatin, particularly since single agent paclitaxel produced inferior results for clinical response, pathologic response, and progression-free survival. It should be noted, however, that there was a higher discontinuation rate on the cisplatin alone arm, primarily because of patient refusal or toxicity. Paclitaxel may add efficacy when a lower dose of cisplatin is used and may change the pattern of toxicity, allowing greater compliance with the regimen.

The **ICON3** trial is the largest trial of paclitaxel or cyclophosphamide given as first-line therapy in ovarian cancer; this trial continues to accrue patients. Information about this study was obtained from a Lancet editorial, which described ICON 3 as a large trial comparing paclitaxel plus carboplatin versus "an appropriate platinum control" (Editorial, Lancet 349: 1635, 1997). This trial had accrued 1254 patients at the time of publication, with a target accrual of 2000 patients. The editorial noted that a representative of BMS and the managing director of the UK office of Bristol-Myers Squibb had claimed superiority for the paclitaxel arm and recommended early closure of the study. An independent data monitoring committee stated in an open meeting on June 2 that the outcome and toxicity data did not mandate early closure, and that the size of this trial made its completion critical to fully evaluating the efficacy of the paclitaxel-cisplatin combination. The committee made a strong recommendation for continuing the trial. A recent publication by Harper (Semin.Oncol. 24[5] Suppl 15: S15-23--S15-25, 1997) and the submission of the protocol document by BMS at the request of the FDA reviewers in the NDA provided additional information on the study design. Previously untreated ovarian cancer patients are randomized to receive paclitaxel 175 mg/m^2 IV over 3 hours in combination with carboplatin given at a dose calculated to provide an AUC of 5 or 6 (depending on the method used to derive creatinine clearance: measured or calculated), or to receive either carboplatin alone or CAP, at the discretion of the investigator. Carboplatin alone is given at a dose calculated to produce an AUC of 5 or 6. The doses in the CAP regimen are cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and cisplatin 50 mg/m^2. All regimens are repeated every 3 weeks for a total of 6 cycles. Patients are randomized 2:1 in favor of the control arm. The primary endpoint of this trial is mortality; secondary endpoints include response, progression-free interval, quality

of life, and health economics. An interim analysis is planned for "mid-1997." This trial to date has accrued almost twice as many patients as the EORTC-Canada study and 3 times as many women entered on GOG 111; when accrual is complete, it will contain 3 times as many patients as the EORTC-Canada study and 5 times as many patients as the GOG study. Review of these results will be important in determining the value of paclitaxel as first-line therapy. Although the trial has not been analyzed, the FDA has requested results of interim analyses if available during the course of the NDA review.

The other GOG trial relevant to this NDA is **GOG 114** (SWOG 9227/ECOG G0114), in which optimally debulked Stage III ovarian cancer patients were randomized to receive cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2 over 24 hours every 21 days for 6 cycles versus carboplatin dosed to produce an AUC of 9 for 2 cycles followed by intraperitoneal cisplatin at a dose of 100 mg/m^2 plus paclitaxel 135 mg/m^2 IV over 24 hours every 21 days for 6 cycles (Ozols RF, Semin.Oncol. 22[3] suppl 6: 78-83, 1995; Alberts DS, Semin.Oncol. 22[5]Suppl 12: 88-90, 1995). This trial originally had a third arm of intravenous cisplatin/cyclophosphamide, but this arm was closed when the pivotal study of this application was reported to show superior survival for the cisplatin/paclitaxel arm. No results are available to date. Because of the early closure of arm 3, no confirmatory data of the results of GOG 111 will be forthcoming.

Waltzman and colleagues conducted a retrospective analysis of ovarian cancer patients treated at **Memorial Sloan-Kettering Cancer Center** with platinum and paclitaxel as first-line therapy (Waltzman R, Phatak N, Venkatraman E, et al. Proc. ASCO 16: 381a, abstract 1358, 1997). One hundred twenty-two patients were identified; 78 received paclitaxel at a dose of 135 mg/m^2 over 24 hours followed by cisplatin 75 mg/m^2, and 44 received paclitaxel 175 mg/m^2 over 3 hours with carboplatin 300-650 mg/m^2. In the advanced stage group (48 patients), the pathologic CR rate was 33%. Advanced stage suboptimal ovarian cancer patients in this series had a median survival of approximately 2 years. These results are similar to those reported in the pivotal trial. This group also separately reported the toxicity for these patients (Waltzman R, Phatak N, Shapiro F, et al. Proc. ASCO 16: 382a, abstract 1359, 1997). The patients who received carboplatin were older (median age of 66 compared to 55 in the cisplatin group) and had a higher chronic disease score. The hospitalization rate was similar in both groups (9% and 8%); one patient treated with carboplatin died during treatment. Because older patients with comorbid conditions were preferentially treated with carboplatin, this retrospective study does not provide an unbiased account of relative toxicity and gives uncontrolled response data.

11.3 Phase I trials of paclitaxel in combination with carboplatin

Because the results of the GOG 111 study have been widely disseminated, paclitaxel and cisplatin are now considered as "standard" therapy for untreated advanced-stage ovarian cancer in the United States and by some groups in Europe. All current GOG studies use paclitaxel-platinum control arms and explore the relative contributions of cisplatin and carboplatin, the optimal infusion duration of paclitaxel (24 compared with 96 hours), and the role of interim debulking surgery during primary chemotherapy. The following publications discuss the paclitaxel-carboplatin combinations; carboplatin was substituted for cisplatin in the CP combination in order to reduce toxicity.

Investigators from the **European Cancer Center** conducted a Phase I trial of paclitaxel and carboplatin in women with stage III (>3 cm) or stage IV ovarian cancer who had not received prior chemotherapy or radiotherapy (Semin.Oncol. 21[5], suppl 8: 34-38, 1994; follow-up reports by ten Bokkel Huinick et al, Semin.Oncol. 22[3] Suppl 6: 97-100, 1995; Semin. Oncol. 24[1] Suppl 2: S2-31--S2-33, 1997). The starting doses were 125 mg/m^2 of paclitaxel as a 3-hour infusion followed by 300 mg/m^2 carboplatin, repeated every 4 weeks. Paclitaxel doses were escalated by 25 mg/m^2 increments alternating with carboplatin dose increments of 50 mg/m^2 (an increase of 100 mg/m^2 was permitted for the first escalation). The study was performed without the use of colony stimulating factors; these factors could be added when dose-limiting toxicity (DLT) for neutropenia was reached. Once the MTD for the 4-week cycle was established, the MTD for a 21-day cycle was determined, starting 2 dose levels below the MTD for the 28 day cycle. Forty-six patients were entered on study with a PS of 0-2. The MTD for the 28 day cycle was 600 mg/m^2 of carboplatin with 225 mg/m^2 of paclitaxel; the corresponding doses for the 21 day cycle were 550 mg/m^2 and 200 mg/m^2 respectively. The primary toxicity was neutropenia which did not exceed 7 days (the threshold for adding G-CSF); thus, the above doses can be administered without the use of growth factors. Non-hematologic toxicity included grade 3 bone pain and myalgia, grade 2 peripheral neuropathy and hypersensitivity, and grade 2 nausea and vomiting. Twenty of 46 patients achieved a clinical complete response (CR) (43.5%), 9 documented pathologically by second-look laparotomy, and 13 of 46 achieved a partial response (PR) (28.3%) for a response rate of 71.8%. Pharmacokinetic studies were performed on these patients (van Warmerdam LJC, Huizing MT, Giaccone G, et al. Semin. Oncol. 24 [1] Suppl 2: S2-97--S2-104, 1997). The carboplatin AUC was not altered by increasing doses of paclitaxel. Although there was no apparent pharmacokinetic interaction between the two drugs, paclitaxel diminished the thrombocytopenia usually seen with carboplatin by an unknown mechanism.

The **GOG 9202** study was a phase I dose-escalation trial of paclitaxel followed by carboplatin, designed to determine the MTD of this combination with and without G-CSF (Ozols RF, Ann.Oncol. 5[suppl 6]: S39-S43, 1994; Ozols RF, Semin.Oncol. 22[3] suppl 6: 78-83, 1995; Ozols RF, Semin.Oncol. 22[5] Suppl 12: 61-6, 1995; Bookman MA et al, Proc.Am.Soc.Clin.Onc 14: 271, 1995 abstract; Bookman MA et al, J. Clin. Oncol. 14: 1895-1902, 1996). Thirty-five previously untreated patients with suboptimal Stage III-IV ovarian cancer were entered. In part 1 of the trial, patients received a fixed dose of paclitaxel at 135 mg/m^2 over 24 hours with escalating doses of carboplatin. Once the MTD was reached, the same combination was given with G-CSF. In part 2 of the trial, the MTD of carboplatin was used with subsequent dose-escalation of paclitaxel to 175 mg/m^2 over 24 hours with G-CSF; if tolerated, paclitaxel was further escalated to 225 mg/m^2. In part 3, the MTD of carboplatin was administered with paclitaxel at 175 mg/m^2 now given over 3 hours without G-CSF; if tolerated, paclitaxel was escalated to 225 mg/m^2 over 3 hours without G-CSF. In this study, carboplatin was dosed by the Calvert formula; the target AUC for dose level one was 5, with subsequent escalations to 7.5 and 10. Cycles were repeated every 21 days.

The results of part 1 indicated that an AUC of 10 for carboplatin produced dose-limiting hematologic toxicity. Carboplatin dosed to a target AUC of 7.5 with a fixed-dose of paclitaxel at 135 mg/m^2 was tolerated with G-CSF; carboplatin dosed to a target AUC of 5 was tolerated without G-CSF. In part 2, both paclitaxel doses (175 and 225 mg/m^2) could be given with

carboplatin at an AUC of 7.5 with G-CSF support. However, even with growth factor support, dose delays and reductions due to neutropenia were common at a paclitaxel dose of 225 mg/m^2 and occurred during the first cycle. At a dose of 175 mg/m^2, no treatment delays or dose reductions were needed during cycles 1-3, but occurred during cycles 4-6. Thus, G-CSF did not allow escalation of paclitaxel when given as a 24 hour infusion. In part 3, the ability of G-CSF to permit dose-escalation of paclitaxel as a 3 hour infusion was examined. At 225 mg/m^2 of paclitaxel, the use of G-CSF allowed full doses only for cycle 1. All subsequent cycles required dose reductions or delays. The MTD of paclitaxel over 3 hours without G-CSF was defined as 175 mg/m^2 , but G-CSF was needed in cycles 4-6 to avoid dose reductions. The predominant toxicity observed in all parts of the trial was hematologic toxicity. Non-hematologic toxicity was uncommon; neuropathy did not exceed grade 2. In terms of efficacy, 24 patients had measurable disease. There were 16 CR and 2 PR (clinical assessments) for a response rate of 75%. Second-look laparotomy was not required in this trial; 9 patients underwent the procedure, two of whom had no pathologic evidence of disease. This trial examined various schedules of paclitaxel administration, with and without G-CSF, and defined the MTDs for paclitaxel and carboplatin.

Bookman and colleagues reported the results of **GOG 9406**, in which patients with suboptimal stage III-IV disease were treated with a 96 hour infusion of paclitaxel at a dose of 120 mg/m^2 followed by carboplatin given at a dose calculated to produce an AUC of 7.5 (Bookman MA et al, J. Clin. Oncol. 14: 1895-1902, 1996). The use of colony stimulating factors was prohibited on the first cycle, but could be used subsequently if needed. Four patients were treated on this protocol. Two of the 4 patients were admitted for febrile neutropenia on the first cycle. During the second cycle, which was given on day 21, the patients met the hematologic criteria for re-treatment, but subsequently experienced rapid hematologic nadirs. The cycle length was changed to 28 days with improvement in the white blood cell counts. Non-hematologic toxicity did not occur in these patients. No efficacy data is available.

Calvert and colleagues at **Newcastle Hospital** performed a Phase I trial of paclitaxel and carboplatin (Semin.Oncol 22[5] Suppl 12: 91-98, 1995). Carboplatin was administered at a dose calculated to produce an AUC of 7; the dose levels of paclitaxel were 150, 175, 200, and 225 mg/m^2 given as a 3 hour infusion prior to carboplatin. Cycles were repeated every 4 weeks. A classic modified Fibonacci scheme was used. At the time of publication, 11 patients had completed 3 dose levels without reaching dose-limiting toxicity. Short-term neutropenia without fever was the predominant toxicity. Non-hematologic toxicities included myalgia and paresthesia. No efficacy data was reported.

Investigators at the **Institute Gustave Roussy** performed a Phase I trial of escalating doses of paclitaxel as a 3 hour infusion in combination with a fixed dose of carboplatin 400 mg/m^2 IV (Lhomme C, Kerbrat P, Lejeune C, et al. Symposium: Emerging Concepts in Clinical Oncology. Paris, October 1995, pps. 25-6 [abstract]). Two parallel groups were assessed: the first group was treated every 21 days and the second group, every 28 days. The starting dose of paclitaxel was 110 mg/m^2, with subsequent elevations to 135, 150, 175, 200, 225, 250, and 275 mg/m^2 in Group 2; the doses were 175, 200, and 225 mg/m^2 in Group 1. Twenty-seven patients had been entered into group 2 and 23 in group 1. Febrile neutropenia was uncommon (2 episodes in group 2 and 1 in group 1). Neutropenia was common but of short duration. Few dose reductions or delays were necessary. Colony stimulating factors were not administered.

Neuropathy, constipation (grade 3, paclitaxel 110 mg/m^2 q 4 wk), and diarrhea (grade 3, paclitaxel 250 mg/m^2 q 4 wk) were the observed non-hematologic toxicities. The neuropathy occurred as grade 2 in 4 patients (paclitaxel 200 mg/m^2 q 4 weeks, 1 patient; paclitaxel 225 mg/m^2 q 3 weeks, 3 patients) and as grade 3 in 1 patient (paclitaxel 225 mg/m^2 q 3 weeks). The MTD had not been reached at 275 mg/m^2 in group 2 nor at 225 mg/m^2 in group 1.

Zamagni and colleagues at **S. Orsola-Malpighi** Hospital began a Phase I trial of 3 hour paclitaxel with carboplatin in chemotherapy-naive women with Stage III-IV ovarian cancer (Zamagni C, Martoni A, Cacciari N, and Pannuti F. Eur. J. Cancer 31A [Suppl 5]: S109, 1995, abstract 510). The starting doses were paclitaxel 125 mg/m^2 and carboplatin 250 mg/m^2, with escalation of paclitaxel by 25 mg/m^2 alternating with escalation of carboplatin by 50 mg/m^2. At the time of publication, 9 patients had been entered and the third dose level reached without identifying the MTD. Toxicities included alopecia, nausea, vomiting, and neutropenia with no grade 4 episodes.

Bolis **(University of Milan)** published the results of a pilot study in 27 patients with Stage III or IV ovarian cancer who were treated with paclitaxel as a 3 hour infusion followed by carboplatin at 300 mg/m^2(Bolis G, Semin.Oncol. 22[6] Suppl 14: 32-4, 1995; Semin. Oncol. 24[1] Suppl 2: S2-23--S2-25, 1997). The starting dose of paclitaxel was 150 mg/m^2 with subsequent escalations in 25 mg/m^2 increments. Therapy was repeated every 28 days for a total of 6 cycles. Second-look laparotomy was used to verify response. The MTD as prospectively defined in the protocol had not been reached at a dose-level of 250 mg/m^2 of paclitaxel. However, at this dose level, 65% of patients required a dose reduction of paclitaxel because of grade 2 neurotoxicity. Other adverse events included hematologic toxicity that did not require hospitalization or the use of colony-stimulating factors, myalgias, mild cardiac toxicity, and hypersensitivity reactions. Twenty-one patients were evaluable for response. Fourteen complete responses (67%) and 3 partial responses (14%) were confirmed pathologically for an overall response rate of 81%.

Meerpohl and colleagues treated ovarian cancer patients with Stages II through IV with paclitaxel given as a 3 hour infusion at a starting dose of 135 mg/m^2 followed by carboplatin dosed to produce an AUC of 5 (Semin.Oncol. 22[6] Suppl 15: 7-12, 1995; Semin. Oncol. 24[1] Suppl 2: S2-17--S2-22, 1997). Cycles were repeated every 21 days for a maximum of 6 cycles. Paclitaxel was escalated first in 25 mg/m^2 increments to a dose of 210 mg/m^2; at dose levels 5 and 6, paclitaxel was reduced to 185 mg/m^2 and carboplatin was given at an AUC of 6, then 7.5. Thirty patients were entered on the trial. The maximum tolerated doses were paclitaxel 185 mg/m^2 and carboplatin dosed to produce an AUC 6. Dose-limiting toxicity was neutropenia. Peripheral neuropathy was found in 17 of 23 patients evaluable for this toxicity; it was grade 1 or 2 with the exception of one case of grade 4 neurotoxicity at dose level 5. Fourteen patients were evaluable for response, with a 57% response rate.

Siddiqui and colleagues performed a Phase I dose-escalation study of paclitaxel and carboplatin in 12 patients with untreated Stage IIb to IV ovarian cancer (Br.J.Cancer 75[2]: 287-94, 1997). Paclitaxel was administered at a starting dose of 150 mg/m^2 over 3 hours followed by carboplatin at a fixed dose of an AUC of 7. Paclitaxel was escalated by 25 mg/m^2. Pharmacokinetics were performed on 9 of these patients. Hematologic toxicity was common, but did not require hospitalization or the administration of colony stimulating factors. The most

common non-hematologic toxicity was peripheral neuropathy. Responses were reported in 8 of 9 patients who had elevated pre-treatment CA-125 levels (normalization of tumor marker). Six patients had pre-treatment CT scans with measurable disease; 5 of these 6 patients had a radiographic CR and the 6th had a laparoscopically documented CR. No MTD was reported.

The **Hellenic Cooperative Oncology Group** randomized 90 women with previously untreated Stage IIC-IV ovarian cancer to receive paclitaxel 175 mg/m^2 as a 3 hour infusion in combination with either carboplatin administered to produce an AUC of 7 or carboplatin administered to produce an AUC of 7 alternating with cisplatin 75 mg/m^2 (Skarlos DV, Aravantinos G, Kosmidis P, et al. Semin. Oncol. 24 [5] Suppl 15: S15-57--S15-61, 1997). In the alternating platinum regimen, carboplatin was given on cycles 1, 3, and 5; cisplatin was given on cycles 2, 4, and 6. Therapy was repeated every 3 weeks for a total of 6 cycles. Sixty-one patients had measurable or evaluable disease; among these women, a 52% CR rate was observed for carboplatin alone compared to a 39% CR rate for the alternating schedule. The partial response rates were 30% and 18% respectively, for overall responses of 82% and 57%. However, to date there is no significant difference in time to progression or survival between the two groups. No significant differences in toxicity have been observed between the two groups.

Markman and colleagues published a retrospective review of the Cleveland Clinic experience with this two-drug combination (Markman M, Kennedy A, Webster K, et al. Semin. Oncol. 24 [5] Suppl 15: S15-26--S-15-29, 1997). Ninety-two patients (80 ovarian cancer patients and 12 patients with other gynecologic malignancies) received carboplatin designed to produce AUCs of 4 (25 patients), 5 (46 patients), 6 (13 patients), or 7.5 (8 patients); they also received paclitaxel at either 135 mg/m^2 (26 patients) or 175 mg/m^2 (66 patients) as a 3 hour intravenous infusion. The regimen was generally well-tolerated. The common adverse events included alopecia (nearly all patients), hypersensitivity reactions (13% of patients with paclitaxel, 3% of patients with carboplatin), peripheral neuropathy (14%), and bone marrow suppression (21% with grade 3-4 neutropenia; 9% with grades 2-4 thrombocytopenia). Sixty-two of the 80 ovarian cancer patients had elevated CA-125 levels; 54 patients had at least a 50% drop in the CA-125 from baseline, and 46 patients had a greater than 90% decrease.

These Phase I trials have defined the MTD of carboplatin in combination with paclitaxel in a variety of schedules, with and without the use of colony stimulating factors. These trials have provided information on the spectrum of toxicities observed with these schedules, but do not provide efficacy data.

11.4 Phase II/III trials of paclitaxel in combination with carboplatin

Adams and colleagues at **Velindre** Hospital enrolled 22 women with untreated advanced ovarian cancer with paclitaxel 175 mg/m^2 over 3 hours on day 1 followed by carboplatin given at a dose calculated to produce an AUC of 7 mg/ml/min on day 21 (Adams M, Mort D, Coleman R, et al. Eur. J. Cancer 31A [Suppl. 5]: S106, 1995, abstract 496). A total of 5 cycles (cycle=49 days) was given. Toxicities associated with paclitaxel were myalgia in 60% of patients, arthralgia 40%, paresthesias 25%, nausea and vomiting 21%, neutropenia 81% (32% grade 3 and 15% grade 4), and alopecia. Toxicities associated with carboplatin included nausea and vomiting in 66% of patients, neutropenia in 81% (28% grade 3 and 15% grade 4), and thrombocytopenia in

72% (grade 3 23%, grade 4 8%). The complete response rate was 36% and the partial response rate was 36% for an overall response rate of 72%. At 18 months, the observed survival is 74%. Although this regimen was well-tolerated, the sequential nature of the therapy does not permit comparison to other trial results.

Two studies have compared the relative efficacies of carboplatin and cisplatin in combination with paclitaxel. A randomized Phase III study of paclitaxel-cisplatin versus paclitaxel-carboplatin in untreated Stage IIB-IV ovarian cancer patients was conducted by **Neijt** and colleagues (Neijt JP and Lund B, Semin.Oncol. 23 [6] Suppl 15: 2-4, 1996; Neijt JP, Hansen M, Hansen SW, et al. Proc. ASCO 16: 352a, abstract 1259, 1997; Neijt JP, Engelholm SA, Witteveen PO, et al. Semin. Oncol. 24 [5] Suppl 15: S15-36--S15-39, 1997). This study was conducted as a cooperative trial by Dutch, Danish, and Swiss academic centers. Copies of the original protocol, the ASCO abstract, transcript, and slides were provided by the sponsor in the NDA. Two hundred eleven patients were randomized to receive paclitaxel 175 mg/m^2 over 3 hours followed by either cisplatin 75 mg/m^2 or carboplatin calculated to produce an AUC of 5, given every 21 days for 6 cycles. Patients with stable disease received 2 additional cycles of chemotherapy; patients with a partial response were to continue therapy until progression or toxicity, and patients with a complete response were to receive 3 additional cycles of therapy. Interval cytoreduction and second-look laparotomy were permitted but not required. An interim analysis was performed in 182 patients (97 PT, 85 T-CBDCA). The patients were well-balanced by pretreatment characteristics. Eleven percent of the patients on each arm had Stage II disease, and 33% of the PT and 35% of the T-CBDCA patients had residual disease less than 1 cm. In both arms, the median number of cycles administered was 6. However, 26% of the patients in the carboplatin arm were able to continue chemotherapy beyond 6 cycles, compared to 13% in the cisplatin-treated patients. Ninety-six patients were evaluable for clinical response. The response rates were 54% for PT and 51% for T-CBDCA. Pathologic response (complete plus residual microscopic) rates were 16% and 19% respectively. These differences were not statistically significantly different. The primary endpoint of this study is time to progression. At the time of analysis, the median follow-up was less than 1 year, with no significant difference between the two arms. Similarly, there were no observed differences in survival or in CA-125 levels as a surrogate for progression between the two arms.

In terms of toxicity, grade 3-4 granulocytopenia occurred in 76% of the T-CBDCA patients and in 52% of the PT patients (p=0.007). The incidence of fever and infection was low and was comparable in both arms. Emesis (grade 2-3) was more common with PT (64%) than with T-CBDCA (46%) [p=0.03]. The sponsor reports that alopecia was more common with PT as well (100% compared to 94%; p=0.037); however, the reviewer feels this difference is not clinically significant. Peripheral neuropathy of any grade was common (34% compared with 20%; difference not significant); the incidence of grade 3 toxicity was 6% for PT compared with 2% for T-CBDCA. Patients on PT developed grade 2-3 neuropathy in a median of 7 months. compared to 10 months for the carboplatin arm (P=0.001).

The authors concluded that with the available preliminary efficacy data, paclitaxel-carboplatin was comparable to paclitaxel-cisplatin but was associated with less severe neurotoxicity. They also cautioned that this study was not designed as an equivalence trial. Thus, efficacy results will be meaningful only if one regimen is superior to the other. From the

available material for review, it is not clear that there is a difference in the degree of neuropathy associated with the two regimens. The authors reported a difference in the time to development of grade 2-3 neuropathy; a careful review of the primary toxicity data and of the clinical evaluation methods and schedule will be necessary to confirm this statement. This trial will not be sufficient to establish comparability of cisplatin and carboplatin in combination with paclitaxel as first-line therapy of ovarian cancer.

du Bois and colleagues conducted a trial of paclitaxel-cisplatin versus paclitaxel-carboplatin in untreated Stage IIb-IV ovarian cancer patients in the AGO, a cooperative group of German institutions (du Bois A, Nitz U, Schroder W, et al. Proc. ASCO 16: 357a, abstract 1272, 1997; du Bois A, Luck HJ, Meier W, et al. Semin. Oncol. 24 [5] Suppl 15: S15-44--S15-52, 1997). Randomization was stratified by optimal versus suboptimal debulking. The sponsor submitted the original protocol, the ASCO abstract, and a copy of the poster in the NDA. An interim analysis was presented at ASCO. Paclitaxel was given at a dose of 185 mg/m^2 over 3 hours; the cisplatin dose was 185 mg/m^2 and carboplatin was given at a dose calculated to produce an AUC of 6. Cycles were repeated every 3 weeks for 6 cycles. Supportive therapy with G-CSF was permitted after an episode of febrile neutropenia, infection, or prolonged neutropenia as defined in the protocol. Patients were not required to undergo second-look laparotomy. The primary objective of the study is to compare PFS between the two arms. A sample size of 660 patients is planned, and accrual was anticipated to be complete in 10/97. An interim analysis of 550 evaluable patients was performed. Patients with optimal debulking had a higher incidence of PS 0, were more likely to have Stage II disease, and were more likely to have non-measurable disease (50% had no residual disease) than patients with suboptimal debulking. Information on dosing was available for 345 patients (170 PT, 175 T-CBDCA). The dose level of cisplatin was maintained over 6 cycles, while the mean dose of carboplatin decreased from 400 mg/m^2 to 370 mg/m^2. Treatment delays were more common with carboplatin than cisplatin (13% v. 9%).

Efficacy data remains blinded. Overall, there are 54 patients with measurable disease at baseline. Among the patients with measurable disease, 22 patients have had a cCR (41%) and 20 (37%) a PR. Review by the data safety monitoring committee did not identify a reason to stop the study early.

Quality of life data was obtained during this study, and a preliminary report in 192 patients was presented for cycle 3 relative to cycle 1 (92 PT, 100 T-CBDCA). The sponsor reports that the data indicate a slightly better outcome for patients on T-CBDCA. However, the curves differ from each other by less than 4%, a clinically insignificant difference. Data from all patients with extended follow up will be needed to evaluate any differences in quality of life.

Myelosuppression was more common with carboplatin (21% grade 3-4 compared to 7% with PT). However, there was no difference in the incidence of fever or infection. Emesis was more common with PT than with the carboplatin-containing arm (18% versus 5%); constipation was more common with T-CBDCA than with PT (16% and 10% respectively). Other toxicities were comparable. Neurologic toxicity overall was similar in the two arms, but grade 2-3 neurotoxicity had a more rapid onset with PT than with T-CBDCA (cycle 2 versus cycle 3; $p < 0.05$).

The authors concluded that administration of either regimen was feasible and safe; efficacy comparisons will require longer follow up.

This trial was designed to evaluate the relative efficacy of cisplatin and carboplatin in combination with paclitaxel. Its sample size will permit a comparison of the two regimens, unlike the Neijt study. To date, there is no information to support the assertion that carboplatin plus paclitaxel is as effective as cisplatin plus paclitaxel.

12.0 Reviewer Summary of NDA 20-262/S-026

The basis for approval of this supplemental NDA is GOG 111, a prospective randomized trial of cisplatin and paclitaxel versus cisplatin and cyclophosphamide as first-line therapy in patients with suboptimally debulked Stage III and Stage IV ovarian cancer. The PT combination resulted in a significant improvement in TTP and OS that was of both statistical and clinical significance. This difference was observed in the FDA analysis of the data as well. The two analyses are summarized below:

Table 28. FDA and sponsor's efficacy analyses

Efficacy Parameter	BMS Analysis			FDA Analysis		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Median survival	35.5 mo	24.2 mo	0.0002	35.5 mo	24.2 mo	0.0002
Median progression-free survival	16.6 mo	13.0 mo	0.0008	16.8 mo	13.4 mo	0.006
Overall clinical response rate	68/113 (60%)	64/127 (50%)	0.153	70/113 (62%)	61/127 (48%)	0.04

The toxicity profile was consistent with previously documented adverse events of paclitaxel. Despite the observed toxicity, patients on PT were more likely to complete the planned therapy (86% versus 78%) and received more dose-intense therapy, indicating the tolerability of the regimen relative to PC.

It is difficult to understand how PT can produce significant improvements in TTP and OS without significantly affecting response rate. It is likely that the lack of significance is due to the difficulty in assessing response in ovarian cancer patients. A recent publication by Thiesse and colleagues outlined reasons for interobserver variability in response assessment (Thiesse P. Ollivier L. Di Stefano-Louineau D, et al. J. Clin. Oncol. 15: 3507-3514, 1997); many of these points apply to the current trial. The authors listed the following difficulties:

- Measurement of nonmaximal or nonperpendicular diameters
- Intraobserver and interobserver variability
- Technical considerations

- ♦ Timing of IV contrast injection on CT scan
- ♦ Incorrect selection of a CT slice for measurement based on anatomic landmarks, which move with respiration, rather than on the slice with the maximal axial tumor diameters
- ♦ Difficulty of measuring tubular-like lesions
- ♦ Need for precise measuring implements when working with film images

• Errors in target selection
  - ♦ Inappropriate use of cystic or calcified masses as tumor markers
  - ♦ Difficulty of assessing lesions in the presence of malignant effusions
  - ♦ Permanently modified organ morphology due to tumor involvement, regardless of tumor regression
  - ♦ Absence of significant contrast between the tumor and adjacent structures
  - ♦ Enlargement of tiny tumor masses not designated as the followable lesion
  - ♦ New lesions that appeared outside the targeted imaging areas
• Intercurrent illness mistaken for tumor

Ovarian cancer is difficult to assess because of its sheet-like growth pattern and associated effusions; its growth pattern contributes to the diagnosis of ovarian cancer at a late stage in the majority of patients. Its natural history, the need for precise imaging and measurement, and the recent surgery in ovarian cancer patients at the time of baseline assessment confound the evaluation process. Despite these limitations, there are suggestions that PT probably does affect response rate. First, the response rates for PT were consistently although not significantly higher than with PC. Second, a different measuring system by different observers (McGuire and colleagues) yielded clinical response rates of 73% and 60% respectively, a significant difference. Third, the response rates of 57% PT and 43% PC in the EORTC study were comparable to the 60% and 50% results reported for GOG 111 by the sponsor; the GOG 132 study reported a 72% clinical response rate for the PT arm. All of these results are concordant.

Because of the difficulties in reliably and reproducibly measuring response, time to progression and survival have been more commonly used as endpoints in oncology trials. The progression free survival in GOG 111 was 16.6 months for PT and 13.0 months for PC. In the EORTC study, the values were 16.6 months and 12 months respectively. Both the absolute values and the relative difference in PFS are comparable between the two studies. Survival measurements were 35.5 months for PT and 24.2 months for PC in GOG 111, comparable to the 35 months and 25 months observed in the EORTC study. These results are summarized in the following table:

Table 29. Results of GOG 111 and the EORTC Intergroup trial

Efficacy Parameter	GOG 111			EORTC#		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Clinical complete response	40/113 (35%)	32/127 (25%)	0.092	58/149 (39%)	40/151 (26%)	
Clinical partial response	28/113 (25%)	32/127 (25%)		27/149 (18%)	25/151 (17%)	
Overall clinical response	68/113 (60%)	64/127 (50%)	0.153	85/149 57%	65/151 43%	0.01
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196	33/70 (47%)	13/55 (24%)	
Microscopic residual disease	25/196 (13%)	8/214 (4%)				
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001	46/70 (66%)*	23/55 (42%)*	
Median progression free survival	16.6 months	13.0 months	0.0008	16.6 months	12 months	0.0001
Median survival	35.5 months	24.2 months	0.0002	35 months	25 months	0.001

* Included complete response plus "macroscopic CR"

Trial results from the literature only; primary data not submitted for review

These two trials provide independent confirmation of the efficacy of paclitaxel and cisplatin as first-line therapy of advanced stage ovarian cancer. In the reviewer's opinion, paclitaxel should be approved for this indication.

Signatures:

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

3/25/08

Grant Williams, M.D.
Team Leader

cc: HFD-150/
Division files
sNDA 20-262/S-026
HFD-150/DIV FILES
/S. Honig
/G. Williams
/D. Spillman

Appendix A. Patient Evaluation Flow Sheet (TAXOL protocol CA129-022; Page 10, GOG protocol 111; Page 218, volume 3 of NDA 20-262)

7.0 STUDY PARAMETERS AND SERIAL OBSERVATIONS

7.1 Tests and Observations

Tests and Observations	Prior to Study	Weekly	During Treatment		Post-treatment	
			Prior to each course	Every 2 cycles	6 wks after completion of therapy	Q 3 mo after completion of therapy
History	X		X			X
Physical Exam	X		X			X
Tumor measurements	X		X			
Performance status	X		X			
Hgb/Hct	X	X	X			
WBC	X	X	X			
Differential	X	X	X			
Platelet count	X	X	X			
Creatinine	X		X			X
Bilirubin	X		X			X
SGOT	X		X			X
Alkaline phosphatase	X		X			X
Ca/PO4/Mg	X		X			X
CA-125	1					X
CXR	X		2			
ECG	X		2			
Urinalysis	X		2			
CT abdomen/pelvis	6			4	5	
Audiogram	2		2			
Reassessment laparotomy					3	
Neuro assess	X				7	

1- Optional but if patient registered for extra points with level drawn it must be repeated prior to each course.
2- As clinically indicated.
3- Mandatory in patient entered as non-measurable if CA-125 < 100. Mandatory in all patients who are in clinical complete remission (except Stage IV patients).
4- If CT is used to follow lesion, repeat scans must be done every 2 courses
5- Mandatory if no 2nd look done
6- Postoperative CT scan is mandatory. Follow-up study is indicated if postoperative scan shows measurable disease if no 2nd look.
7- 4-6 weeks after last treatment

NOTE: THE ABOVE GUIDELINES FOR FOLLOW-UP STUDIES, WHILE REQUIRED FOR PROPER MEDICAL CARE OF THE PATIENT, RECOGNIZE THAT CIRCUMSTANCES MAY NECESSITATE MINOR DEVIATIONS FROM TIME TO TIME, WHICH ARE PERMISSIBLE WITHIN THE JUDGEMENT OF THE RESPONSIBLE INVESTIGATOR OR HIS DESIGNATED REPRESENTATIVE.

Appendix B. Oncologic Drugs Advisory Committee questions and vote

sNDA 20-262/SE1-026: Taxol™ (paclitaxel), Bristol-Myers Squibb Pharmaceutical Research Institute

Proposed Indication: First-line or second-line therapy for the treatment of advanced carcinoma of the ovary

Study Design:

One multicenter trial, GOG 111 (CA139-022), was submitted for review. This study was a prospective randomized comparison of cyclophosphamide and cisplatin versus paclitaxel and cisplatin as first-line therapy of patients with suboptimal Stage III and Stage IV ovarian cancer. The primary endpoint was progression-free survival; survival was the secondary endpoint; response was a tertiary endpoint. The efficacy findings from the study report and from the FDA analysis are presented below:

Table 1. GOG 111 Efficacy

Efficacy Parameter	BMS Analysis			FDA Analysis		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Median survival	35.5 mo	24.2 mo	0.0002	35.5 mo	24.2 mo	0.0002
Median progression-free survival	16.6 mo	13.0 mo	0.0008	15.7 mo	12.6 mo	0.002
Overall clinical response rate	68/113 (60%)	64/127 (50%)	0.153	70/113 (62%)	61/127 (48%)	0.04

Note: The FDA TTP analysis was updated after ODAC; the review reflects the correct figures for TTP: 16.8 months for PT and 13.4 months for PC

Question 1. Is trial GOG 111 an adequate and well-controlled trial demonstrating the efficacy and safety of paclitaxel in combination with cisplatin in patients with advanced stage ovarian cancer?

Yes - 9 No - 0

Question 2. Should paclitaxel in combination with cisplatin be approved for the first-line treatment of patients with advanced ovarian cancer?

Yes - 9 No - 0

Discussion: The studies and their analyses were all considered to be of very high quality and the clinical response of paclitaxel and cisplatin showed a significantly improved clinical response over the cyclophosphamide and cisplatin control arm.

Appendix C. Labeling Review

Medical Officer Labeling Review

Application:	sNDA 20-262/SE1-026
Sponsor:	Bristol-Myers Squibb Pharmaceutical Research Institute
Drug:	Paclitaxel
Proposed Indication:	Paclitaxel in combination with cisplatin for first-line therapy of advanced ovarian cancer
Letter Date:	10/7/98
Review Date:	2/26/98

As this application is an efficacy supplement, most of the label has been reviewed in the past. A recent efficacy supplement prompted re-review of the label. This review will address revisions made by the sponsor in the current application. These revisions are noted in volume 1, pages 23-41. An amendment was submitted 2/19/98 with further revisions. The following page numbers refer to the label pages in the amendment:

Page 1: Dianne Spillman, Project Manager, noted a change in wording that now reads
She will chcek the accuracy of this statement with the PharmTox reviewers.

Page 3: Dianne Spillman noted a discrepancy in the spelling of She will check the correct spelling with the PharmTox reviewers.

Page 3:

The sponsor's proposed revision is as follows:

The biopharmaceutical reviewer, Safaa S. Ibrahim, Ph.D., states that this revision should be deleted (review dated 2/3/98), as no data has been submitted for review. The statement should remain the same as the original statement in the current package insert:

Reviewer Note:

This comment was sent to the sponsor with the biopharmaceutical review. In a facsimile dated 3/10/98, the sponsor agreed to retain the original statement.

Page 4:

The sponsor's efficacy table is as follows:

Efficacy in the Phase 3 First-line Ovarian Carcinoma Study

The table should be corrected as follows; reviewer revisions in bold italics:

Efficacy in the Phase 3 First-line Ovarian Carcinoma Study

These revisions are based on the reviewer's analysis of clinical response. The sponsor was informed of these differences in a facsimile dated 2/6/99. The sponsor replied on 2/25/98; review of these responses is incorporated into the above revisions.

The pathologic response rate includes a combination of complete pathologic response (pCR) and microscopic residual disease. The pathologic response rate was significantly better on the paclitaxel-cisplatin arm, but there was no significant difference in pathologic complete response rate between the two arms. As the pCR has been associated with an improved outcome in ovarian cancer patients. it is important to include this parameter in this table.

We recommend that the sponsor add p-values to this table, which are more meaningful to clinicians than confidence intervals. The confidence intervals can be deleted if the sponsor chooses to save space.

Page 5: Adverse events table

A. Corrections to the stated rates

The rate of infections should be

cyclophosphamide/cisplatin, rather than respectively.

The rate of all hypersensitivity reactions on taxol/cisplatin should be

The rate of any symptoms from peripheral neuropathy for taxol/cisplatin should read

These revisions are based on a MS Access query of the submitted database.

B. Additions

Page 12:

The sponsor's proposed revision is as follows:

This line should read:

Page 18: The sponsor's proposed revision is

The revision should read

Page 19: The sponsor added a sentence about the incidence of Grade IV neutropenia in ovarian cancer patients treated with PT. Additional information about febrile neutropenia should be inserted.

Page 21: The sponsor should add information about the diarrhea seen in GOG 111 to the section.

Page 22: Under , the last sentence states

In GOG 111, 17% of PT patients compared to 10% of PC patients experienced asthenia. The additional information gained from the clinical trial should be discussed instead of conveying the impression that the only available information is from voluntary safety reports.

Page 23:

A. The sponsor deleted

No new data has been submitted that demonstrates the optimal regimen for paclitaxel administration; this sentence should be retained in the labeling, slightly altered as given below.

B.

Ovarian cancer

The sponsor's proposed revision is as follows (sections revised by the reviewer are in bold print):

This section should read as follows:

For previously untreated patients, the submitted trial used Taxol in combination with cisplatin. There is no information on the efficacy of carboplatin in this patient population. Second, this trial used paclitaxel given as a hour infusion. The Division has not reviewed data utilizing ε hour infusion.

For the 120-day Safety Update Review, see 3-25-98 Medical Officer Review .