3.1.5.2 Primary Efficacy Endpoint Analyses

The first interim analysis was conducted by BCIRG after 322 DFS event (data cut-off date: June 30, 2005). Based on the sponsor's summary of DFS using the FEVAL dataset, the results shows that the comparison of each Herceptin treated arm (AC→TH or TCH versus AC→T) appears to have crossed the pre-specified O'Brien Fleming Boundary (nominal α=0.0002) and shows significantly lower risk of DFS in the Herceptin treated arms. The hazard ratios based on the Cox's proportional hazards model was 0.49 (with 95% C.I. = [0.37, 0.64], p-value<0.0001) and 0.61 (with 95% C.I. = [0.47, 0.79], p-value=0.00013) for AC→TH versus AC→T and TCH versus AC→T, respectively.

Table 11 Sponsor's Summary of Disease Free Survival (using FEVAL data) – First Interim analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	147 (13.7%)	77 (7.2%)	98 (9.1%)
Stratified analysis			
Hazard ratio [a]	NA	0.49	0.61
95% CI	NA	(0.37, 0.65)	(0.47, 0.79)
p-value [b]	NA	0.0000005	0.000153

a Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
b Stratified log-rank p-value.

Reviewer's comments:

- *It was noted that the boundary was not calculated based on the protocol specified method (1-sided $\alpha/2$ = 0.0125 for each Herceptin-containing arm vs.* AC→T *arm). If the boundary was calculated based on the protocol specified level, the O'Brien-Fleming boundary would be 0.00002, then the comparison between TCH arm versus* AC→T *arm may not cross the boundary at the first interim analysis.*

To confirm the sponsor's results, the reviewer replicated the BCIRG's analysis (using the June 30, 2005 cutoff date) based on the ITT population. It is noted that the BCIRG's first interim analysis was based on FEVAL population. The re-analysis results are close to those from the sponsor's analyses (shown in the following table).

Table 12 Reviewer's Summary of Disease Free Survival (using ITT data) – First Interim analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	156 (14.5%)	89 (8.3%)	106 (9.9%)
Stratified analysis			
Hazard ratio [a]	NA	0.52	0.62
95% CI	NA	(0.40, 0.67)	(0.49, 0.80)
p-value [b]	NA	< 0.0001	0.0001

a Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
b Stratified log-rank p-value.

Although the BCIRG indicated that the boundary for the comparison between each Herceptin containing arm versus AC→T arm was crossed, BCIRG continued to follow-up the patients and performed the second interim analyses based on 474 DFS events (using November 1, 2006 as the cutoff date). Both Herceptin treated arms continued to show beneficial effect as compared with the AC→T arm. The hazard ratios based on the Cox's proportional hazards model was 0.61 (with 95% C.I. = [0.49, 0.76] and the nominal p-value <0.0001) and 0.67 (with 95% C.I. = [0.54, 0.83] and the nominal p-value=0.0003) for AC→TH versus AC→T and TCH versus AC→T, respectively.

The summary of DFS shows that the most dominant DFS events were the distant relapses and very few deaths contributed to the first event of the disease-free survival (AC→T: 5; AC→TH:5; and TCH:7).

Table 13 Sponsor's Summary of Disease Free Survival – Second Interim Analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
First event [a]	195 (18.2%)	134 (12.5%)	145 (13.5%)
Distant recurrence	141 [a]	89	97
Local/regional recurrence [b]	25	19	26
Second primary cancer	24 [a]	21	15
Death	5	5	7
Stratified analysis			
Hazard ratio [c]	NA	0.61	0.67
95% CI	NA	(0.49, 0.76[e])	(0.54, 0.83)
p-value [d]	NA	< 0.0001	0.0003

a First event modify by the reviewer.
b First event modify by the reviewer. The value is the first event for each patient, either local or regional recurrence.
c Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
d Stratified log-rank p-value.
e The 95% C.I. for the comparison between AC→TH vs. AC→T was revised by the reviewer. The sponsor's original 95% C.I. is [0.49, 0.77].

Reviewer's comments:

- *In the second interim analysis, the comparison between TCH and* AC→T *arms crossed the O'Brien-Fleming boundary even if the boundary would have been calculated based on the 1-sided $\alpha/2 = 0.0125$ level (nominal $\alpha=0.0008$).*
- *Sponsor censored patients who did not have a DFS event at the last contact date or the cutoff date, whichever occurs earlier. The sponsor's last contact date was defined as the last follow-up date and randomization date. In order to define the last follow-up date, the sponsor select the last date from the following dates: last LVEF assessment date, last ECG date, physical examination date, cardiac AE or regular assessment dates, hematology and chemistry assessment dates, vital sign assessment date and last scan date.*

To evaluate the robustness of the treatment effect based on different censoring time calculation, the reviewer performed the time to DFS analysis by censoring the patients who did not have DFS event at the last scan date. If the last scan date is missing, the patients were censored at the last survival follow-up date. If the censoring date is still missing, the last contact date based on the definition similar to that used by the sponsor was used. Based on the revised censoring

scheme, this reviewer obtained very similar results to those shown on the sponsor provided table for the second interim analysis for DFS (i.e. Hazard ratios [95% CI] are 0.61 [0.49, 0.76]) and 0.66[0.53, 0.82] for AC→TH vs. AC→T and TCH vs. AC→T, respectively).

- *Based on the protocol, the TCH arm started the follow-up visit about 1.5 months earlier than the follow-up visit for the AC→TH and AC→T arms. This earlier scheduled visit occurred 6 weeks after the EOC visit in the TCH arm and coincided with the end of the chemotherapy visit for the AC→TH and AC→T arms. During the follow-up visits, the clinical visit time for TCH arm was scheduled consistently 1.5 months earlier than the schedules timing planned for the AC→TH and AC→T arms to ensure equal duration between visits among all three arms. Due to such time staggering, all the subsequent visits after visit 1 during follow-up in TCH arm was 1.5 months later than the previous schedule visit time for the other two arms. To evaluate whether such timing difference may affect the DFS results, a sensitivity analysis was performed by assuming that DFS events (for patients with a DFS event) and the last contact date (for patients without a DFS event) occurred 1.5 months earlier than their actual event time or last contact time for the TCH arm. The results still indicate a significant beneficial effect in favor of the TCH arm (nominal p-value=0.0009, HR=0.70, 95% C.I. = [0.56, 0.87]).*
- *The patient allocation to treatment arms was not a stratified randomization, but an allocation that adjusts on the margin (not for combination of factors) for center, lymph nodal status and hormonal receptor status. A stratified randomization performs for each strata (which is a combination of levels) a random allocation of patients to treatment arms. A stratified analysis first performs individual comparisons within each strata (within each strata patients were randomized to treatment arms) and then integrates these comparisons into a single result. Since patients were not randomized within each strata, a stratified analysis may not be appropriate for the primary analysis. Since an adjusted analysis was sought based on lymph nodal status and hormonal receptor status, a Cox proportional hazards model with treatment indicators as factors and nodal status indicators and an ER/PR status indicator as the covariates was additionally performed. The results of that analysis are a HR = 0.61 (95 % C.I. = [0.49, 0.76]) and HR = 0.67 (95 % C.I. = [0.54, 0.83]) for*

AC→TH vs. AC→T and TCH vs. AC→T, respectively (very close to the sponsor's results for a stratified Cox's model).

In addition an unstratified log rank test was performed. The results indicate a nominal p-value of <0.0001 and 0.0006 for AC→TH vs. AC→T and TCH vs. AC→T, respectively. The corresponding estimates from a Cox model with treatment as a factor (no covariates) are HR =0.63 (95 % C.I. = [0.51, 0.78]) and HR=0.69 (95 % C.I. = [0.56, 0.85]) for AC→TH vs. AC→T and TCH vs. AC→T, respectively.

Sponsor performed several sensitivity analyses for DFS based on a) FEVAL dataset, b) excluding second primary cancer; c) excluding metastasis disease and HER-2 negative or d) non-breast cancer second primary cancer for comparison between AC→TH vs. AC→T and TCH vs. AC→T (see the following two tables). All results appear to be consistent with the primary analysis of DFS. The sponsor's analysis for distant recurrence also shows nominally significant results in favor of AC→TH and TCH arm versus AC→T arm.

Table 14 Sponsor's Sensitivity Analyses for Efficacy Endpoint: *AC→T* versus *AC→TH*

	AC→T	AC→TH	Hazard Ratio (95% CI) [a]	P-value[b]
	(n = 1073)	(n = 1074)		
	Number of events			
DFS event	195	134	0.61 (0.49, 0.76)	< 0.0001
Death (OS event)	80	49	0.58 (0.40, 0.83)	0.0024
DFS event (FEVAL)	192	128	0.60 (0.48, 0.75)	< 0.0001
DFS, excluding second primary cancer	179	117	0.58 (0.46, 0.74)	< 0.0001
DFS, excluding non–breast cancer second primary cancer [c]	180	121	0.60 (0.48, 0.76)	< 0.0001
DFS, excluding metastatic disease or who were HER2-negative	194	134	0.61 (0.49, 0.76)	< 0.0001
Distant recurrence	144	95	0.59 (0.46, 0.77)	< 0.0001

a Relative to the AC→T arm. Estimated using Cox regression stratified by number of positive nodes and hormone receptor status.
b Stratified log-rank p-value
c Revised by the reviewer (see comments below)

Table 15 Sponsor's Sensitivity analyses for Efficacy Endpoint: *TCH* versus *AC→TH*

	AC→T	TCH	Hazard Ratio (95% CI) [a]	P-value[b]
	(n = 1073)	(n = 1075)		
	Number of events			
DFS event	195	145	0.67 (0.54, 0.83)	0.0003
Death (OS event)	80	56	0.66 (0.47, 0.93)	0.0182
DFS event (FEVAL)	192	142	0.67 (0.54, 0.83)	0.0003
DFS, excluding second primary cancer	179	134	0.68 (0.54, 0.85)	0.0006
DFS, excluding non–breast cancer second primary cancer [c]	180	134	0.67 (0.54, 0.84)	0.0006
DFS, excluding metastatic disease or who were HER2-negative	194	144	0.67 (0.54, 0.84)	0.0003
Distant recurrence	144	103	0.65 (0.50, 0.84)	0.0008

DFS = disease-free survival; FEVAL = final evaluation of patients; OS = overall survival.
a Relative to the AC→T arm. Estimated using Cox regression stratified by number of positive nodes and hormone receptor status.
b Stratified log-rank p-value
[c] Revised by the reviewer (see comments below)

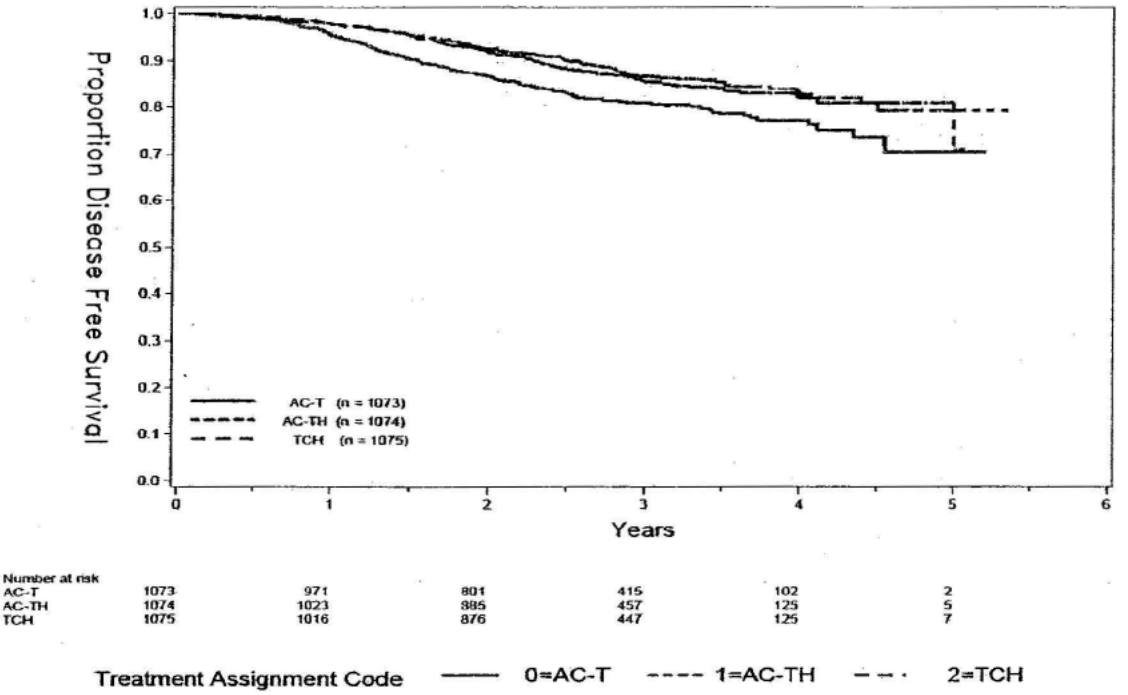
Reviewer's comments:

Per medical officer's request, a re-analysis was performed by removing 2 disease recurrence events (patients 30138, 30364, because their locoregional recurrence was not confirmed) and remove all DFS events due to the secondary primary except 8 patients (patients 32624, 31961, 30852, 31520, 33184, 31815, 31998, 31420 who had another breast primary tumor). The re-analysis results are similar to the sponsor's results that exclude non-breast secondary primary cancer (the nominal p-values are <0.0001 and 0.0006 for AC→TH versus AC→T and TCH versus AC→T, respectively).

Note : Based on the discussion in the office of Oncology meeting (4/7/08), the office decided that the definition of DFS events should exclude non-breast cancer related secondary primary tumor. The results shown in this analysis are close to the sponsor's proposed results including all secondary primary tumor and will be used as the primary analysis results.

The following figure shows this reviewer's calculated Kaplan-Meier estimate plot for disease free survival based on the November 1, 2006 cutoff date.

Figure 1 Kaplan-Meier Estimates for Disease Free Survival (Second Interim Analysis)



Reviewer's comments:

- *A conclusion that adding Herceptin to TC (docetaxel + carboplatin) is beneficial would additionally involve extrapolation (e.g. assuming TC is worse than AC→T). To respond to the agency's request, the sponsor stated in the 2/29/08 submission that anthracycline-based regimens are superior to non-anthracycline-based regimens with respect to DFS and OS (quoted study EBCTCG 2005 from the Early Breast Cancer Trialists' Collaborative Group) in early stage breast cancer with HER2 overexpression. At this time, anthracyclie-based chemotherapy regimens are the standard of care in the treatment of HER2-positive early stage breast cancer. The sponsor also quoted a few breast cancer study results based on metastatic setting:*

  (1) The results of two pilot phase II trials indicate that TCH were active based on objective tumor response rate (ORR) in HER-2 positive breast cancer in metastatic settings (ORR=79% in BCIRG101; ORR=58% in BCIRG102).

  (2) A phase III trial demonstrated that Herceptin+docetaxel arm was more efficacious based on overall response rate, TTP (Time to Progression) and OS as compared with docetaxel alone arm in first line metastatic setting (In

study M77001: ORR=61% vs. 36%; TTP=10.6 months vs. 6.1 months; OS=27.7 months vs. 18.3 months).

(3) The addition of carboplatin to paclitaxel and Herceptin also shows significant improved response rate and TTP as compared with Herceptin+paclitaxel in HER2-overexpressed metastatic breast cancer setting (ORR=52% vs. 36%; TTP=11.9 months vs. 6.8 months; by Robert et al., 2004).

The sponsor indicates that TCH was chosen to offer the possibility of a less cardiotoxic regimen with improved efficacy for the adjuvant treatment of early stage HER2-positive breast cancer. Since most of the sponsor's justification is based on metastatic setting, whether AC→T is an adequate comparator arm will be subject to further justification.

3.1.5.3 Secondary Efficacy Endpoint Analyses

There was no proposal about the alpha allocation for the secondary endpoints in the protocol. Also, there was no pre-planned interim analysis for the overall survival and the significance level for the evaluation of the overall survival was not pre-specified, so the OS results can not be confirmed.

For the first interim analysis, the sponsor stated in the clinical study report that at the time of the first interim analysis (cut off date: June 30, 2005), the number of deaths was not sufficient for statistical evaluation (AC→T: 36 [3.4%]; AC→TH: 20 [1.9%]; and TCH: 28 [2.6%]). Based on this number of deaths (n=84, i.e. from data based on the Final Evaluation-FEVAL process), the sponsor indicates that the OS results did not show nominal significance at the first interim analysis (see the following table).

Table 16 Sponsor's Summary of Overall Survival (using FEVAL data) – First Interim Analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	36 (3.4%)	20 (1.0%)	28 (2.6%)
Stratified analysis			
Hazard ratio [a]	NA	0.52	0.71
95% CI	NA	(0.30, 0.90)	(0.43,1.17)
p-value[b]	NA	0.0172	0.1784

a Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
b Stratified log-rank p-value.

To confirm the results, the reviewer performed analysis of OS based on the ITT population. Based on the submitted data and June 30, 2005 cutoff date, the reviewer obtained n=48 (4.5%) for AC→T, 26 (2.4%) for AC→TH and 31 (2.9%) for TCH arm (a total of 105 deaths). Based on this results from the ITT population, the results of OS still did not seem to cross the boundary if the O'Brien Fleming nominal significance level for evaluation of DFS were used for evaluation of OS (α=0.0002),. This reviewer's summaries of the first interim analysis results for the overall survival are shown in the following table below:

Table 17 Reviewer's Summary of Overall Survival (using ITT data) – First Interim analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	48 (4.5%)	26 (2.4%)	31 (2.9%)
Stratified analysis			
Hazard ratio [a]	NA	0.51	0.61
95% CI	NA	(0.32, 0.82)	(0.39, 0.96)
p-value[b]	NA	0.0043	0.0320

a Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
b Stratified log-rank p-value.

At the time of the second interim analysis, a total of 185 deaths were observed (AC→T: 80; AC→TH: 49; and TCH: 56). The results indicate a favorable results of each Herceptin treated arms versus the AC→T arm. The hazard ratios based on the Cox's

proportional hazards model was 0.58 (with 95% C.I. = [0.40, 0.83], the nominal p-value =0.0024) and 0.66 (with 95% C.I. = [0.47, 0.93], the nominal p-value=0.0182) for AC→TH versus AC→T and TCH versus AC→T, respectively.

Table 18 Sponsor's Summary of Overall Survival (using ITT data) – Second Interim analysis

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event	80 (7.5%)	49 (4.6%)	56 (5.2%)
Stratified analysis			
Hazard ratio [a]	NA	0.58	0.66
95% CI	NA	(0.40, 0.83)	(0.47, 0.93)
p-value[b]	NA	0.0024	0.0182

a Relative to AC→T. Estimated using Cox model stratified by number of positive nodes and hormonal receptor status.
b Stratified log-rank p-value.

Reviewer's comments:

- *The sponsor censored the patients who were still alive at the cutoff date at the last contact date defined similarly to those used for the DFS analysis.*

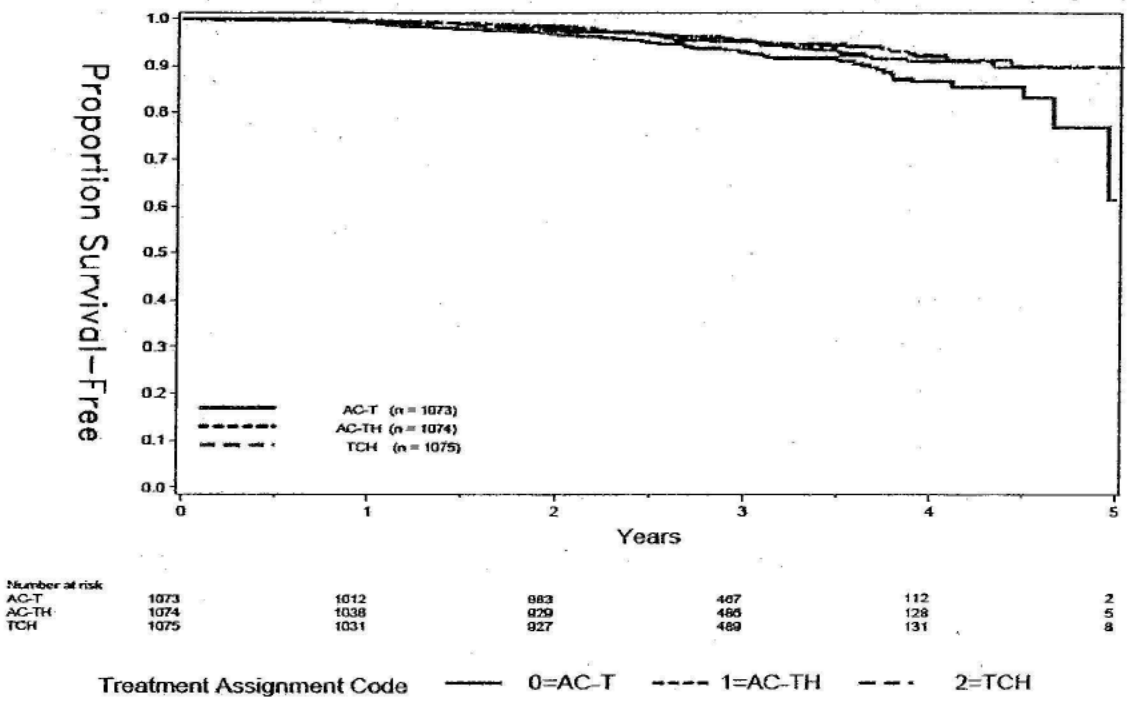
  To evaluate the robustness of the treatment effect based on different censoring mechanism, this reviewer performed an OS analysis by censoring the patients who did not have a DFS event at the last follow up date. If the last follow-up date is missing, the last contact date based on the definition similar to that used for the DFS analysis was used. Based on the revised censoring scheme, the reviewer obtained similar results to those shown on the sponsor provided table for the second interim analysis for OS (i.e. nominal p-values are 0.0026 and 0.0179 for AC→TH vs. AC→T and TCH vs. AC→T, respectively).

- *According to amendment 4 of the protocol, it indicates that if both of the comparisons between each Herceptin containing arm versus AC→T reach statistical significance, then compare the two Herceptin-containing arms at α-level, otherwise stop. Beside these descriptions, the protocol did not allocate alpha for the secondary endpoints and did not plan interim analyses for overall survival. Therefore, the significance level for the comparison of each Herceptin*

containing arm versus AC→T arm for overall survival can not be determined.

The Kaplan-Meier estimates for overall survival calculated by this reviewer are presented in the following figure (based on the November 1, 2006 cutoff date):

Figure 2 Kaplan-Meier estimates for Overall Survival (Second Interim Analysis)



Sponsor summarized the sites of first distant disease recurrence (shown in the following table). The most common sites of distant disease recurrence were the liver for AC→TH and AC→T arms and central nervous system (CNS) for TCH arm.

Table 19 Sponsor's Summary of Sites of Distant Recurrence

Status	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Any distant disease recurrence	144 (13.4%)	95 (8.8%)	103 (9.6%)
Multiple liver lesions	50 (4.7%)	26 (2.4%)	18 (1.7%)
Multiple bone lesions	43 (4.0%)	21 (2.0%)	21 (2.0%)
Multiple lung lesions	35 (3.3%)	24 (2.2%)	24 (2.2%)
Central nervous system	26 (2.4%)	23 (2.1%)	26 (2.4%)
Other	15 (1.4%)	11 (1.0%)	19 (1.8%)
Ipsilateral supraclavicular lymph node	13 (1.2%)	6 (0.6%)	9 (0.8%)
Other distant nodes	13 (1.2%)	14 (1.3%)	12 (1.1%)
Solitary bone lesion	9 (0.8%)	9 (0.8%)	11 (1.0%)
Solitary lung lesion	7 (0.7%)	4 (0.4%)	7 (0.7%)
Solitary liver lesion	4 (0.4%)	8 (0.7%)	5 (0.5%)
Contralateral breast cancer	3 (0.3%)	0 (0.0%)	0 (0.0%)
Skin [a]	1 (0.1%)	1 (0.1%)	1 (0.1%)

[a] Other than specific in local or regional relapse.

3.1.6 Sponsor's Conclusions and Reviewer's Conclusions/Comments

The sponsor's conclusion for efficacy include

- Results of the protocol-specified second efficacy interim analysis demonstrated that Herceptin given as part of either an anthracycline-based (AC→TH) or non-anthracycline-based (TCH) adjuvant treatment regimen results in a clinically meaningful and statistically significant improvement in DFS relative to AC→T irrespective of nodal status. For the primary efficacy endpoint DFS, the risk was reduced by 39% (95% CI : 23%, 51%, p<0.0001) in the AC→TH arm relative to AC→T arm; and the risk was reduced by 33% (95% CI: 17%, 46%, =0.0003) in the TCH arm relative to AC→T arm.
- The DFS benefit in all clinically important subgroups, including subgroup based on age, menopausal status, hormone receptor status, nodal status, tumor size, nuclear grade and surgery or radiation therapy, was consistent with the treatment effect in the overall population.
- There was a clinically meaningful and statistically significant improvement in the duration of OS. The risk of death was reduced by 42% (95% CI: 17%, 60%,

p=0.0024) in the AC→TH arm relative to AC→T arm; and the risk of death was reduced by 34% (95% CI: 7%, 53%, =0.0182) in the TCH arm relative to AC→T arm.

In summary, the sponsor concluded that the magnitude of the clinical benefit observed in this trial favors the use of Herceptin in this population of women, who have a high risk for disease recurrence and subsequent death from metastatic breast cancer, including women with high-risk, node-negative HER-2 positive early breast cancer.

This reviewer concluded that

- The comparisons of AC→TH vs. AC→T and TCH vs. AC→T crossed the O'Brien-Fleming boundary (nominal significance level of 0.0002) at the first interim analysis based on a total of 351 DFS events.
- Based on the second interim analysis results (474 DFS events, using November 1, 2006 as the cutoff date), both Herceptin treated arms continued to show beneficial effect as compared with the AC→T arm. The hazard ratios based on the Cox's proportional hazards model was 0.60 (with 95% C.I. = [0.48, 0.76] and the nominal p-value <0.0001) and 0.67 (with 95% C.I. = [0.54, 0.84] and the nominal p-value=0.0006) for AC→TH versus AC→T and TCH versus AC→T, respectively.
- The beneficial results based on DFS in each Herceptin arm relative to the AC→T arm are consistent in many subgroups, such as Hormonal receptor status, age <65, node + or -, menopause status, KPS=100. However, the beneficial effect was less clear in some subgroups, such as patients age ≥65, KPS<100 and tumor size <2 cm. The beneficial effect of Herceptin treated arms based on DFS also appears to be robust based on various sensitivity analyses.

(b) (4)

3.2 Evaluation of Safety

3.2.1 Introduction

In this section, cardiac endpoints and analyses of cardiac adverse events for study BCIRG 006 will be discussed and the evaluation results for symptomatic and asymptomatic cardiac events will be presented.

3.2.2 Safety Endpoints

Symptomatic Cardiac Adverse Event

All adverse experiences related to cardiac toxicities were graded based on NCI-CTC version 2.0. A clinically significant cardiac event was defined as the occurrence of one or more of the following:

- cardiac death (all non-septic deaths due to study treatment will be reviewed)
- grade 3 or 4 cardiac left ventricular ejection fraction (congestive heart failure)
- grade 3 or 4 arrythmias
- grade 3 or 4 cardiac ischemia / infarction.

These symptomatic grade 3 or 4 cardiac events were confirmed by the Independent Cardiac Review Panel (ICRP).

Congestive heart failure (CHF) was summarized according to three criteria:

- CHF with signs/symptoms in association with an absolute decrease of LVEF > 15% from baseline and below LNL (lower limit of normal)
- CHF with signs/symptoms in association with an absolute decrease of LVEF > 10% from baseline and below LNL
- CHF with signs/symptoms from a clinical standpoint, regardless of LVEF decline.

Asymptomatic LVEF decline

According to the protocol, left ventricular ejection fraction was measured at baseline and 3, 4.5, 6, 9, 18 and 42 months after randomization. This schedule was adjusted for each patient according to the actual number of cycles of chemotherapy received.

A clinically significant asymptomatic decline in LVEF was defined as an absolute reduction in LVEF of 15% or more from baseline and a LVEF value of less than the lower limit of normal.

For the primary analysis of the asymptomatic LVEF decline, any LVEF measured with a technique different than the one used at baseline was excluded.

An additional analysis was performed based on an absolute decline of 10% or more from baseline in LVEF that is also below 50%.

According to the protocol, a new observed asymptomatic cardiac abnormality would be confirmed within 1 month. The confirmation was calculated using a 28 day window for the second evaluation.

Time to the first LVEF decline (defined as the date of randomization to the date of the first LVEF that meets the definition of asymptomatic LVEF decline -- 10% and 15% decline definitions) analyses would be performed. Patients who have not experienced such a decline would be censored at their last LVEF examination.

For time to first clinically significant asymptomatic cardiac event, data from patients not experiencing an event were censored at the earliest date of the last LVEF assessment or data cut-off date (1 November 2006). Data from patients with no post-randomization follow-up were censored on Day 1 (stated in section 9.7.3 Missing data).

3.2.3 Safety Analysis Method

Any patient who started at least one cycle of study chemotherapy or Herceptin® will be included in analysis of safety parameters. Patients are grouped according to the treatment received during the chemotherapy phase of the study.

In the Genentech's SAP, censoring time for time to safety event analyses was specified. For analysis of time to first symptomatic cardiac event, patients not experiencing an event will be censored at the earliest of the following data cutoff date (11/1/06), date of last follow-up assessment, or date of last contact. For time to first clinically significant asymptomatic cardiac event, patients not experiencing an event will be censored at the earliest of the following: the date of last LVEF assessment, data cutoff date (11/1/06), date of last follow-up assessment or date of last contact.

3.2.4 Sponsor's Safety Results and Statistical Reviewer's Findings/Comments

In this section, the chemotherapy and Herceptin exposure, sponsor's results in cardiac events and the reviewer's evaluation of the LVEF assessment will be presented.

3.2.4.1 Chemotherapy, Herceptin Exposure and Results of Cardiac Event and LVEF Assessment

Safety analyses were based on safety population (defined as the group of patients who received at least one dose of study medication).

Chemotherapy Exposure and discontinuation

The sponsor provides summaries of the exposure for doxorubicin, cyclophosphamide and docetaxel as well as platinum salts. There was no noticeable difference between the treatment arms.

A summary of discontinuation of chemotherapy was provided by the sponsor. TCH arm had slightly higher percentage (95.6%) of patients completed protocol specified number of cycles as compared with the percentages in AC→T and AC→TH arms (91.2% and 92.4% for AC→T and AC→TH arms, respectively). The most frequent reason for premature discontinuation of chemotherapy was non-cardiac adverse event (3.9%, 3.7% 2.1% for AC→T, AC→TH and TCH arm, respectively)... Early discontinuation of chemotherapy due to a cardiac adverse event was rare (0.4%, 0.2% and 0.7% for AC→T, AC→TH and TCH arm, respectively).

Herceptin Exposure and discontinuation

In the original protocol, following chemotherapy, patients in both the AC→TH and TCH arms were to receive 2 mg/kg doses of Herceptin weekly for a year from the first Herceptin administration. However, in Amendment 2 (dated 7/30/2001), the frequency of Herceptin administration during the monotherapy was changed from once every week to once every 3 weeks. There were 43 patients who had started Herceptin monotherapy prior to the amendment (19 and 24 for AC→TH and TCH arms, respectively). Of these 43 patients, 32 continued to receive Herceptin monotherapy on a weekly basis, while the remaining 11 patients switched from a once weekly to a once-every-3-week schedule.

A summary of Herceptin exposure is shown in the following table. The median duration (378 days) and the median total dose (107.4 and 109.5 for AC→TH and TCH arms, respectively) of Herceptin appear to be compatible between AC→TH and TCH arms.

Table 20 Sponsor's Summary of Herceptin Exposure – Safety Population

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Duration (days)			
n	NA	1045	1056
Mean (SD)	NA	336.0 (102.6)	360.1 (73.7)
Median	NA	378	378
Range	NA	21–1046	21–685
Total dose (mg/kg)			
n	NA	1045	1056
Mean (SD)	NA	95.3 (30.1)	103.0 (24.1)
Median	NA	107.4	109.5
Range	NA	3.9–157.3	4.0–272.0

Summaries of Herceptin discontinuation were provided by the sponsor. In general, TCH arms appear to have higher percentage of patients completing the Herceptin treatment prior to the end of chemotherapy and during the monotherapy.

Prior to the end of chemotherapy, more patients in TCH arm had completed Herceptin therapy (91% and 95% of patients in AC→TH and TCH arms, respectively). The most

frequent reason for Herceptin discontinuation is Herceptin toxicity (3.3% and 1.2% for AC→TH and TCH arms, respectively).

There are more patients discontinued Herceptin during monotherapy than that prior to the end of chemotherapy. During the monotherapy, more patients in TCH arm had completed Herceptin therapy than those in the AC→TH arm (75% and 87% of patients in AC→TH and TCH arms, respectively). During the monotherapy, the most often reason for Herceptin discontinuation was significant cardiac disease (3.9% and 1.1% for the AC→TH and TCH arms, respectively).

3.2.4.2 Symptomatic Cardiac Events

The sponsor summarized the protocol defined symptomatic cardiac events confirmed by the ICRP in the following table. The most frequent occurred symptomatic cardiac events was grade 3/4 CLVF (0.3%, 1.9% and 0.4% for AC→T, AC→TH and TCH, respectively).

Table 21 Sponsor's Summary of Symptomatic Cardiac Events per the ICRP Occurring at Any Time during the Study (Safety Population)

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
CHF (Grade 3/4 CLVF)	3 (0.3%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0 (0.0%)	2 (0.2%)	2 (0.2%)
Grade 3/4 arrhythmia	3 (0.3%)	2 (0.2%)	6 (0.6%)
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any symptomatic cardiac event [a]	6 (0.6%)	23 (2.2%)	12 (1.1%)

CHF = congestive heart failure; CLVF = cardiac left ventricular function
[a] A patient could be included in more than one event type category; therefore, the "any symptomatic cardiac event row" is less the sum of number of events in a given column.

- *The sponsor also presented the 3-year cumulative incidence for the symptomatic cardiac events (0.5%, 2.36% and 1.16% in the* AC→T, AC→TH and TCH, respectively) and *the 3-year cumulative incidence of Grade 3 or 4 CLVF events (CHF) (0.3%, 2.06% and 0.4% in the* AC→T, AC→TH and TCH, respectively). In these two presentations, AC→TH arm had the highest 3-year cumulative incidence rate for the symptomatic cardiac events.

3.2.4.3 Asymptomatic Cardiac Events

According to the protocol, left ventricular ejection fraction was measured at baseline and 3, 4.5, 6, 9, 18, and 42 months after randomization. The sponsor provided a summary of compliance of LVEF assessment. The overall results indicate that all three arms appear to have compatible compliance rates (percentage of actual LVEF evaluations over expected LVEF evaluations: 81%, 85% and 84% for AC→T, AC→TH and TCH arm, respectively).

Sponsor's summary of asymptomatic cardiac events is presented in the following table based on the data which were obtained using the same methods (MUGA scan or echocardiograms) for the baseline and post-baseline LVEF assessments.

Table 22 Sponsor's Summary of Asymptomatic and Symptomatic LVEF Declines by Baseline Events (Safety Population)

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Absolute decline of > 15% from baseline and to a value below the LLN*	43 (4.1%)	109 (10.2%)	36 (3.4%)
Absolute decline of > 10% from baseline and to a value below 50%	60 (5.7%)	130 (12.2%)	48 (4.5%)
Symptomatic and/or asymptomatic decline of > 15%, below the LLN*	45 (4.3%)	115 (10.8%)	47 (4.5%)

*LLN = lower limit of normal.

Since LVEF provides more objective measurement of cardiac adverse events, this reviewer performed several analyses based on LVEF changes and post baseline LVEF values to confirm the summary results which appear on the proposed labeling (shown in the following table). These analyses indicate that AC→TH arm had higher incidence rates based on all criteria as compared with rates in the AC→T and TCH arm.

Table 23 Reviewer's Summary of the Asymptomatic LVEF Change or Post-baseline Values during the Study (Safety Population)

	AC→T (n = 1050)	AC→TH (n = 1068)	TCH (n = 1056)
Post-baseline LVEF <50%	96(9.14%)	181(16.95%)	90(8.52%)
LVEF< LLN* and ≥15% decrease from baseline	43(4.10%)	109(10.21%)	36(3.41%)
LVEF<50% and ≥10% decrease from baseline	67(6.38%)	141(13.20%)	62(5.87%)
LVEF<50% and ≥16% decrease from baseline	34(3.24%)	104(9.74%)	35(3.31%)
LVEF absolute decrease of ≥10%, <20%	352(33.52%)	470(44.01%)	360(34.09%)
LVEF absolute decrease ≥20%	56(5.33%)	141(13.20%)	66(6.25%)

*LLN = lower limit of normal.

Reviewer's comments:

- *These summaries are based on all LVEF events after time of randomization.*
- *Based on table 59 of the sponsor's clinical study report, AC→TH arm shows consistently higher median LVEF level drop from 4.5 months up to 42 months (at months 42, the median LVEF change from baseline are -2.5%, 0% and -1% for AC→TH, TCH and AC→T, respectively). The longer term effect (longer than 42 months) of the Herceptin + chemotherapy on the change in LVEF can not be determined from the current data.*

- *In the adverse reaction section of the labeling, the sponsor provided a cumulative incidence plots of time to first LVEF decline of ≥10% from baseline and to below 50% with death as the competing events for 2-year periods (based on EL Korn, FJ Dorey. Applications of crude incidence curves. Statistics in Medicine 1992, 11, 813-829). In this time-to-event type of analysis, time 0 is the initiation of docetaxel or Herceptin + docetaxel for the AC → T and AC → TH arms and the date of randomization for the TCH arm. Since the time 0 for AC → T and TCH arms was not comparable and the sponsor's original plots only included data up to 2 years, the sponsor was asked to provide the cumulative incidence plots based on all available data using the randomization date as the time 0 for all arms. The sponsor provided the revised cumulative incidence plots on 4/10/08. The plots show that the cumulative incidence of the significant LVEF drop in AC → TH arm continues to be higher than the other two arms through 42 months.*

3.2.5 Sponsor's Conclusions and Reviewer's Comment

For the cardiac safety analysis, the sponsor concluded that

- The 3-year cumulative incidence of all symptomatic cardiac events and symptomatic CHF (Grade 3 or 4 CLVF) are the highest in the AC→TH arm (see the reviewer's comment on the symptomatic cardiac events section).
- The TCH regimen is a safe and efficacious treatment option with lower incidence (relative to AC→T) of symptomatic cardiac events overall and CHF specifically.

In cardiac safety analysis based on the change and post-baseline LVEF, the reviewer concluded that

- The result shows that AC→TH arm had the highest incidences of post-baseline LVEF <50% (9.1%, 17.0% and 8.5% for AC→T, AC→TH and TCH arms, respectively) and significant LVEF drop (post-baseline LVEF <50% and change of LVEF from baseline ≥10%; 6.4%, 13.2% and 5.9% for AC→T, AC→TH and TCH arms, respectively) among three treatment arms. There was not much difference in the incidences of post-baseline LVEF<50% and significant LVEF drop between AC→T and TCH arms.

4 Findings in Special/Subgroup Populations

This section provides summary statistics (hazard ratio, median survival time, count of patients) based on selected subgroups for DFS and the incidence rates of post-baseline LVEF<50%, LVEF ≥10% reduction from baseline and a significant LVEF drop.

4.1 Gender

Only female patients were included in the study.

4.2 Race

The racial information was not collected for this study, so no summary is provided. However, a subgroup analysis for DFS based on geographic region is provided in the Appendix.

4.3 Age

Sub-group analyses based on age subgroup (<65, ≥ 65 years old) for DFS were performed by this reviewer. The *AC→TH and TCH* arm showed a lower risk in disease free survival as compared with the *AC→T* arm in patients younger than 65 years old. However, the risk reduction was not observed in patients 65 years or older. Due to the small sample size, such results should be interpreted with caution.

Table 24 Reviewer's Summary of Disease Free Survival by Age Subgroup : *AC→TH vs. AC→T*

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio *AC→TH vs. AC→T*
Age	<65	2024	0.00000	0.60(0.47,0.75)
	>=65	123	0.41000	1.42(0.62,3.24)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

Table 25 Reviewer's Summary of Disease Free Survival by Age Subgroup : *TCH vs. AC→T*

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio *TCH vs. AC→T*
Age	<65	2013	0.00100	0.68(0.54,0.85)
	>=65	135	0.79500	0.89(0.37,2.15)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

AC→TH arm appears to have the highest incidences of the post-baseline LVEF<50%, LVEF ≥10% reduction from baseline and significant LVEF drop as compared with the AC→T arm. The higher incidence rates of these LVEF events are consistently shown in both age <65 years old and ≥65 years old.

Table 26 Reviewer's Summary of LVEF changes or post LVEF value by Age Subgroup

LVEF endpoint	Age group	AC→T # events/ # total(%)	AC→TH # events/ # total(%)	TCH # events/ # total(%)
LVEF<50% and ≥10% decrease from baseline		67/1050(6.38%)	141/1068(13.20%)	62/1056(5.87%)
<65		62/986(6.29%)	127/1010(12.57%)	57/985(5.79%)
≥65		5/64(7.81%)	14/58(24.14%)	5/71(7.04%)
LVEF<50%		96/1050(9.14%)	181/1068(16.95%)	90/1056(8.52%)
<65		91/986(9.23%)	166/1010(16.44%)	84/985(8.53%)
≥65		5/64(7.81%)	15/58(25.86%)	6/71(8.45%)
LVEF ≥10% reduction from baseline		365/1050(34.76%)	485/1068(45.41%)	374/1056(35.42%)
<65		343/986(34.79%)	457/1010(45.25%)	347/985(35.23%)
≥65		22/64(34.38%)	28/58(48.28%)	27/71(38.03%)

4.4 Other Special/Subgroup Populations

Additional subgroup analyses based on several baseline prognostic factors were performed by this reviewer (see Appendix) for disease-free survival event. The AC→TH and TCH arm had consistently lower risk of a disease free survival event, except in several cases where the numbers of patients are small and the trend is less clear. In this section, the subgroup analysis is based on high risk nodal status, performance status and tumor size.

The AC→TH and TCH arms show lower risk of DFS as compared with the AC→T arm in both high risk node negative and positive subgroups as well as in the performance ≥100 subgroup. However, the benefit of AC→TH or TCH treatment is less clear in the performance <100 subgroup

Table 27 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *AC→TH versus AC→T*

Endpoint	Level	# of patients	P-value[a]	Hazard Ratio AC→TH vs. AC→T
High Risk Node	NEGATIVE	615	0.00100	0.35(0.19,0.67)
	POSITIVE	1532	0.00200	0.68(0.54,0.87)
Performance status	KARNOFSKY PS<100	438	0.88800	0.97(0.60,1.55)
	KARNOFSKY PS=100	1709	<0.0001	0.56(0.44,0.72)
Pathological tumor size	<=2	850	0.14200	0.73(0.48,1.11)
	>2	1297	<0.0001	0.58(0.45,0.75)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

Table 28 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *TCH versus AC→T*

Endpoint	Level	# of patients	P-value[a*]	Hazard Ratio TCH vs. AC→T
High Risk Node	NEGATIVE	616	0.02500	0.53(0.30,0.92)
	POSITIVE	1532	0.00500	0.72(0.57,0.90)
Performance status	KARNOFSKY PS<100	430	0.53300	1.16(0.73,1.83)
	KARNOFSKY PS=100	1718	<0.0001	0.59(0.46,0.76)
Pathological tumor size	<=2	870	0.29000	0.80(0.53,1.21)
	>2	1277	0.00100	0.64(0.50,0.82)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

5 Summary and Conclusions

Genentech submitted study BCIRG006, a multinational, randomized, open-label, active controlled clinical trial for Herceptin as an adjuvant treatment for patients with HER2-positive, early stage, node-positive or high-risk node-negative breast cancer trial.

In study BCIRG006, a total of 3222 patients were randomized to AC → T, AC → TH and TCH arms, respectively. Patient assignment to treatment was based on a stochastic minimization scheme with center, status of axillary lymph nodes involved and hormonal receptor status as factors.

The protocol specified that three interim analyses would be conducted at the number of DFS events of 300, 450 and 650, respectively. The first interim analysis was conducted by BCIRG after 322 DFS event (data cut-off date: June 30, 2005) using FEVAL data and the second interim analysis (data cut-off date : Nov. 1, 2006) was conducted based on 474 events. This data submission is based on the data from the second interim

analysis.

In this study, the primary efficacy endpoint of this trial is disease-free survival and the secondary efficacy endpoints include overall survival and quality of life.

5.1 Summary of Collective Evidence

The efficacy results demonstrated that the TCH arms had a statistical significant treatment effect based on the disease free survival (excluding non-breast cancer secondary malignancy) for adjuvant breast cancer (p=0.0006 hazard ratio=0.67, 95% C.I. = [0.54, 0.84] for TCH vs. AC→T) (see section 3.1.5.2 Primary Efficacy Endpoint Analyses). The beneficial treatment effect of arms containing Herceptin is consistently demonstrated in various subgroups (see Section 4 Findings in Special/Subgroup Populations).

The results for TCH arm from study BCIRG 006 confirm the beneficial treatment effect of the 1-year Herceptin on disease free survival for adjuvant breast cancer (p<0.0001 based on log-rank test; hazard ratio=0.54, 95% C.I. = [0.44, 0.67]) from HERA study. The results also further confirm the beneficial treatment effect of Herceptin in combination of chemotherapy in adjuvant breast cancer based on the joint analysis of two previous trials (NSABP B31 and NCCTG 9831; Hazard ratio of 0.48, 95% C.I. = [0.39, 0.59], comparing patients who received doxorubicin and cyclophsphamide followed by paclitaxel alone: AC→T or paclitaxel plus Herceptin: AC→T+H; see the Herceptin label for further details).

In cardiac event assessment of study BCIRG 006, the TCH arm appears to have similar incidence rates in post-baseline LVEF<50% (8.5% and 9.1% for TCH and AC→T, respectively) and significant LVEF drop (5.9% and 6.4% for AC→TH and AC→T, respectively) as compared with the rates in the AC→T arm.

The incidence rates of the LVEF related endpoints in TCH arm also appear to be lower than those of the 1-year Herceptin arm observed in HERA and the AC→TH arm observed in the combined study results. The incidence rates of the worst post-baseline LVEF <50% for 1- year Herceptin was 8.6% in HERA; while the incidence rates of

significant drop in LVEF value was 7.0% for 1-year Herceptin of HERA. The incidence rates of the worst post-baseline LVEF <50% was 22.8% for AC→TH in the joined analysis; while the incidence rates of the significant drop in LVEF value was 18.3% for AC→TH in the joined analysis.

5.2 Summary of Statistical Issues

The major statistical/data issues are summarized as follows:

(b) (4)

- Based on the protocol, the TCH arm started the follow-up visit about 1.5 months earlier than the follow-up visit for the AC→TH and AC→T arms. This earlier scheduled visit occurred 6 weeks after the EOC visit in the TCH arm and coincided with the end of the chemotherapy visit for the AC→TH and AC→T arms. During the follow-up visit, the schedule clinical visit time for TCH arm occurred consistently earlier by 1.5 months as compared with the scheduled timing for the AC→TH and AC→T arms. However, an exploratory analysis performed to assess the effect of the timing difference shows that the difference in timing of study visits does not appear to affect the efficacy results.
- A conclusion that adding Herceptin to TC (docetaxel + carboplatin) is beneficial would additionally involve extrapolation (e.g. assuming TC is worse than AC→T). The sponsor provided information on 2/29/08 in response to the agency's requests of justification on how the TCH effect is attributed to Herceptin rather than other components in the treatment arm. Since most of the sponsor's justification is based on the metastatic setting, whether AC→T is an adequate comparator arm will be subject to further justification. For details on the sponsor's response see section 3.1.5.2 Primary Efficacy Endpoint Analyses.

5.3 Conclusions and Recommendations

Based on the BCIRG006 study, the results demonstrated a beneficial treatment effect of Herceptin-containing arm (TCH) on disease free survival (excluding non-breast cancer secondary malignancy) for adjuvant breast cancer (p=0.0006 based on stratified log-rank test; hazard ratio=0.67, 95% C.I. = [0.54, 0.84]). This beneficial treatment effect of Herceptin containing arm on disease free survival appears to be consistent across various subgroups and is robust based on several sensitivity analyses.

(b) (4)

The TCH arm appears to have similar incidence rates of the events defined by the change or post baseline LVEF level (e.g. post-baseline LVEF<50% and significant LVEF drop) as compared with the rates in the AC→T arm.

6 Appendix

6.1 Additional Subgroup Analysis for Disease-Free Survival

Table 29 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors : *TCH versus AC→T*

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio TCH vs. AC→T
ER and PR status	ER+ and/or PR+	1156	0.11100	0.78(0.57,1.06)
	ER- and PR-	992	0.00100	0.61(0.45,0.83)
Estrogen receptor status	NEGATIVE	1084	0.00200	0.63(0.47,0.84)
	POSITIVE	1063	0.11400	0.77(0.55,1.07)
	UNKNOWN	1	NA	NA
Progesterone receptor status	NEGATIVE	1261	0.01500	0.72(0.55,0.94)
	POSITIVE	854	0.01400	0.63(0.43,0.91)
	UNKNOWN	33	0.67700	1.67(0.15,18.46)
Geographic Region	ASIA	104	0.81700	0.84(0.19,3.75)
	EUROPE	911	0.00200	0.59(0.42,0.82)
	MIDDLE EAST	85	0.61500	1.28(0.49,3.31)
	NORTH AMERICA	755	0.04400	0.68(0.47,0.99)
	OCEANIA	217	0.61500	0.85(0.46,1.59)
	SOUTH AFRICA	31	0.93600	1.06(0.28,3.94)
	SOUTH AMERICA	45	0.40800	0.49(0.09,2.67)
Tumor Histopathology	INFILTRATING DUCTAL	1952	0.00100	0.68(0.54,0.85)
	INFILTRATING LOBULAR	68	0.86900	1.11(0.34,3.63)
	OTHER	128	0.44000	0.67(0.24,1.85)

Hormonal therapy	AROMATASE INHIBITOR	115	0.71200	0.83(0.32,2.19)
	OTHER HORMONAL THERAPY	43	NA	NA
	TAMOXIFEN AND AROMAT	255	0.05100	0.36(0.13,1.00)
	TAMOXIFEN ONLY	664	0.13900	0.76(0.52,1.09)
Menopause Status	POST-MENOPAUSAL	727	0.05700	0.70(0.48,1.01)
	PRE-MENOPAUSAL	1109	0.01100	0.68(0.50,0.91)
	UNKNOWN, AGE <= 50 Y	129	0.38400	0.70(0.31,1.56)
	UNKNOWN, AGE > 50 YR	183	0.32300	0.70(0.34,1.42)
Metastatic Disease Status	NO	2143	0.00100	0.69(0.55,0.85)
	YES	5	NA	NA
Nuclear Grade	GRADE CANNOT BE ASSESSED	89	0.08200	0.38(0.13,1.13)
	MODERATELY DIFFERENT	601	0.34700	0.81(0.53,1.25)
	POORLY DIFFERENTIATE	1410	0.00100	0.64(0.50,0.84)
	UNDIFFERENTIATED	6	NA	NA
	WELL DIFFERENTIATED	42	0.29900	2.46(0.45,13.45)
Radiation status	NO	809	0.13700	0.76(0.53,1.09)
	YES	1339	0.00200	0.66(0.50,0.86)
Radiation/lumpectomy/mastectomy	Lumpectomy only	154	0.60300	0.80(0.34,1.88)
	Lumpectomy+radiation	406	0.03300	0.51(0.27,0.95)
	Mastectomy only	569	0.07100	0.67(0.44,1.03)
	Mastectomy+radiation	559	0.06900	0.73(0.52,1.02)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

7 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: **Date:** April 21, 2008

Yuan-Li Shen 4-21-08

Dr. Yuan-Li Shen
Mathematical Statistician

Concurrence:

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CC:

HFD-107/ Gootenberg, Keegan, Fedenko, Laughner,
HFD-150/Cortazar
HFD-711/Chakravarty, Rothmann, Shen
HFD-700/Nevius

This review consists of 50 pages
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103792/5187/5189

OTHER REVIEW(S)

Division of Drug Marketing,
Advertising, and Communications

Internal Consult

****Pre-decisional Agency Information****

To: Erik Laughner, Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Division of Drug Marketing, Advertising and Communications, CDER

Date: April 28, 2008

Re: **Herceptin (Trastuzumab)**
STN BL 103792/5189
Comments on draft labeling

In response to your consult request dated August 16, 2007, DDMAC has reviewed Genentech, Inc.'s proposed labeling for Trastuzumab and offers the following comments. Comments are provided for the working version of the draft labeling (working copy sent by electronic mail on March 26, 2008). These comments were provided verbally during the April 3, 2008, labeling meeting.

103792/5189: to expand the indication for Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 overexpressing, node-positive, or high-risk node-negative breast cancer

(b) (4)

(b) (4)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892-4555

Date: January 23, 2008

To: file STN 103792 (license 1048)

From : Wendy Weinberg, Quality Reviewer, DMA
Through: Patrick Swann, Deputy Directory, DMA

Subject: CMC review and categorical exclusion for:
BLA 103792/5187

Sponsor: Genentech, Inc.

Submitted: June 28, 2007

PDUFA goal: April 28, 2007

Sponsor Contact: Erin Jones, (650) 467-1183

Recommendation: Approval.

Reviewer's comments: This study relied on both FDA-licensed Herceptin manufactured at Genentech, and EU-approved Herceptin manufactured by Roche at their facility in Penzberg, Germany. The comparability of the Genentech- and Roche-manufactured Herceptin was reviewed under STN 103792-5175. (b) (4) results of physicochemical and biological assessments support sufficient comparability to rely on the Roche material in this study for expansion of Genentech's Herceptin license.

Summary: This is an efficacy supplement to the Herceptin BLA to expand the indication of Herceptin to the adjuvant treatment of HER2 overexpressing, node-positive or high-risk node-negative breast cancer, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel.

This supplement is based on efficacy and safety data from Study BCIRG.006, conducted by the Breast Cancer International Research Group (BCIRG) and sponsored by Aventis Pharma Global Medical Affairs (now Sanofi-Aventis Global Medical Affairs Oncology) and Genentech, Inc.

I. CMC information:

There is no CMC section to the supplement. The only information the team could identify regarding product used in the study was contained within Section 8 of the sBLA (Clinical Data), in the BCIRG.006 clinical study report, dated June 14, 2007, in section 5.3.5.1 "Study reports of controlled clinical studies pertinent to the claimed indication." Within this report, section 9.4.2, "Investigational plan/identification of investigational product (p42/43), states that "Herceptin and the appropriate solvent were supplied by Genentech for US sites and by Sanofi-Aventis for sites in other countries....Herceptin was supplied in single dose or multidose vials depending on the country".

A. Suitability of material used in trial:

A request for additional product information was conveyed to Genentech as part of a list of required information on Aug 1, 2007 and read as follows: "Please provide source information for the Herceptin material used in the supporting trials. If product used was not FDA licensed, a comparability assessment will be necessary." This was a reiteration of a similar question conveyed with regard to the HERA study submitted under STN 103792-5175.

Amendment 002 to STN 103792-5187 was submitted on August 15, 2007, and included a response to this question. The same documentation was also submitted as STN 103792-5175, amendment 10 (response to question 2). ***Additional information was requested and received during the review of STN 103792-5175. As a follow-up regarding the product used in both STN 103792-5187 and STN 103792-5189, I called Rob Mills on January 14, 2008, and asked for clarification of the source of the Herceptin provided by Sanofi-Aventis as described in the clinical summary report, section 9.4.2. He sent a letter to me by email on January 17, 2008, to be officially submitted on January 18, 2008, which states that the Herceptin Drug Product provided by Sanofi-Aventis was manufactured by either Genentech, Inc. or F. Hoffmann-La Roche Ltd. It also cross-references the comparability data in STN103792/5175 as appropriate for the product used in the BCIRG studies under review in STN 103792-5187 and STN 103792-5189.***

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion: ***The manufacture and characterization of the Penzberg-manufactured material was reviewed under STN 103792-5175, and deemed to be sufficiently comparable to FDA-licensed material to support expansion of Genentech's Herceptin license. Refer to CMC review of STN 103792-5175 for details.***

B. Acceptability of endotoxin levels at elevated dose

As taken from the draft label changes presented in the initial submission, an alternative dosing schedule of 6 mg/kg dose once every 3 weeks as a 30 minute intravenous infusion is proposed. (b) (4)

Conclusion: ***This is acceptable.***

II. Environmental Analysis:

Qualification for a categorical exclusion from the Environmental Assessment requirement is claimed in Item 20, section 1.12.14, as specified in 21 CFR Section 25.15(d), under 21 CFR 25.31(c). This section applies to action on an NDA, abbreviated application, application for marketing approval of a biological product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. It is stated that, to the applicant's knowledge, no extraordinary circumstances exist. There is no information indicating that additional environmental information is warranted.

Conclusion: ***The categorical exclusion claim is appropriate.***

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892-4555

Date: January 23, 2008

To: file STN 103792 (license 1048)

From: Wendy Weinberg, Quality Reviewer, DMA
Through: Patrick Swann, Deputy Directory, DMA

Subject: CMC review and categorical exclusion for:
BLA 103792/5189

Sponsor: Genentech, Inc.

Submitted: June 29, 2007

PDUFA goal: May 4, 2008

Sponsor Contact: Erin Jones, (650) 467-1183

Recommendation: Approval.

Reviewer's comments: This study relied on both FDA-licensed Herceptin manufactured at Genentech, and EU-approved Herceptin manufactured by Roche at their facility in Penzberg, Germany. The comparability of the Genentech- and Roche-manufactured Herceptin was reviewed under STN 103792-5175. (b) (4) results of physicochemical and biological assessments support sufficient comparability to rely on the Roche material in this study for expansion of Genentech's Herceptin license.

Summary: this is an efficacy supplement to the Herceptin BLA to expand the indication of Herceptin to the adjuvant treatment of HER2 overexpressing, node-positive or high-risk node-negative breast cancer, as part of a treatment regimen containing docetaxel and carboplatin (STN 103792-5189).

This supplement is based on efficacy and safety data from Study BCIRG.006, conducted by the Breast Cancer International Research Group (BCIRG) and sponsored by Aventis Pharma Global Medical Affairs (now Sanofi-Aventis Global Medical Affairs Oncology) and Genentech, Inc.

I. CMC information:

There is no CMC section to the supplement. The only information the team could identify regarding product used in the study was contained within Section 8 of the sBLA (Clinical Data), in the BCIRG.006 clinical study report, dated June 14, 2007, in section 5.3.5.1 "Study reports of controlled clinical studies pertinent to the claimed indication." Within this report, section 9.4.2, "Investigational plan/identification of investigational product (pages 42-43), states that "Herceptin and the appropriate solvent were supplied by Genentech for US sites and by Sanofi-Aventis for sites in other countries....Herceptin was supplied in single dose or multidose vials depending on the country". ***Thus, this study relied on both FDA-licensed Herceptin manufactured at Genentech, and EU-approved Herceptin manufactured by Roche at their facility in Penzberg, Germany. No information was initially submitted in this supplement on the comparability of these two sources of Herceptin.***

A. Suitability of material used in trial:

A request for additional product information was conveyed to Genentech as part of a list of required information on Aug 1, 2007 for both STN 103792-5187 and 5189, and read as follows: "Please provide source information for the Herceptin material used in the supporting trials. If product used was not FDA licensed, a comparability assessment will be necessary." This was a reiteration of a similar question conveyed with regard to the HERA study submitted under STN103792-5175.

Amendment STN 103792-5189.002 was submitted on August 15, 2007 in response to this question, and included documentation of comparability of Penzberg- and Genentech-manufactured Herceptin. The same documentation was also submitted as STN 103792-5175, amendment 10 (response to question 2) and as STN 103792-5187.002 (response to question 6). ***Additional information was requested and received during the review of STN 103792-5175. As a follow-up regarding the product used in both STN 103792-5187 and STN 103792-5189, I called Rob Mills on January 14, 2008, and asked for clarification of the source of the Herceptin provided by Sanofi-Aventis as described in the clinical summary report, section 9.4.2. He sent a letter to me by email on January 17, 2008, to be officially submitted on January 18, 2008, which states that the Herceptin Drug Product provided by Sanofi-Aventis was manufactured by either Genentech, Inc. or F. Hoffmann-La Roche Ltd. It also cross-references the comparability data in STN 103792/5175 as appropriate for the product used in the BCIRG studies under review in STN 103792-5187 and STN 103792-5189.***

(b) (4)

(b) (4)

(b) (4)

Conclusion: ***The manufacture and characterization of the Penzberg-manufactured material was reviewed under STN 103792-5175, and deemed to be sufficiently comparable to FDA-licensed material to support expansion of Genentech's Herceptin license. Refer to CMC review of STN 103792-5175 for details.***

B. Acceptability of endotoxin levels at elevated dose

As taken from the draft label changes presented in the initial submission, an alternative dosing schedule of 6 mg/kg dose once every 3 weeks as a 30 minute intravenous infusion is proposed.

(b) (4)

Conclusion: ***Endotoxin levels are acceptable under this dosing regimen.***

II. Environmental Analysis:

Qualification for a categorical exclusion from the Environmental Assessment requirement is claimed in Item 20, section 1.12.14, as specified in 21 CFR Section 25.15(d), under 21 CFR 25.31(c). This section applies to action on an NDA, abbreviated application, application for marketing approval of a biological product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. It is stated that, to the applicant's knowledge, no extraordinary circumstances exist. There is no information indicating that additional environmental information is warranted.

Conclusion: ***The categorical exclusion claim is appropriate.***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103792/5187/5189

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

08/28/07

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 103792/5187 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 06/29/07 **Action Date:** 04/28/08

HFM _____ **Product and Proprietary names/dosage form:** _____

Applicant: Genentech, Inc. **Therapeutic Class:** N/A

Indication(s) previously approved:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2 overexpressing, (b) (4) breast cancer.
- As a single agent for treatment of HER2 overexpressing breast cancer after failure of one or more chemotherapy regimens.
- In combination with paclitaxel for first line treatment of HER2 overexpressing breast cancer.
- As part of a treatment regimen containing doxorubicin (A), cyclophosphamide (C), and paclitaxel, with Herceptin weekly administration for 52 weeks

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: HERCEPTIN WITH DOXORUBICIN, CYCLOPHOSPHAMIDE, AND DOCETAXEL FOR ADJUVANT TREATMENT OF HER2 OVEREXPRESSING NODE-POSITIVE OR HIGH RISK NODE-NEGATIVE BREAST CANCER

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ☐ **Partial Waiver** ☐ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☑ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max____	**kg**____	**mo.**_____	**yr.** 17	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**_____	**yr.**____	**Tanner Stage**_____
Max____	**kg**____	**mo.**_____	**yr.**____	**Tanner Stage**_____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Erik Laughner

Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 103792/5189 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 07/05/07 **Action Date:** 05/04/08

HFM _____ **Product and Proprietary names/dosage form:** _____

Applicant: Genentech, Inc. **Therapeutic Class:** N/A

Indication(s) previously approved:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2 overexpressing, (b) (4) breast cancer.
- As a single agent for treatment of HER2 overexpressing breast cancer after failure of one or more chemotherapy regimens.
- In combination with paclitaxel for first line treatment of HER2 overexpressing breast cancer.
- As part of a treatment regimen containing doxorubicin (A), cyclophosphamide (C), and paclitaxel, with Herceptin weekly administration for 52 weeks

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: OHERCEPTIN WITH DOCETAXEL AND CARBOPLATIN FOR ADJUVANT TREATMENT OF HER2 OVEREXPRESSING NODE-POSITIVE OR HIGH RISK NODE-NEGATIVE BREAST CANCER

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ☐ **Partial Waiver** ☐ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☑ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**_____	**yr.**0___	**Tanner Stage**_____
Max____	**kg**____	**mo.**_____	**yr.**17__	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**_____	**yr.**____	**Tanner Stage**_____
Max____	**kg**____	**mo.**_____	**yr.**____	**Tanner Stage**_____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Erik Laughner

Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

1.3.3 Debarment Certification

Genentech hereby certifies that it has not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the investigation of Trastuzumab in the BCIRG 006 efficacy supplement 103792/5189.

Signed by: _____ August 22, 2007

Todd W. Rich, M.D.
Vice President
Clinical and Commercial Regulatory Affairs

Date

LICENSING ACTION RECOMMENDATION

(Required for all BLA supplements without a Completion Package)

Applicant: Genentech, Inc. **BLA #:** 103792/5187

Product (established and proprietary names):
Herceptin/Trastuzumab

Indication / Requested change:
Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for the adjuvant treatment of HER2 over-expressing, node-positive or high-risk node-negative, breast cancer

RECOMMENDED ACTION

■ Approval: ☐ Refusal to File: ☐ Denial of application / supplement:

RECOMMENDATION BASIS
(Select all that apply)

☐ Refusal to File Memo
☐ Denial of Application/Supplement Memo

■ Approval Action - Discipline Reviews
■ Approval Action - 2° Review
☐ Approval Action - 3° Review

☐ Review of labeling
- ■ Package Insert – Content
- ☐ Package Insert – SPL Data Elements
- ☐ Package Insert - PLR Format
- ☐ Patient Package Insert
- ☐ Medication Guide
- ☐ Container / Carton (OBP review)

☐ DMPQ Establishment inspections completed

☐ DSI BiMo inspections completed

☐ OBP Review of Protocols for lot no.(s) _____

☐ OBP Review of Test Results for lot no.(s) _____

☐ Review of Environmental Assessment
- ☐ FONSI included ■ Categorical Exclusion

CLEARANCE – FDA PRODUCT RELEASE
Required for Non-Specified Products Only

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REGULATORY REVIEW

■ Compliance status checked - Acceptable

☐ Compliance status checked – Hold (Requires justification for approval action)

☐ Compliance status check not required

Regulatory Project Manager (RPM) _____ Date: 05/16/08

Chief, Project Management (CPMS) _____ Date: 5/22/08

FINAL CLEARANCE

Cross-Discipline Team Leader (if assigned) _____ Date: _____

Responsible Division Director Patricia Keegan Date: 5-22-08

Form: LARM (CDER – 10/2006)

LICENSING ACTION RECOMMENDATION
(Required for all BLA supplements without a Completion Package)

Applicant: Genentech, Inc. **BLA #:** 103792/5189

Product (established and proprietary names):
Herceptin/Trastuzumab

Indication / Requested change:
Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 over-expressing, node-positive, or high-risk node-negative breast cancer

RECOMMENDED ACTION

■ Approval: ☐ Refusal to File: ☐ Denial of application / supplement:

RECOMMENDATION BASIS
(Select all that apply)

☐ Refusal to File Memo
☐ Denial of Application/Supplement Memo

■ Approval Action - Discipline Reviews
■ Approval Action - 2° Review
☐ Approval Action - 3° Review

☐ Review of labeling
- ■ Package Insert – Content
- ☐ Package Insert – SPL Data Elements
- ☐ Package Insert - PLR Format
- ☐ Patient Package Insert
- ☐ Medication Guide
- ☐ Container / Carton (OBP review)

☐ DMPQ Establishment inspections completed

☐ DSI BiMo inspections completed

☐ OBP Review of Protocols for lot no.(s) _____

☐ OBP Review of Test Results for lot no.(s) _____

☐ Review of Environmental Assessment
- ☐ FONSI included ■ Categorical Exclusion

CLEARANCE – FDA PRODUCT RELEASE
Required for Non-Specified Products Only

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REGULATORY REVIEW

■ Compliance status checked - Acceptable

☐ Compliance status checked – Hold (Requires justification for approval action)

☐ Compliance status check not required

Regulatory Project Manager (RPM) _____ Date: 05/16/08

Chief, Project Management (CPMS) _____ Date: 5/22/08

FINAL CLEARANCE

Cross-Discipline Team Leader (if assigned) _____ Date: _____

Responsible Division Director Patricia Keegan Date: 5-22-08

Form: LARM (CDER – 10/2006)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

To: Regulatory File 103792/5187 and 103792/5189

From; Katherine Fedenko,Clinical Reviewer K. Fedenko 5/29/2008
Office of Oncology Drug Products/Division of Biologic Oncology Products

Subject: Addendum to Executive Summary. Section 1.2 Recommendations on Postmarketing Actions. Final Language of PMR's/PMC.

Required Phase 4 Commitments

1. To provide an update of cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic cardiac event.

   The timetable submitted on April 24, 2008, by Genentech states that the trial will be conducted according to the following schedule:

Completion of 5-year follow-up:	June 30, 2009
Final Report Submission:	March 31, 2010

2. To perform a DDI trial in metastatic cancer patients to evaluate the impact of Herceptin on Carboplatin pharmacokinetics and to evaluate the impact of Carboplatin on Herceptin pharmacokinetics. Herceptin concentrations in the DDI trial will be compared to clinical pharmacokinetic data from clinical trials BO16348, BO15935, and WO16229.

   The timetable submitted on May 13, 2008, by Genentech states that the trial will be conducted according to the following schedule:

Protocol submission:	March 31, 2009
Study Initiation:	September 30, 2009
Final report submission:	January 31, 2013

Other Phase 4 Requests

1. To provide an update of efficacy from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 10 years of follow-up, with an interim update of efficacy at 5-years of follow-up.

   The timetable you submitted on April 24, 2008, states that you will conduct this trial according to the following schedule:

Completion of 5-year follow-up:	June 30, 2009
5-year DFS and OS update	March 31, 2010
Completion of 10-year follow-up	June 30, 2014
Final report submission (10-year DFS and OS update)	March 31, 2015.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 15, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: PMR classification of cardiac PMC for 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

Note: DDI PMC will be classified as PMR under FDAAA. See PMC section of action package.

To perform a DDI study in metastatic cancer patients to evaluate the impact of Herceptin on Carboplatin pharmacokinetics and to evaluate the impact of Carboplatin on Herceptin pharmacokinetics. Herceptin concentrations in the DDI study will be compared to clinical pharmacokinetic data from clinical studies BO16348, BO15935, and WO16229.

The timetable you submitted on May 13, 2008, states that you will conduct this trial according to the following schedule:

Protocol submission:	March 31, 2009
Study Initiation:	September 30, 2009
Final report submission:	January 31, 2013.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 13, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Acceptance of Proposed DDI PMC for sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

Note: DDI PMC will be classified as PMR under FDAAA.

From: Laughner, Erik
Sent: Tuesday, May 13, 2008 1:58 PM
To: 'Erin Jones'
Subject: RE: Genentech Language for Proposed DDI PMC (HERCEPTIN)

Hi Erin,

FDA finds the PMC acceptable. The FDA letter will issue as soon as it has received final clearance. I imagine within a day or two.
Please follow-up with a formal amendment.

Sincerely,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Tuesday, May 13, 2008 11:43 AM
To: Laughner, Erik
Subject: FW: Genentech Language for Proposed DDI PMC (HERCEPTIN)
Importance: High

Hi Erik,

Genentech's revised DDI PMC language is below; as mentioned earlier, please let me know if a short teleconference to discuss with our PK representatives would be helpful.

> Genentech will perform a drug-drug interaction study in metastatic cancer patients to evaluate the impact of Herceptin on Carboplatin pharmacokinetics. To evaluate the impact of Carboplatin on Herceptin pharmacokinetics, Herceptin concentrations in the DDI study will be compared to clinical pharmacokinetic data from Clinical studies BO16348, BO15935, and WO16229. A detailed protocol will be submitted by March 31,

2009. The study will be initiated by September 30, 2009. A final study report will be submitted by January 31, 2013.

The Herceptin concentration data obtained in these q3 week studies were similar regardless of the population (adjuvant breast cancer and metastatic breast cancer) and chemotherapy administration; BO16348 was studied in adjuvant breast cancer patients following chemotherapy, BO15935 in metastatic breast cancer patients in combination with Taxol, and WO16229 in metastatic breast cancer patients as a single agent.

Kind regards,
Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Monday, May 12, 2008 12:57 PM
To: Erin Jones
Subject: RE: Genentech Language for Proposed DDI PMC (HERCEPTIN)
Importance: High

Hi Erin

I'm still waiting on final comments on this, but one issue that came up was for Genentech to identify in the PMC the source of the data for this cross-study comparison of Herceptin PK effects . Previous clinical pharmacokinetic data is too vague.

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Monday, May 12, 2008 1:47 PM
To: Laughner, Erik
Subject: RE: Genentech Language for Proposed DDI PMC (HERCEPTIN)
Importance: High

Hello Erik,

Please find the revised DDI PMC language below:

(b) (4)

If the Agency requires additional clarity for the proposal, our PK scientist is available to discuss. Genentech does agree that 3 years is a considerable amount of time to complete this PK study; however, we calculate enrollment will be impeded due to the lack of available HER2+ patients and dispassionate Investigators.

Kind regards,
Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, May 09, 2008 6:23 AM

To: Erin Jones
Subject: Genentech Language for Proposed DDI PMC (HERCEPTIN)
Importance: High

Hi Erin,

FDA would you to clarify the PMC. As observed clinically and stated in the product label, paclitaxel increased herceptin exposure, and therefore you should evaluate the effect of carboplatin on Herceptin PK as well. Can you fix the PMC language?

(b) (4)

Please confirm receipt.

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Friday, May 09, 2008 1:25 AM
To: Laughner, Erik
Subject: RE: BCIRG ACTION STATUS
Importance: High

Good morning Erik,

Below is Genentech's proposal for the BCIRG Herceptin DDI PMC:

(b) (4)

Please contact me if you have any questions.

Kind regards,
Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 8, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Thursday, May 08, 2008 1:01 PM
To: 'Erin Jones'
Subject: RE: Herceptin Label- FDA edit to footnote "g"

Thanks Erin,

On the first page of the label, please make sure that the revision date is 05/08.

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Thursday, May 08, 2008 12:54 PM
To: Laughner, Erik
Subject: FW: Herceptin Label- FDA edit to footnote "g"
Importance: High

Hi Eric,

The Agency's proposed language is acceptable without additional clarification. I will revise the label and email a word document to you and submit the PI to the application.

Regards,
Erin

From: Laughner, Erik

Sent: Thursday, May 08, 2008 12:20 PM

To: 'Erin Jones'

Subject: FW: Herceptin Label- FDA edit to footnote "g"

Erin,

See if this new edit will work.

Erik

FDA requests the following additional labeling change (addition of footnote "g", to TCH and AC-TH rows) for Table 6,

Table 6
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
Studies 1 + 2[e]				
AC→TH (n =1872)	133	0.48a (0.39, 0.59) p=< 0.0001b	62	0.67 p=NSd
AC→T (n = 1880)	261		92	
Study 3				
Chemo→ Herceptin (n =1693)	127	0.54 (0.44, 0.67) p=< 0.0001c	31	0.75 p=NSd
Chemo→ Observation (n = 1693)	219		40	
Study 4f				

TCH (n=1075)	134	0.67 (0.54 – 0.84) p=0.0006b,g	56	
AC→TH (n=1074)	121	0.60 (0.48 – 0.76) p=< 0.0001bg	49	
AC→T (n=1073)	180		80	

CI = confidence interval.

a Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

b stratified log-rank test.

c log-rank test.

d NS= non-significant.

e Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC®T) or paclitaxel plus Herceptin (AC®TH)

f Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC®T) or docetaxel plus Herceptin (AC®TH); docetaxel and carboplatin plus Herceptin (TCH).

g. A two-sided alpha level of 0.025 for each comparison

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Thursday, May 08, 2008 1:28 AM
To: Laughner, Erik
Subject: Herceptin BCIRG PI responses
Importance: High

Hello Erik,

The team has drafted the DDI carbo-Herceptin PMC language and GNE management is currently reviewing – I hope to have something for you by Friday morning.

(b) (4)

These procedures are outlined in pages 60 and 65 in the CSR:

> CSR page 60:
> A "step-down" testing procedure was used to compare the control arm AC–T to each Herceptin-containing arm, AC–TH and TCH, using the log-rank test stratified for nodal status (0 vs. 1–3 vs. ε 4) and hormone receptor status (ER and/or PR positive vs. negative), at an α /2 level to account for multiple testing. If both of the previous were statistically significant, then comparison of the two Herceptin-containing regimens could be conducted at the α level of significance. All tests of hypotheses were two sided. Details regarding the statistical revisions to the planned interim analyses are provided in Section 9.7.2.

CSR page 65-66

Following the initial sample size calculations, additional interim analyses were added, and a "step-down" testing procedure was proposed to allow for comparison of the control arm (AC–T) with each Herceptin-containing arm (AC–TH and TCH) at a level equal to α/2 to account for multiple testing. If both of these comparisons reached statistical significance, a comparison of the two Herceptin-containing arms would be conducted at a significance level of α. The revised analysis schedule called for three interim efficacy analyses to be conducted when 300, 450, and 650 DFS events, respectively, had been observed and a main analysis to be conducted when 900 DFS events had been observed (to avoid any confusion, the previously called "final" analysis was called the "main" analysis to reflect the fact that two follow-up confirmatory analyses would be performed, 3 and 5 years after the main analysis). With the revised assumptions as well as the final number of 3222 randomized patients, the trial was powered to detect a 7% difference between the control arm (AC–T) and each Herceptin-containing arm (i.e., a 23.7% reduction in risk), assuming a 5-year DFS of 70% in the control arm. Table 10 summarizes the original and revised statistical considerations.

(b) (4)

we are available to discuss this concern at the Agency's earliest convenience.

Kind regards,
Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 7, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Wednesday, May 07, 2008 1:23 PM
To: 'Erin Jones'
Subject: BCIRG ACTION STATUS
Importance: High

Hi Erin,

I'm sorry to report that during the final Division level review of these supplements, several outstanding issues need to be addressed prior to the letter issuing:

1. FDA went back to the April 2007 pre-sBLA minutes and note under comment 12, the following discussion:

17-April-2007 GNE Pre-meeting response:
In support of the combined administration of docetaxel and Herceptin, the JP16003 pharmacokinetic interaction study will be filed with the BCIRG.006 supplement. There was no indication of an interaction of concurrent administration of Herceptin on docetaxel pharmacokinetics. In addition, no evidence was found for a pharmacokinetic interaction of concurrent administration of docetaxel on Herceptin pharmacokinetics. No drug-drug interaction studies have been performed with carboplatin and Herceptin.

18-April-2007 Discussion / Outcome:
FDA asked whether there are any ongoing studies to determine interaction between carboplatin and Herceptin. GNE confirmed that we have none. GNE mentioned that we do have some data on cisplatin and Herceptin from Phase I/II studies.

FDA indicated that we need to perform a DDI study for carboplatin and Herceptin, and stated that we can provide our study plan and conduct it as part of a PMC.

May 30, 2007, FDA Clarification: FDA asked whether there are any ongoing studies to determine interaction between carboplatin and Herceptin. GNE confirmed that they have

none. GNE mentioned that they do have some data on cisplatin and Herceptin from Phase I/II studies.

FDA indicated that GNE needs to perform a DDI study for carboplatin and Herceptin, and stated that GNE can provide their study plan for FDA review and comments, and conduct the study as part of a PMC.

FDA is requesting that as a condition for approval of the BCIRG supplements, Genentech provide a PMC to conduct a drug interaction
study to determine the interaction between carboplatin and Herceptin in breast cancer patients. Suggested milestones could be:
Protocol (or amendment) Submission: December 2008
Study Start (FPE): June 2009
Report submission: December 2010

Please provide language.

2. In addition, under preBLA meeting comments 13, can you clarify what is the status for the Final Study Report for PMC #6?

3. FDA requests the following additional labeling change (b) (4) .

(b) (4)

[redacted]

I know you are traveling, but I will be available until 4PM today or in the office early tomorrow morning.

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 05/05/08

From: Erik Laughner, DBOP/OODP/CDER

Subject: Internal Memo regarding review Safety Update for STN 103792/5187 and 5189

See page 107 of clinical review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 05/05/08

From: Erik Laughner, DBOP/OODP/CDER

Subject: Internal Memo regarding review of financial disclosure for STN 103792/5187 and 5189

See page 18 of clinical review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 5, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, May 05, 2008 8:29 AM
To: 'Erin Jones'
Subject: Herceptin Label BCIRG additional change 050508
Importance: High

Hi Erin,

Under Section 1.2 (Metastatic Breast Cancer) of the label, FDA has become aware of an oversight following the HERA supplement 103792/5175.

(b) (4)

As this will be "new" a vertical line will also need to go here for changes.

Please confirm receipt of this email.

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 2, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: Teleconference with Genentech to discuss review clock.

I spoke with Erin Jones at Genentech regarding the status of the supplements under review. I noted that FDA would not be able to take action on the supplements today, as the letter was working its way through clearance (regarding the new FDAAA regulations). I indicated that FDA would target an action during the following week, although we could not give an exact date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: Genentech Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Wednesday, April 30, 2008 11:47 AM
To: 'Erin Jones'
Subject: Herceptin BCIRG final draft label
Importance: High

Erin,

Can you confirm that figure 3, Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event., is (b) (4)

Please confirm receipt.

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Wednesday, April 30, 2008 1:57 AM
To: Laughner, Erik
Subject: Herceptin BCIRG final draft label
Importance: High

Hello Erik,

Genentech acknowledges and accepts the Agency's numeric values for Study 4 in Thrombosis/Embolism Section of the draft PI "2.5% and 3.7% vs. 2.2% [Study 4]". (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Attached, are clean and redline versions of the final draft BCIRG label consistent with the Agency's proposed language in both word and pdf formats. Please contact me if you have any further questions or comments.

Thank-you,
Erin

Erin E. Jones, MS | Sr. Manager, Clinical Regulatory | Genentech Inc.

1 DNA Way, South San Francisco, CA 94080

☎ 650 467 1183| ✉ jones.erin@gene.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 29, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: Genentech Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, April 29, 2008 4:45 PM
To: 'Erin Jones'
Subject: FW: Herceptin 103792/5187&5189 Thrombotic Events

Erin,

Please confirm receipt.

Subject: Herceptin 103792/5187&5189 Thrombotic Events

Deep
mbophlebits pt # 4_

Enclosed is an attached file cross referencing patient numbers in the safety population with "deep thrombophlebitis" events from the CARDAE dataset for BCIRG 006. These numbers and case reports confirm the FDA analysis below and will be used to support the updated information in the Herceptin label, section 6, for thrombosis/embolism.

FDA Reviewer's Incidence of Deep Thromophlebitis Events

Safety Population	AC→T (n-1050)	AC→TH (n=1068)	TCH (n=1056)
Deep Thrombophlebitis			
All	23 (2.2%)	27 (2.5%)	39 (3.7%)
Grade 3/4	19 (1.8%)	25 (2.3%)	31 (2.9%)
SAE	7 (0.7%)	11 (1.0%)	14 (1.3%)

Erik

Appears this way on the original

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 28 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: Genentech Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

NOTE: attachments in email were provided to the Sponsor as a word file, CheckDFS 042808.doc as well as data file: chkdfs.sas.

From: Laughner, Erik
Sent: Monday, April 28, 2008 2:43 PM
To: 'Erin Jones'
Subject: FW: (b) (4)

Erin,

Please see FDA response:

(b) (4)

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Monday, April 28, 2008 12:47 PM
To: Laughner, Erik
Subject: Table 6 and Figure 5 of PI

Hello Erik,
Another housekeeping item; would you please forward to the Statistical Reviewer for agreement?
(b) (4)

(b) (4)

Thank-you,
Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 28, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: Genentech Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, April 28, 2008 10:35 AM
To: 'Erin Jones'
Subject: FW: changes to BCIRG label.
Importance: High

Hi Erin,
See below. Thanks, Erik

(b) (4)

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Friday, April 25, 2008 5:19 PM
To: Laughner, Erik
Subject: RE: A couple of formatting changes to BCIRG label.
Importance: High

Thanks Erik,

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Thank-you,

Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 25, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA labeling; 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Friday, April 25, 2008 10:16 AM
To: 'Erin Jones'
Subject: 042408 FDA Labeling BCIRG
Importance: High

Erin,

Please see FDA labeling in red-line.

042408 FDA
edline.doc (670 KB..

I believe that after this version, we are finished with the major points.

Please confirm receipt.

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

12 pages immediately following withheld - Draft Labeling
b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 25, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: Genentech Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

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From: Laughner, Erik
Sent: Friday, April 25, 2008 3:25 PM
To: 'Erin Jones'
Subject: A couple of formatting changes to BCIRG label.

Erin,

Here a couple of additional "formatting" changes to the label while you have it:

1. In Highlights, "WARNING" in the boxed warning should be bolded.

2. Delete "**1.14.1.2 Annotated Draft Labeling Text"** at the top of the labeling.

3. (b) (4)

4. "Trastuzumab" should be "trastuzumab" (lower case small first letter) throughout the labeling. Note that in a few sections it is still capitalized, 2.3, 7, 11, 16, and at the end of labeling in the sponsor information table.

Please confirm receipt.

Thanks,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 23, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: Genentech Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

NOTE: attachments in email were actual DFS listing were provided to the Sponsor as a word file, DFS listing.doc as well as data file: dfs.sas7bdat

---

From: Laughner, Erik
Sent: Wednesday, April 23, 2008 1:26 PM
To: 'Erin Jones'
Subject: Provided data per tcon today; BCIRG

Erin,

Please see attached data. Please confirm receipt.

Can you please tell me who attended the tcon on your end?

Thanks,

Erik
Here is the listing of DFS data that I agreed to send to the sponsor. The variable documentation was also included.

Because it may be helpful if they have the electronic data to do the comparison, I also included the derived SAS dataset.
Please note that the SAS procedure that I used was shown below:

(b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 23, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: Teleconference with Genentech to discuss (b) (4)

FDA Attendees:

Yuan Li Shen, Ph.D.
Erik Laughner, M.S.

Genentech Attendees:

(b) (6)
James Reimann
Fan Zhang
Erin Jones

Discussion: Genentech requested a brief telecon with the FDA statistical reviewer (b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 22, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: PMR classification of cardiac PMC for 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

Note: Cardiac PMC will be classified as PMR under FDAAA. See PMC section of action package.

---

2. Cardiac safety update at 5 years of follow-up from all 3 treatment arms in BCIRG006

To provide an update of cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic cardiac event. The completion of 5-year follow-up will occur by June 30, 2009 and the 5-year cardiac update will be submitted to the FDA by March 31, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 22, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, April 22, 2008 12:22 PM
To: Erin Jones
Subject: FW: BCIRG clarification request
Importance: High

Erin,

Please see FDA response. Please confirm receipt.

Thanks,

Erik

(b) (4)

On Table 6, FDA obtained n for TCH arm=134; p-value (stratified log rank test)=0.0006 with HR=0.67 (95%CI=[0.54,0.84]) for the comparison of TCH vs AC-T.

Please note that in FDA's calculation, for patients with censored or DFS event date after Nov. 01, 2006 cut off date, the censored or DFS event date will be set to Nov. 01, 2006.

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Monday, April 21, 2008 8:35 PM
To: Laughner, Erik
Subject: FW: BCIRG clarification request
Importance: High

Hello Erik,

Genentech would like to thank the FDA statistician for sharing with the additional information on the DFS analysis. With the additional clarification provided by the FDA on April 21, Genentech has obtained a consistent number of DFS events for both AC-TH (121 events) and AC-T (180 events) arms; with a HR of 0.60 (0.48, 0.76), and a stratified log-rank p-value of p=<0.0001.

For the TCH arm, on April 8th the FDA provided an analysis of 134 events and a HR of 0.67 (0.54 – 0.84). (b) (4)

(b) (4)

(b) (4)

Thank-you for your efforts,

Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 22, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: Teleconference with Genentech to discuss review clock.

In response to an email, I spoke with Erin Jones at Genentech regarding the status of the supplements under review. I noted that no major amendments were anticipated and FDA would take action on both supplements simultaneously. I indicated that the PMCs had been agreed and that final labeling should be resolved by the end of the week.However, I noted that FDA would not meet the first PDUFA goal for the efficacy supplement 5187 and would target the PDUFA goal date for the second application, 5189. Mr. Jones acknowledged and noted that he planned to provide a response to the 042108 FDA labeling by Wednesday (04/23).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 22, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA acceptance to Genentech proposed PMCs for 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

Note: Cardiac PMC will be classified as PMR under FDAAA.

From: Laughner, Erik
Sent: Tuesday, April 22, 2008 1:00 PM
To: 'Erin Jones'
Subject: RE: FDA Revised PMCs BCIRG

Erin,

We are fine with the revised PMC language. Please send in the final wordings as an amendment to the supplements.

Please confirm receipt.

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Monday, April 21, 2008 2:35 PM
To: Laughner, Erik
Subject: RE: FDA Revised PMCs BCIRG
Importance: High

Hi Eric,

I've provided a revised draft of the PMCs for the Agency's review. The language in the efficacy PMC (1) was revised for readability (no impact); the asymptomatic was removed from the cardiac PMC (2). Genentech feels there is limited amount of information to be gained from a narrative on asymptomatic events, apart from LV changes.

Proposed text:

1. **Updated efficacy data at 10 years of follow-up from all 3 treatment arms in BCIRG006, with an interim update at 5 years of follow-up**

   To provide an update of efficacy from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 10 years of follow-up, with an interim update of efficacy at 5-years of follow-up. The completion of 5-year follow-up will occur by June 30, 2009 and the 5-year DFS and OS update will be submitted to the FDA by March 31, 2010. The completion of 10-year follow-up will occur by June 30, 2014 and the 10-year DFS and OS update will be submitted to the FDA by March 31, 2015.

2. **Cardiac safety update at 5 years of follow-up from all 3 treatment arms in BCIRG006**

   To provide an update of cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic cardiac event. The completion of 5-year follow-up will occur by June 30, 2009 and the 5-year cardiac update will be submitted to the FDA by March 31, 2010.

Thanks,

Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Monday, April 21, 2008 6:57 AM
To: Erin Jones
Subject: FDA Revised PMCs BCIRG

Hi Erin,

Please see slight edits to your proposed PMC language. Please let me know if this is acceptable to Genentech.

Please confirm receipt of this email.

Thanks,

Erik

<<FDA revised PMCs 042108.doc>>

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
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http://www.fda.gov/cder/Offices/OODP/about.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Proposed Labeling; STN 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, April 21, 2008 11:41 AM
To: 'Erin Jones'
Subject: FDA Labeling 042108 BCIRG
Importance: High

042108 FDA edline.doc (846 KB..

Erin,

Please see FDA labeling for 04/21/08. There are 2 comments to Genentech in the label. Please confirm receipt and provide an estimated time for a response.

Thanks,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

12 pages immediately following withheld - Draft Labeling b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, April 21, 2008 1:06 PM
To: Erin Jones
Subject: FW: BCIRG clarification request

Erin,

Slight edit. Please confirm receipt.

Thanks,

Erik

(b) (4)

The following are the discrepancies found in the analysis of the efficacy data:
The following patients were censored: AC-T : 31517, 31594.
AC-TH : 31179.
The following patient was considered as having an event: TCH: 30364

Pathological confirmation was mandatory for local relapses and regional relapses.

31179 had a primary left breast cancer, the histopathology report of the second right breast primary was DCIS according to the CRF. DCIS is not considered by FDA as a component of DFS.
31517 had a primary right breast cancer treated by lumpectomy and radiation. a second right breast cancer diagnosed by stereotactic needle biopsy is not available in the CRF.
31594 had a primary left breast cancer, the histopathology report of the second right breast primary is not available in the CRF.

Patient 30364 treated in the TCH arm experienced a regional relapse on 08 AUG2003 in a lymph node. The diagnosis was made by a chest CT scan. This patient did not have a pathologic confirmation of the local relapse therefore, was not counted as a loco-regional relapse event. The patient died on (b) (6) and should be counted as an event at the time of death.

In addition, patient 30942 treated in the TCH arm had a left quadrantectomy followed by adjuvant radiotherapy for a T1N0M0 breast cancer. The new primary on the left breast was DCIS. Therefore, this patient should be censored.

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Friday, April 18, 2008 1:01 AM
To: Laughner, Erik
Subject: BCIRG clarification request
Importance: High

Hello Erik,

I believe this is the last question for clarification; after following the same algorithm provided by the FDA, including the same exceptions made to the patients in each arm (b) (4)

The FDA analysis resulted in the censoring of 15, 13, and 11 events of non-breast second primary tumors in the AC-T, AC-TH, and TCH arms respectively, for a total of 39 events. The GNE analysis results in the censoring of 13, 12, and 12 events of non-breast second primary tumors in the AC-T, AC-TH, and TCH arms respectively, for a total of 37 events.

Specifically, the following patients were censored in the GNE analysis following the algorithm provided by the FDA:

AC-T (13): 30165, 30293, 30491, 30581, 30623, 31075, 31210, 31343, 31455, 31515, 31576, 31755, 32861
AC-TH (12): 30643, 30990, 31369, 31402, 31503, 31548, 31954, 32009, 32481, 32537, 32578, 33215

TCH (12): 30138, 30364, 30479, 30688, 30825, 31185, 31510, 32148, 32461, 32823, 32976, 33186

Genentech would like to ask if the FDA statistician can provide the patient IDs by treatment arm for those were censored as a result of excluding non-breast second primary tumors as a DFS event and the codes used for excluding non-breast second primary tumors as DFS.

Thank-you for your assistance,
Erin

Erin E. Jones, MS | Sr. Manager, Clinical Regulatory | Genentech Inc.

1 DNA Way, South San Francisco, CA 94080

☎ 650 467 1183| ✉ jones.erin@gene.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA revisions to Genentech proposed PMCs for 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, April 21, 2008 10:16 AM
To: Erin Jones
Subject: FW: BCIRG clarification request
Importance: High

Erin,

Please see FDA response below. Please confirm receipt.

Sincerely,

Erik

The following are the discrepancies found in the analysis of the efficacy data .

The following patients were censored: **AC-T : 31517, 31594.**
AC-TH : 31179.

The following patient was considered as having an event: **TCH: 30364**

Pathological confirmation was mandatory for local relapses and regional relapses.

31179 had a primary left breast cancer, the histopathology report of the second right breast primary was DCIS according to the CRF. DCIS is not considered by FDA as a component of DFS.

31517 had a primary right breast cancer treated by lumpectomy and radiation. a second right breast cancer diagnosed by stereotactic needle biopsy is not available in the CRF.

31594 had a primary left breast cancer, the histopathology report of the second right breast primary is not available in the CRF.

Patient 30364 treated in the TCH arm experienced a regional relapse on 08 AUG2003 in a lymph node. The diagnosis was made by a chest CT scan. This patient did not have a pathologic confirmation of the local relapse therefore, was not counted as a loco-regional relapse event. The patient died on (b) (6) and should be counted as an event at the time of death.

In addition, patient 30942 treated in the TCH arm had a left quadrantectomy followed by adjuvant radiotherapy for a T1N0M0 breast cancer. The new primary on the left breast was DCIS. Therefore, this patient should be censored.

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Friday, April 18, 2008 1:01 AM
To: Laughner, Erik
Subject: BCIRG clarification request
Importance: High

Hello Erik,

I believe this is the last question for clarification; after following the same algorithm provided by the FDA, including the same exceptions made to the patients in each arm (b) (4)

The FDA analysis resulted in the censoring of 15, 13, and 11 events of non-breast second primary tumors in the AC-T, AC-TH, and TCH arms respectively, for a total of 39 events. The GNE analysis results in the censoring of 13, 12, and 12 events of non-breast second primary tumors in the AC-T, AC-TH, and TCH arms respectively, for a total of 37 events.

Specifically, the following patients were censored in the GNE analysis following the algorithm provided by the FDA:

AC-T (13): 30165, 30293, 30491, 30581, 30623, 31075, 31210, 31343, 31455, 31515, 31576, 31755, 32861
AC-TH (12): 30643, 30990, 31369, 31402, 31503, 31548, 31954, 32009, 32481, 32537, 32578, 33215
TCH (12): 30138, 30364, 30479, 30688, 30825, 31185, 31510, 32148, 32461, 32823, 32976, 33186

Genentech would like to ask if the FDA statistician can provide the patient IDs by treatment arm for those were censored as a result of excluding non-breast second primary tumors as a DFS event and the codes used for excluding non-breast second primary tumors as DFS.

Thank-you for your assistance,
Erin

Erin E. Jones, MS | Sr. Manager, Clinical Regulatory | Genentech Inc.

1 DNA Way, South San Francisco, CA 94080

☎ 650 467 1183| ✉ jones.erin@gene.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA revisions to Genentech proposed PMCs for 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

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Note: Cardiac update PMC will be classified as PMR under FDAAA.

From: Laughner, Erik
Sent: Monday, April 21, 2008 9:57 AM
To: Erin Jones
Subject: FDA Revised PMCs BCIRG

Hi Erin,

Please see slight edits to your proposed PMC language. Please let me know if this is acceptable to Genentech.

Please confirm receipt of this email.

Thanks,

Erik

Please find our draft proposed PMCs for the BCIRG applications:

1. **Updated efficacy data at 10 years of follow-up from all 3 treatment arms in BCIRG006, with an interim update at 5 years of follow-up**

(b) (4)

30,,2014. The updated 10-year DFS and OS data will be submitted to the FDA by March 31, 2015.

2. **Cardiac safety update at 5 years of follow-up from all 3 treatment arms in BCIRG006**

To provide an update on cardiac safety from all 3 treatment arms in Study BCIRG006 at the time when the last patient enrolled reaches 5 years of follow-up. The update will include analysis of per-protocol defined cardiac events, changes in LVEF measurements, and narratives for any patients who developed a new per-protocol defined symptomatic (b) (4) cardiac event. The completion of 5-year follow-up will occur by June 30, 2009 and the 5-year cardiac update will be submitted to FDA by March 31, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: STN 103792/5187 and 5189; Internal Team Labeling Meeting

---

FDA Attendees:

Patricia Keegan, M.D.
Katherine Fedenko, M.S., CRNP
Mark Rothmann, Ph.D.
Yuan Li Shen, Ph.D.
Erik Laughner, M.S.
Patricia Cortazar, M.D.

Discussion: This internal meeting was held to discuss FDA proposed revisions to the BCIRG label proposed by Genentech in an email dated 04/17/08.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 17, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: Teleconference with Genentech to discuss review clock.

I spoke with Erin Jones at Genentech and noted that FDA was likely not going to meet the first PDUFA goal because of resolved PMC and labeling issues which prevented the review staff from completing their reviews and allowing for time for internal regulatory sign-off. Mr. Jones acknowledged.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 17, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

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From: Laughner, Erik
Sent: Thursday, April 17, 2008 10:07 AM
To: 'Erin Jones'
Subject: RE: Request revision to Debarment Certifications for Efficacy Supplements 103792/5187 and 103792/5189

Hi Erin,

Can you tell me in what amendment these were provided?

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Thursday, August 23, 2007 11:14 AM
To: Laughner, Erik
Cc: Hughes, Monica L
Subject: RE: Request revision to Debarment Certifications for Efficacy Supplements 103792/5175, 103792/5187 and 103792/5189

Hello Erik,

Please find attached, revised Debarment certifications for BCIRG supplements 103792/5187 and 103792/5189. I would like to hold formal submission of these two documents and lump with the next amendment.

Monica,

I am still working (b) (4) on the revised Debarment certificate for the HERA 103792/5175 supplement, and will hopefully have within the next week. Please contact me with any questions.

Thank-you,

Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Wednesday, August 15, 2007 8:49 AM
To: Erin Jones
Cc: Hughes, Monica L
Subject: Request revision to Debarment Certifications for Efficacy Supplements 103792/5175, 103792/5187 and 103792/5189
Importance: High

Hi Erin,

For Genentech efficacy supplements: 103792/5175, 103792/5187 and 103792/5189, the submitted debarment certification states:

"This is to certify that Genentech has not and will not use, in any capacity, the services of any US investigators debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with study XXXX that investigated the product Herceptin"

The current certifications are problematic because the way it is worded is:

- Limited to U.S. individuals
- Limited to investigators instead of "all persons" - "all persons" is defined in the guidance (see below)
- Limited to "study" xxx instead of more broadly to the application.

The guidance http://www.fda.gov/cder/guidance/1700dft.pdf states:

"Under the Act, the term *person* includes an individual, partnership, corporation, and association. The Agency regards *services* in connection with the application to include any services related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application. Persons whose services were used in any capacity in connection with the application include, but are not limited to, the following:

- Employees of the applicant
- Certain contractors and their employees (e.g., contract research organizations whose studies were used in the application)

- Certain subcontractors and their employees (e.g., consultants hired by a contract research organization)
- Clinical investigators
- Persons contributing data and information contained in a drug master file (DMF) or public master file (PMF), incorporated by reference in the application."

We request that you submit a new debarment certification that conforms with the requirement of the Act. Please provide the requested resubmission as an amendment to your BLA supplements as soon as possible.

Sincerely,

Erik S. Laughner, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER
FDA

From: Laughner, Erik
Sent: Thursday, April 17, 2008 9:48 AM
To: 'Erin Jones'
Subject: FW: Genentech Request for FDA Clarification: (b) (4)

Erin,

(b) (4)

Erik

6 pages immediately following withheld - Draft Labeling
b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 15, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, April 15, 2008 4:06 PM
To: 'Erin Jones'
Subject: BCIRG Information Request; post tcon

Hi Erin,

We have one additional request: Please fix Table 5 using randomization as time 0 for study 4.

Our attendees today at the tcon:

Erik Laughner
Patricia Keegan
Mark Rothmann
Yuan Li Shen
Patricia Cortazar
Katherine Fedenko
William Pierce

Please confirm receipt of this email.

Thanks,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 15, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: Teleconference with Genentech to discuss labeling revisions.

FDA Attendees:
Patricia Keegan, M.D.
Katherine Fedenko, M.S., CRNP
Mark Rothmann, Ph.D.
Yuan Li Shen, Ph.D.
Erik Laughner, M.S.
Patricia Cortazar, M.D.
William Pierce, Pharm. D.

Genentech Attendees:
Anne Blackwood-Chirchir
Erin Jones
Karen Jones
Todd Rich
James Reimann
David Schenkein
Fan Zhang

Background: In order for Genentech to provide a revised label in response to FDA's proposed revisions of 04/08/08, the Sponsor requested a telecon to discuss several unresolved issues. Genentech in advance of the meeting provided the following discussion points:

Discussion Points for FDA BCIRG.006 Labeling Teleconference

Section 2.1 Recommended Doses and Schedules/Adjuvant Treatment, Breast Cancer

Concern:
Given the variability within administration schedules across the adjuvant breast cancer treatment regimens, Genentech feels identifying the number of weeks of Herceptin dosing is critical.

Proposed Revision:
Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:
During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

2 pages immediately following withheld - Draft Labeling b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 14, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, April 14, 2008 12:42 PM
To: 'Erin Jones'
Subject: BCIRG Information Request

Erin,

Please see FDA information request.

Please confirm receipt.

Thanks,

Erik

The agency could not reproduce the results in Table 2 dated April 10, 2008. Please submit the SAS program that generated the results in Table 2 (t_lvefinc.sas) and the SAS program that created the dataset LVEF (d_lvef.sas). Also, please provide a brief description on what changed in the codes compared with the codes that generate the results in the current labeling (i.e. different time 0 for TCH and AC-T/AC-TH).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 14, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, April 14, 2008 8:41 AM
To: 'Erin Jones'
Subject: FW: BCIRG Information Request- Revised.
Importance: High

Erin,

Please see our response to your request for clarification below. Please confirm receipt.

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Friday, April 11, 2008 11:54 AM
To: Laughner, Erik
Subject: RE: BCIRG Information Request- Revised.
Importance: High

Hello Erik,

Please find the following response/ question/ meeting request:

- Attached, please find responses to your questions below; they will be formally submitted to the application Monday.

(b) (4)

- Would it be possible to arrange for a teleconference next week to discuss the Agency's proposed Herceptin label; please let me know the Agency's availability?

Kind regards,

Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, April 04, 2008 7:22 AM
To: Erin Jones
Subject: RE: BCIRG Information Request- Revised.

Slight revisions to this request.

Please confirm receipt.

Erik

From: Laughner, Erik
Sent: Friday, April 04, 2008 9:02 AM
To: 'Erin Jones'

Subject: BCIRG Information Request
Importance: High

Hi Erin,

Please see the following FDA information requests:

1. Please provide a summary of why or why not the following patients were included as cardiac events in the CARDAE,xpt data set:

PT #
30750
30866
30311
30344
30564
30708
32089
32681

2. Please navigate in the BCIRG 006 submission where to locate dataset CARDMAP. Please explain how CARDMAP was created. Some of the variables (e.g. gneevt, gnecat) included in the GNECARD appears to come from CARDMAP, but they do not seem to be from the CRF. (b) (4)

(b) (4)

(b) (4)

Please confirm receipt of this email. An expedited response would be appreciated.

Thanks,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 8, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Proposed Labeling; STN 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, April 08, 2008 3:34 PM
To: 'Erin Jones'
Subject: FDA Proposed Labeling BCIRG
Importance: High

Hello Erin,

Please see FDA proposed labeling for the BCIRG supplements. Attached are red-line and clean versions. FDA requests that Genentech provide a response by Monday morning, 04/14/08.

040808 FDA CLEAN label.doc (6... 040808 FDA REDLINE label.pdf ..

Please confirm receipt of this email.

Thanks,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

27 pages immediately following withheld - Draft Labeling b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 4, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Friday, April 04, 2008 10:22 AM
To: 'Erin Jones'
Subject: RE: BCIRG Information Request- Revised.

Slight revisions to this request.

Please confirm receipt.

Erik

From: Laughner, Erik
Sent: Friday, April 04, 2008 9:02 AM
To: 'Erin Jones'
Subject: BCIRG Information Request
Importance: High

Hi Erin,

Please see the following FDA information requests:

1. Please provide a summary of why or why not the following patients were included as cardiac events in the CARDAE,xpt data set:
   PT #
   30750
   30866
   30311
   30344
   30564
   30708
   32089

32681

2. **Please navigate in the BCIRG 006 submission where to locate dataset CARDMAP.** Please explain how CARDMAP was created. Some of the variables (e.g. gneevt, gnecat) included in the GNECARD appears to come from CARDMAP, but they do not seem to be from the CRF. (b) (4)

(b) (4)

(b) (4)

Please confirm receipt of this email. An expedited response would be appreciated.

Thanks,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 03, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: STN 103792/5187 and 5189; Internal Team Labeling Meeting

---

FDA Attendees:

Patricia Keegan, M.D.
Katherine Fedenko, M.S., CRNP
Mark Rothmann, Ph.D.
Yuan Li Shen, Ph.D.
Erik Laughner, M.S.
Patricia Cortazar, M.D.
Mark Rothmann, Ph.D.
William Pierce, Pharm. D.
Carol Broadnax

Discussion: This internal meeting was held to discuss FDA proposed revisions to the BCIRG label proposed by Genentech in an email dated 03/26/08.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 1, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, April 01, 2008 1:15 PM
To: 'Erin Jones'
Subject: FDA information Request

Hi Erin,

Please see FDA information request below:

Clarify in the original BCIRG 006 submission where the death narratives are for the following patient's:

PT #	Death Cause Reported
30685	Sudden Death
30947	Complications of Hypercalcemia
30365	Unknown
30422	Septic Shock
31218	Unknown
31549	Unknown
30073	Pulmonary Consolidation
30341	Unknown
30390	Cerebral Stroke
32172	Cranial Trauma with Acute Subdural Hematoma

Please confirm receipt of this email.

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 25, 2008

From: Erik Laughner, M.S., Regulatory Health Project Manager, Team Leader
DBOP/OODP/OND/CDER/FDA

Subject: BL 103792/5187 and 5189: Results for establishment evaluation request

---

The attached information was provided by CDER/DMPQ. The establishment evaluation request was found be acceptable for approval of these supplements.

Laughner, Erik

To: Kiel, Hea S
Subject: RE: Request for Establishment Evaluation Request for Herceptin (trastuzumab) BL STN 103792/5187 and 5189

From: Kiel, Hea S
Sent: Tuesday, March 25, 2008 3:30 PM
To: Laughner, Erik
Cc: CDER-TB-EER
Subject: FW: Request for Establishment Evaluation Request for Herceptin (trastuzumab) BL STN 103792/5187 and 5189
Importance: High

Erik,

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the Therapeutic Biologic-EER request below. There are no pending or ongoing compliance actions to prevent approval of BL STN 103792/5187 and 5189 at this time. The following are the current status for the submitted sites:

(b) (4)

HeaSuk Kiel
Consumer Safety Officer
FDA/CDER/OC/DMPQ/HFD-323
Phone: 301-796-3246
Fax: 301-847-8741

From: Laughner, Erik
Sent: Tuesday, March 11, 2008 8:47 AM
To: CDER-TB-EER
Cc: Randazzo, Giuseppe
Subject: Request for Establishment Evaluation Request for Herceptin (trastuzumab) BL STN 103792/5187 and 5189
Importance: High

Hello,

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 25, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, March 25, 2008 2:22 PM
To: 'Erin Jones'
Subject: RE: FDA Information Request; Herceptin BCIRG Supplements
Importance: High

Hi Erin,

Our statistician has a few questions about the summary of patient disposition for all periods combined:

Please clarify how the summary of patient disposition for all periods combined was calculated (Table 6 in the appendix), particularly with respect to:

1. Numbers of patients with treatment discontinuation from three periods (during receiving chemotherapy, during receiving Herceptin concurrently with chemotherapy and during receiving Herceptin monotherapy) can not be added up and equated to the numbers in the overall table (e.g. number of patients discontinued treatment in AC-TH arm in the overall summary is 289, but based on the numbers from all three periods, the number is 81+72+106=259). Please clarify the discrepancies.

2. If a patients had more than one reason for treatment discontinuation in one period (or in separated periods), what assumption was made for the calculation?

3. There were only a few patients with a missing reason for treatment discontinuation in the separated disposition tables (see Table 12 in the CSR), but the overall summary of patient disposition had 126 and 82 missing reasons for AC-TH and TCH arms, respectively. Please explain the discrepancies.

Please confirm receipt of this email.

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

-----Original Message-----
From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Thursday, March 20, 2008 7:16 PM
To: Laughner, Erik
Subject: RE: FDA Proposed Labeling

Hi Erik,

Attached, is the response document for the March 7th BCIRG requests. The response document and ancillary data have been formally submitted to the two BCIRG applications today. Please contact me if you have any questions.

Thank-you,
Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 11, 2008

From: Erik Laughner, M.S., Regulatory Health Project Manager, Team Leader
DBOP/OODP/OND/CDER/FDA

Subject: BL 103792/5187 and 5189: Request for a establishment evaluation request

---

The attached information was forwarded to CDER/DMPQ for an establishment evaluation request to ensure Genentech's manufacturing facilities had no ongoing compliance actions or investigations.

Laughner, Erik

From: Laughner, Erik
Sent: Tuesday, March 11, 2008 8:47 AM
To: CDER-TB-EER
Cc: Randazzo, Giuseppe
Subject: Request for Establishment Evaluation Request for Herceptin (trastuzumab) BL STN 103792/5187 and 5189

Importance: High

Attachments: estab-descr.pdf

Hello,

estab-descr.pdf

I would like to request an establishment evaluation request for Genentech's Herceptin product for an upcoming approval on 04/28/08 for 2 related efficacy supplements 103792/5187 and 103792/5189. These supplements will have an action simultaneously.

I am attaching relevant manufacturing information.

lease contact me if any additional information is required.

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 10, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, March 10, 2008 4:22 PM
To: 'Erin Jones'
Subject: RE: FDA Information Request; Herceptin BCIRG Supplements

Hi Erin,

We confirm your comment for #1.

Please confirm receipt of this email.

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Monday, March 10, 2008 2:33 PM
To: Laughner, Erik
Subject: RE: FDA Information Request; Herceptin BCIRG Supplements

Thank-you, Erik

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Monday, March 10, 2008 11:31 AM
To: jones.erin@gene.com
Subject: FW: FDA Information Request; Herceptin BCIRG Supplements

Erin,

Here are responses for 2 and 3. Still waiting on 1.

Please confirm receipt.

Tx .

Erik

2. We would like to confirm that we will provide the SAS program ***for Study 4*** used to generate Table 5.

FDA response : Yes, the request is for study BCIRG 006.

3. Table 12 of the BCIRG 006 CSR lists disposition of all randomized patients broken down by status of Entered Chemotherapy, Entered Herceptin during Chemotherapy, and Entered Herceptin Monotherapy. We would like to confirm that you are requesting that the data in this table be condensed into a single list of reasons for discontinuation, regardless of period.

FDA response : Yes.

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Friday, March 07, 2008 8:13 PM
To: Laughner, Erik
Subject: RE: FDA Information Request; Herceptin BCIRG Supplements

Hello Erik,

We are compiling the data requested in your email from earlier today. To ensure we're including the information the reviewers are looking for, we would appreciate clarification on the following questions:

(b) (4)

2. We would like to confirm that we will provide the SAS program ***for Study 4*** used to generate Table 5.

3. Table 12 of the BCIRG 006 CSR lists disposition of all randomized patients broken down by status of Entered Chemotherapy, Entered Herceptin during Chemotherapy, and Entered Herceptin Monotherapy. We would like to confirm that you are requesting that the data in this table be condensed into a single list of reasons for discontinuation, regardless of period.

Thank you for the clarifications.

Regards,
Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, March 07, 2008 5:28 AM
To: Erin Jones
Subject: FDA Information Request; Herceptin BCIRG Supplements
Importance: High

Hi Erin,

FDA has the following comment/information requests for the BCIRG supplements under review:

For Clinical Reviewer:

1. Adverse event data in the BCIRG 006 CSR is displayed with reporting all three arms combined (ACT, ACTH, TCH) AEs as ≥ 5% of all patients at any time during the study and increased by ≥ 2% in either Herceptin containing arms relative to the control arm. Please note that the FDA will be reporting all adverse events separately as Herceptin containing arms vs control in order to better characterize toxicity of arms. (ACT vs ACTH, ACT vs TCH). It is recommended that GNE perform a similar analysis.

For Statistical Reviewer:

2. Please provide SAS programs that generate **Table 5** [Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4] and **Figure 3** [Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event] in the label.

3. Please provide an overall patient disposition table. Currently, patient disposition is summarized by Period.

Please provide this information by COB 03/21/08.

Please confirm receipt of this email.

Sincerely,

Erik Laughner, RPM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 7, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Friday, March 07, 2008 8:28 AM
To: 'Erin Jones'
Subject: FDA Information Request; Herceptin BCIRG Supplements
Importance: High

Hi Erin,

FDA has the following comment/information requests for the BCIRG supplements under review:

For Clinical Reviewer:

1. Adverse event data in the BCIRG 006 CSR is displayed with reporting all three arms combined (ACT, ACTH, TCH) AEs as ≥ 5% of all patients at any time during the study and increased by ≥ 2% in either Herceptin containing arms relative to the control arm. Please note that the FDA will be reporting all adverse events separately as Herceptin containing arms vs control in order to better characterize toxicity of arms. (ACT vs ACTH, ACT vs TCH). It is recommended that GNE perform a similar analysis.

For Statistical Reviewer:

2. Please provide SAS programs that generate **Table 5** [Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4] and **Figure 3** [Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event] in the label.

3. Please provide an overall patient disposition table. Currently, patient disposition is summarized by Period.

Please provide this information by COB 03/21/08.

Please confirm receipt of this email.

Sincerely,

Erik Laughner, RPM

Appears this way on original

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 4, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Proposed Labeling; STN 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, March 04, 2008 3:50 PM
To: 'Erin Jones'
Subject: FDA Proposed Labeling

Hi Erin,

Please see FDA draft labeling for Herceptin. There is a red-lined PDF and a clean word file.

We request a response/revised label within 14 days.

Please confirm receipt.

BCIRG Label DA030408.pdf (311.

BCIRG Label CLEAN FDA030408.do...

Sincerely,

Erik S. Laughner, M.S.
Regulatory Project Manger
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
http://www.fda.gov/cder/Offices/OODP/about.htm

28 pages immediately following withheld - Draft Labeling b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: February 20, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Wednesday, February 20, 2008 12:28 PM
To: 'Erin Jones'
Subject: FW: FDA Request for Information- Herceptin BCIRG

Hi Erin,

Yes- we are requesting data/literature that compares anthracyclines - cyclophosphamide followed by docetaxel with carboplatin – docetaxel.

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Wednesday, February 20, 2008 12:16 PM
To: Laughner, Erik
Subject: RE: FDA Request for Information- Herceptin BCIRG

Hello Erik,

The team is investigating the Agency's request for information and has a clarification question:

For BCIRG, is the Reviewer stating that anthracyclines - cyclophosphamide followed by docetaxel is not an appropriate control arm for docetaxel – carboplatin – Herceptin; and requesting data/literature that compares anthracyclines - cyclophosphamide followed by docetaxel with carboplatin – docetaxel?

We would like to confirm the Agency is also not asking to compare anthracyclines - cyclophosphamide followed by docetaxel against cyclophosphamide – docetaxel (or paclitaxel)?

Thank-you,
Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, February 19, 2008 5:02 AM
To: Erin Jones
Subject: FDA Request for Information- Herceptin BCIRG
Importance: High

Hi Erin,

FDA has the following request re: Herceptin

In study BCIRG, the comparison between the control arm (AC followed by taxol) and the experimental arm (taxol-carboplatin-herceptin) does not isolate the effect of Herceptin. Please provide data which support that the effects seen on DFS can be attributed primarily to Herceptin rather than other components of the treatment arm. Data/literature reprints summarizing the results of randomized trials comparing AC followed by T to with CT in the setting of adjuvant breast cancer would best serve this purpose.

Please confirm receipt of this email.

Sincerely,

Erik Laughner, RPM
DBOP/OODP/CDER/FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: February 19, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Tuesday, February 19, 2008 8:02 AM
To: 'Erin Jones'
Subject: FDA Request for Information- Herceptin BCIRG
Importance: High

Hi Erin,

FDA has the following request re: Herceptin

In study BCIRG, the comparison between the control arm (AC followed by taxol) and the experimental arm (taxol-carboplatin-herceptin) does not isolate the effect of Herceptin. Please provide data which support that the effects seen on DFS can be attributed primarily to Herceptin rather than other components of the treatment arm. Data/literature reprints summarizing the results of randomized trials comparing AC followed by T to with CT in the setting of adjuvant breast cancer would best serve this purpose.

Please confirm receipt of this email.

Sincerely,

Erik Laughner, RPM
DBOP/OODP/CDER/FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 12, 2008

From: Erik Laughner, M.S. DBOP/OODP/CDER

Subject: STN 103792/5187 and 5189; Internal Team Labeling Meeting

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FDA Attendees:

Patricia Keegan, M.D.
Katherine Fedenko, M.S., CRNP
Yuan Li Shen, Ph.D.
Erik Laughner, M.S.
Patricia Cortazar, M.D.

Discussion: This internal meeting was held to discuss FDA proposed revisions to the BCIRG label proposed by Genentech (contains integrated 103792/5175 HERA labeling)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 31, 2008

From: Erik S. Laughner, DBOP/OODP/CDER

Subject: Mid-Cycle Summary BLA 103792/5187 and 5189

This mid-cycle meeting for efficacy supplements 103792/5187 and 5189 was a face-to-face, internal, FDA meeting.

Product: Herceptin (Trastuzumab)

Sponsor: Genentech

Proposed Use: 103792/5187 (Submitted on June 28, 2007; Received on June 29, 2007): to expand the indication for Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for the adjuvant treatment of HER2 overexpressing, node-positive, or high-risk node-negative breast cancer

103792/5189 (Submitted on June 29, 2007; Received on July 5, 2007): to expand the indication for Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 overexpressing, node-positive, or high-risk node-negative breast cancer

Milestones/Scheduled Internal/Sponsor Meetings: assuming 10 month clock and joint review; **action dates below therefore based on earliest received supplement):**

First Committee Meeting: July 25, 2007
Filing Action: August 28, 2007
Deficiencies Identified Letter (74 day letter): September 11, 2007
Applicant Orientation Meeting: September 21, 2007
Mid Cycle/Labeling Meetings: To be Scheduled
Action Due Date: April 28, 2008

Items Covered:

1. Mid-cycle agenda sheet with indications and milestones for review cycle.

   Discussion: Labeling meetings scheduled for February 2008.

2. Sponsor redline version of package insert

3. Presentations by Katherine Fedenko, Patricia Cortazar, and Yuan-Li Shen.

Discussion: Efficacy presentation reviewed Sponsor's proposed indications, study design, endpoints, and assessments. Statistical presentation reviewed SAP, calculations, DFS, assessments, claims for OS. Safety presentation reviewed patient disposition, eligibility deviations, cross-over, deaths, AEs (specific discussion on cardiac events).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 23, 2008

From: Erik Laughner, M.S., Regulatory Health Project Manager, Team Leader
DBOP/OODP/OND/CDER/FDA

Subject: BL 103792/5187 and 5189: Request for Categorical Exclusion

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Please see Dr. Wendy Weinberg's CMC review dated 01/23/08 granting the request for categorical exclusion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 23, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

-----Original Message-----
From: Laughner, Erik
Sent: Wednesday, January 23, 2008 10:35 AM
To: 'Erin Jones'
Subject: RE: Labeling Update for BCIRG Supplements

Hi Erin,

It is my understanding that we are doing a joint review and will take action on the supplements concurrently (if possible). It would be good to submit to both supplements (a condensed label with the ACTH and TCH combined). Please note that in the coverletter.

If a situation should arise in the future that suggests that only one supplement looks like it would move forward, we can then have you revise the labeling with only the ACTH or TCH data.

Does that sound agreeable?

Thanks,

Erik

-----Original Message-----
From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Wednesday, January 23, 2008 10:27 AM
To: Laughner, Erik
Subject: Re: Labeling Update for BCIRG Supplements

Hello Erik,
We are currently updating the BCIRG labeling, would the Review group like 2 labels or 1 condensed label with ACTH and TCH incorporated?
Thanks,
Erin

----- Original Message -----
From: Laughner, Erik <Erik.Laughner@fda.hhs.gov>
To: Erin Jones
Sent: Wed Jan 23 05:24:28 2008
Subject: Labeling Update for BCIRG Supplements

Hi Erin,

Can you provide a submission date of the revised PLR labeling for the current BCIRG supplements?

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 16, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Wednesday, January 16, 2008 12:32 PM
To: 'Erin Jones'
Subject: Herceptin info request

Hi Erin,

Additional information request:

Patient # 31517 had a primary right breast cancer treated by lumpectomy and radiation. a second right breast cancer diagnosed by stereotactic needle biopsy is not available in the CRF. Please submit the pathology report.

Patient # 31594 had a primary left breast cancer, the histopathology report of the second right breast primary is not available in the CRF. Please submit the pathology report.

Please confirm receipt of this email.

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 14, 2008

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, January 14, 2008 2:16 PM
To: 'Erin Jones'
Subject: FW: Herceptin sBLA request for information

Hi Erin,

We have an additional request for feedback:

Please ask the sponsor to provide the following information from Listings 16.2/1 and 16.2/2:
1) Explain what were the non-cardiac related adverse events that lead to early discontinuation of chemotherapy.
2) Explain what were the "other" reasons for discontinuation.

Thanks,

Erik Laughner, RPM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: November 26, 2007

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Monday, November 26, 2007 10:40 AM
To: 'Erin Jones'
Subject: STNs 103792/5187 and 103792/5189; Request for Information
Importance: High

Dear Erin,

I hope you had a nice holiday. FDA has the following information requests for 103792/5187 and 5189:

1. Please explain the discrepancies found between incidence of adverse events reported in the laboratory datasets CHMC and HEMC (raw data) compared to PATLAB (derived).

FDA acknowledges new datasets (PATLAB) are forthcoming based on November 2, 2007, communication. Errors were discovered in the institution's upper limit of normal values and in the conversion of lab values to standard units for the BCIRG006 hematology and chemistries datasets submitted in sBLA 103792/5187 and 5189.

2. Please explain the term "unmapped" found within the variable "Preferred Term" of the AE dataset.

3. Provide an AE dataset that is limited to patients who received at least one dose of any drug in the proposed regimens.

4. Please merge the AE dataset including COSTART terms with the CARDAE dataset.

5. Provide justification for failure to confirm relapse pathologically for each patient with a DFS event where pathological confirmation was not performed as per protocol.

6. Please explain where neutropenic events without fever were captured in the datasets.

We request that that this information be submitted within 30 days. Please confirm receipt of this email.

Sincerely,

Erik Laughner, RPM
DBOP/OODP/CDER/FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: November 6, 2007

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Wednesday, November 07, 2007 9:04 AM
To: 'Erin Jones'
Subject: RE: Herceptin; BCIRG006 communication

Hi Erin,

Will GNE plan to submit the corrected raw data to datasets; CHMC.xpt (chemistry lab results) and HEMC.xpt (hematology lab results as an amendment?

Thanks,

Erik

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Monday, November 05, 2007 6:17 PM
To: Laughner, Erik
Subject: BCIRG006 communication

Hello Erik,

Attached is a communication that will be submitted to the two Herceptin BCIRG applications on data discrepancies that were communicated to us by the BCIRG cooperative group. I would ask that your Review group evaluate our summary of findings and notify me if you would like to have a further discussion on the matter.

Thank-you,
Erin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 15, 2007

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

---

From: Laughner, Erik
Sent: Wednesday, August 15, 2007 11:49 AM
To: 'Erin Jones'
Cc: Hughes, Monica L
Subject: Request revision to Debarment Certifications for Efficacy Supplements 103792/5175, 103792/5187 and 103792/5189
Importance: High

Hi Erin,

For Genentech efficacy supplements: 103792/5175, 103792/5187 and 103792/5189, the submitted debarment certification states:

"This is to certify that Genentech has not and will not use, in any capacity, the services of any US investigators debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with study XXXX that investigated the product Herceptin"

The current certifications are problematic because the way it is worded is:

- Limited to U.S. individuals
- Limited to investigators instead of "all persons" - "all persons" is defined in the guidance (see below)
- Limited to "study" xxx instead of more broadly to the application.

The guidance http://www.fda.gov/cder/guidance/1700dft.pdf states:

"Under the Act, the term *person* includes an individual, partnership, corporation, and association. The Agency regards *services* in connection with the application to include any services related to the collection, monitoring, evaluation, analysis,

or reporting of data or information that appears or is specifically incorporated by reference in the application. Persons whose services were used in any capacity in connection with the application include, but are not limited to, the following:
- Employees of the applicant
- Certain contractors and their employees (e.g., contract research organizations whose studies were used in the application)
- Certain subcontractors and their employees (e.g., consultants hired by a contract research organization)
- Clinical investigators
- Persons contributing data and information contained in a drug master file (DMF) or public master file (PMF), incorporated by reference in the application."

We request that you submit a new debarment certification that conforms with the requirement of the Act. Please provide the requested resubmission as an amendment to your BLA supplements as soon as possible.

Sincerely,

Erik S. Laughner, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER
FDA

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

JOINT 103792/5187 +

STN: 5189 Product: HERCEPTIN Applicant: Genentech

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD HYBRID

Filing Meeting: Date 08/15/07 Committee Recommendation (circle one): File RTF

RPM: _____ 08/15/07
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ✗ Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ☒ Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
including list of all establishment sites and their registration numbers	Y N	
If foreign applicant, US Agent signature.	Y N	
Comprehensive Table of Contents	Y N	
Debarment Certification with correct wording (see * below)	Y N	– NEED TO TWEAK SLIGHTLY ASK SPONSOR TO FIX
User Fee Cover Sheet	Y N	
User Fee payment received	Y N	
Financial certification &/or disclosure information	Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Pediatric rule: study, waiver, or deferral	Y N	WAIVER FULL
Labeling:	Y N	
PI –non-annotated	Y N	
PI –annotated	Y N	
PI (electronic)	Y N	
Medication Guide	Y N	
Patient Insert	Y N	
package and container	Y N	
diluent	Y N	
other components	Y N	
established name (e.g. USAN)	Y N	
proprietary name (for review)	Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
legible	Y N	
English (or translated into English)	Y N	
compatible file formats	Y N	
navigable hyper-links	Y N	
interpretable data tabulations (line listings) & graphical displays	Y N	
summary reports reference the location of individual data and records	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ protocols for clinical trials present ☐ all electronic submission components usable (e.g. conforms to published guidance)	Y N Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	N/A
if CMC supplement: ☐ description and results of studies performed to evaluate the change ☐ relevant validation protocols ☐ list of relevant SOPs	 Y N Y N Y N	N/A
if clinical supplement: ☐ changes in labeling clearly highlighted ☐ data to support all label changes ☐ all required electronic components, including electronic datasets (e.g. SAS)	 Y N Y N Y N	N/A
if electronic submission: ☐ required paper documents (e.g. forms and certifications) submitted	Y N	Yes

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? ~ PMC # 1 ORIGINAL APPROVAL

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: NO
- Dates:

Recommendation (circle one): File RTF

RPM Signature: Branch Chief concurrence:

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Clinical overview [2.5]	Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y N	No comparison and analyses across studies
❑ Biopharmaceutics and associated analytical methods	Y N	NA
❑ Clinical pharmacology [includes immunogenicity]	Y N	NA
❑ Clinical Efficacy [for each indication]	Y N	
❑ Clinical Safety	Y N	
❑ Synopses of individual studies	Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y N	
Tabular Listing of all clinical studies [5.2]	Y N	
Study Reports and related information [5.3]	Y N	
❑ Biopharmaceutic	Y N	NA
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	NA
❑ Pharmacokinetics (PK)	Y N	NA
❑ Pharmacodynamic (PD)	Y N	NA
❑ Efficacy and Safety	Y N	
❑ Postmarketing experience	Y N	NA
❑ Case report forms	Y N	
❑ Individual patient listings (indexed by study)	Y N	NA
○ electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
❑ legible	Y N	
❑ English (or certified translation into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

NA

Is an Advisory Committee needed?

NA

Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

Reviewer: Yu-Li Shen / 08/14/07 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: _____ Division Director: Alaka Chakravarty 8/14/07
(signature/ date) (signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Clinical overview [2.5]	Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y N	
◻ Biopharmaceutics and associated analytical methods	Y N	N/A
◻ Clinical pharmacology [includes immunogenicity]	Y N	
◻ Clinical Efficacy [for each indication]	Y N	
◻ Clinical Safety	Y N	
◻ Synopses of individual studies	Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y N	N/A Note: Hybrid eCTD, no XML back bone
Tabular Listing of all clinical studies [5.2]	Y N	
Study Reports and related information [5.3]	Y N	
◻ Biopharmaceutic	Y N	N/A
◻ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
◻ Pharmacokinetics (PK)	Y N	
◻ Pharmacodynamic (PD)	Y N	N/A
◻ Efficacy and Safety	Y N	
◻ Postmarketing experience	Y N	
◻ Case report forms	Y N	
◻ Individual patient listings (indexed by study)	Y N	
o electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
◻ legible	Y N	
◻ English (or certified translation into English)	Y N	
◻ compatible file formats	Y N	

Examples of Filing Issues	Yes?	If not, action & status
☒ navigable hyper-links	Y (N)	Hyper-link not working
☐ interpretable data tabulations (line listings) & graphical displays	(Y) N	Roadmap→Index→"*Overall Summary*"
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation:		Note: U.S. sites IRB, Non-U.S. sites IDMC
☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	Note; Declaration of Helsinki statement included. IDMC committee member provided
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y N	N/A Note; No U.S IND held for this application
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A Note; No U.S IND held for this application
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	N/A Note; No U.S IND held for this application

Examples of Filing Issues	Yes?	If not, action & status
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	
data supporting the proposed dose and dose interval	Y N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	CMC comparability information not provided. Requested information to Sponsor on 8/1/2007. CFR 312.120 (b)(4) Note: "On the Application to Market" Chemisty section not checked as part of submission (see attached document)
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	See Above
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
BCIRG 006	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Integrated Summary of Safety/Integrated Summary of Efficacy was requested from the Sponsor on August 01, 2007.

Is clinical site(s) inspection (BiMo) needed?
During the clinical trial site audits occurred to both U.S. and non-U.S. sites.

Is an Advisory Committee needed?
Per Dr. Richard Pazdur on August 06, 2007, following new information regarding Topo IIa-HER2 expression-anthracycline therapy , the application to ODAC was discussed for public awareness.

Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

Reviewer: Katherine Fedenko K. Fedenko : Clinical Reviewer
(signature/ date) 8/09/2007

Concurrence:

Branch Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Clinical overview [2.5]	Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y N	
❑ Biopharmaceutics and associated analytical methods	Y N	
❑ Clinical pharmacology [includes immunogenicity]	Y N	
❑ Clinical Efficacy [for each indication]	Y N	
❑ Clinical Safety	Y N	
❑ Synopses of individual studies	Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y N	
Tabular Listing of all clinical studies [5.2]	Y N	
Study Reports and related information [5.3]	Y N	
❑ Biopharmaceutic	Y N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	1P16003 study
❑ Pharmacokinetics (PK)	Y N	
❑ Pharmacodynamic (PD)	Y N	
❑ Efficacy and Safety	Y N	
❑ Postmarketing experience	Y N	
❑ Case report forms	Y N	
❑ Individual patient listings (indexed by study)	Y N	
o electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
❑ legible	Y N	
❑ English (or certified translation into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records ❑ protocols for clinical trials present ❑ all electronic submission components usable	Y N Y N Y N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements ❑ conducted in compliance with requirements for informed consent	 Y N Y N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y N	
drug interaction studies communicated as during IND review as necessary are included	Y N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	Y N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electronic datasets complete & usable?	BiMo sites identified?
BC1R006	(Y) N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Will discuss

Is an Advisory Committee needed?

Will discuss with Pat Keegan new topo II amplicon data might require presenting sBLA to ODAC.

Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

Reviewer: PGarzar (signature/ date) Type (circle one): Clinical Clin/Pharm Statistical

Concurrence:

Branch Chief: _____ (signature/ date) Division. Director: _____ (signature/ date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 15, 2007

From: Erik S. Laughner, DBOP/OODP/CDER

Subject: Filing Meeting Summary BLA 103792/5187 and 5189

This joint filing meeting for efficacy supplements 103792/5187 and 5189 was a face-to-face, internal, FDA meeting.

Product: Herceptin (Trastuzumab)

Sponsor: Genentech

Proposed Use: 103792/5187 (Submitted on June 28, 2007; Received on June 29, 2007): to expand the indication for Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel, for the adjuvant treatment of HER2 overexpressing, node-positive, or high-risk node-negative breast cancer

103792/5189 (Submitted on June 29, 2007; Received on July 5, 2007): to expand the indication for Herceptin, as part of a treatment regimen containing docetaxel and carboplatin, for the adjuvant treatment of HER2 overexpressing, node-positive, or high-risk node-negative breast cancer

Milestones/Scheduled Internal/Sponsor Meetings: assuming 10 month clock and joint review; **action dates below therefore based on earliest received supplement):**

First Committee Meeting: July 25, 2007
Filing Action: August 28, 2007
Deficiencies Identified Letter (74 day letter): September 11, 2007
Applicant Orientation Meeting: September 21, 2007
Mid Cycle/Labeling Meetings: To be Scheduled
Action Due Date: April 28, 2008

Items Covered:

Deficiencies identified?
Filing Memos Completed/ Any major issues?

Discussion: Supplements can be filed, however there are several issued which have been identified and can be conveyed to the Sponsor in the filing letter.

FDA reviewer noted the recent data from Dennis Salmon at UCLA regarding topo II data and anthracycline therapy and whether Genentech was willing to comment on this? Will need to discuss with Dr. Keegan.

Scheduling of Mid-Cycle, labeling meetings/Consults?

Discussion: mid-cycle will be scheduled around month 5-6 of the review clock with labeling meetings shortly thereafter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 10, 2007

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin email and tcon.

In response to an email provided to Erin Jones (see below), Mr. Jones called back to note that a response to FDA's 08/01/07 requests would be provided on/about 08/15/07. Mr. Jones noted that in response to the source information for the Herceptin material used in the supporting trials, Genentech would provide the same information as provided in the current efficacy supplement under review (with Monica Hughes, RPM). Comparability assessments would be provided.

From: Laughner, Erik
Sent: Friday, August 10, 2007 12:30 PM
To: 'Erin Jones'
Subject: FW: Request for Information
Importance: High

Hi Erin,

Do you have an update on the time frames for these requests? Our CMC reviewer is especially interested in a response for item 6 as apparently this issue came up with the current supplement 103792/5175.

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 2, 2007

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

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From: Laughner, Erik
Sent: Thursday, August 02, 2007 9:23 AM
To: 'Erin Jones'
Subject: FW: Request for Information

Hi Erin,

Please see below.

Tx,

Erik

From: Fedenko, Katherine
Sent: Thursday, August 02, 2007 9:22 AM
To: Laughner, Erik
Subject: RE: Request for Information

Good morning Erik,

Please have GNE provide the following:

- CSR, supporting data presentations, Listing of patients
- Primary Data Listings
- Any Secondary Data display
- Study documentation
- Blank Case report Forms with instructions sheet

- Efficacy Analyses
- Safety Analyses
- Pharmacokinetic analysis
- Assessment of data completeness at the time of clinical data cut-off
- Summary data tables, graphs, and listings
- Discussions
- Conclusions
- References
- Appendices

Thanks,
Kathy

Katherine Fedenko
Clinical Reviewer
Division of Biologic Oncology Products
FDA/CDER/OND/OODP
Office Phone # 301-796-2320

From: Erin Jones [mailto:jones.erin@gene.com]
Sent: Wednesday, August 01, 2007 6:21 PM
To: Laughner, Erik
Subject: RE: Request for Information

Erik,

We would be happy to provide Katherine Fedenko a desk copy; can you please confirm with her specifically which sections are desired? My inclination would be to provide her the following clinical material:

-CSR, including all protocol versions (minus CRFs and patient listings)

-Clinical Overview

Thanks,

Erin

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Wednesday, August 01, 2007 11:40 AM
To: Erin Jones
Subject: Request for Information
Importance: High

Hi Erin,
Upon initial review of the supplements, the following information is requested:

1. A copy of the most recent protocol prior to database closure (November 1, 2006)
2. Protocol amendment history summary and full language text of all amendments
3. Please map out raw text term to MedDRA v.10 . Provide the following additional hierarchal terms;

   - Preferred term (PT)
   - Higher level term (HLT)
   - Higher Level Grouping Term (HLGT)
   - System Organ Class (SOC)

   Provide coding dictionary in a PDF document verbatim → preferred term and preferred term → verbatim

4. We request data in CDISC (clinical data interchange standards consortium) format (http://www.cdisc.org)
5. We are unable to locate the Integrated Summary of Safety or Integrated Summary of Efficacy. Please provide summaries or navigation instructions from submission roadmap.

   http://www.fda.gov/cder/regulatory/ersr/Iss_ISE_clarification.htm

6. Please provide source information for the Herceptin material used in the supporting trials. If product used was not FDA licensed, a comparability assessment will be necessary.

In addition, a clinical reviewer, Katherine Fedenko, has a request for 1 paper desk copy of each supplement. They may be mailed directly to her office at: WO22, Room 2342, 10903 New Hampshire Avenue, Silver Spring, MD 20903.

Let me know if you have any questions. I can be reached directly at 301-796-1393.
Cheers,

Erik S. Laughner, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER
FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 1, 2007

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information Regarding Genentech's sBLA Submissions 103792/5187 and 103792/5189 for (Trastuzumab) Herceptin

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From: Laughner, Erik
Sent: Wednesday, August 01, 2007 2:40 PM
To: 'Erin Jones'
Subject: Request for Information
Importance: High

Hi Erin,

Upon initial review of the supplements, the following information is requested:

1. A copy of the most recent protocol prior to database closure (November 1, 2006)

2. Protocol amendment history summary and full language text of all amendments

3. Please map out raw text term to MedDRA v.10 . Provide the following additional hierarchal terms;

   - Preferred term (PT)
   - Higher level term (HLT)
   - Higher Level Grouping Term (HLGT)
   - System Organ Class (SOC)

   Provide coding dictionary in a PDF document verbatim → preferred term and preferred term → verbatim

4. We request data in CDISC (clinical data interchange standards consortium) format (http://www.cdisc.org)

5. We are unable to locate the Integrated Summary of Safety or Integrated Summary of Efficacy. Please provide summaries or navigation instructions from submission roadmap.

http://www.fda.gov/cder/regulatory/ersr/lss_ISE_clarification.htm

6. Please provide source information for the Herceptin material used in the supporting trials. If product used was not FDA licensed, a comparability assessment will be necessary.

In addition, a clinical reviewer, Katherine Fedenko, has a request for 1 paper desk copy of each supplement. They may be mailed directly to her office at: WO22, Room 2342, 10903 New Hampshire Avenue, Silver Spring, MD 20903.

Let me know if you have any questions. I can be reached directly at 301-796-1393.

Cheers,

Erik S. Laughner, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER
FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 25,2007

From: Erik Laughner, DBOP/OODP/CDER

Subject: Efficacy Supplement 103792/5187 and 5189 First Committee Meeting

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This joint first committee meeting for efficacy supplements 103792/5187 and 5189 was a face-to-face, internal, FDA meeting. Attendees included Patricia Keegan, Erik Laughner, Hong Zhao, Yuan Li-Shen, Katherine Fedenko, Karen Jones, and Patricia Cortazar.

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sBLA 103792/5187 and 5189
Herceptin (Trastuzumab)
First Committee Meeting Agenda
07/25/07

TWO SUPPLEMENTS TO BE REVIEWED TOGETHER FROM DATA DERIVED FROM BCIRG PHASE III STUDY

User Fees Paid for both Supplements on June 11, 2007

103792/5187: Submitted on June 28, 2007
Received on June 29, 2007

HERCEPTIN WITH DOXORUBICIN, CYCLOPHOSPHAMIDE, AND DOCETAXEL FOR ADJUVANT TREATMENT OF HER2 OVEREXPRESSING NODE-POSITIVE OR HIGH RISK NODE-NEGATIVE BREAST CANCER

103792/5189: Submitted on June 29, 2007
Received on July 5, 2007 (delay of receipt b/c of FDA electronic loading issues?)

HERCEPTIN WITH DOCETAXEL AND CARBOPLATIN FOR ADJUVANT TREATMENT OF HER2 OVEREXPRESSING NODE-POSITIVE OR HIGH RISK NODE-NEGATIVE BREAST CANCER

Review Team:

Erik Laughner, Regulatory Project Manager
Katherine Fedenko, Clinical Analyst/Clinical Reviewer (which supplement to review?)

Patricia Cortazar, Clinical Reviewer
Wendy Weinberg, Product Reviewer (needed?)
Angela Men, Clinical Pharmacology Reviewer
Yuan Li Shen, Statistical Reviewer

Items to be covered:

1. General Comments/Milestones for Applications Received (assuming 10 month standard clock and joint review of both supplements, action dates therefore based on earliest supplement):

   First Committee Meeting: Completed Today
   Filing Action: August 28, 2007
   Deficiencies Identified Letter (74 day letter) : September 11, 2007
   Action Letter: April 28, 2007 (for STN 103792/5187)

   Discussion: Kathy Fedenko will be lead on 5187 supplement and Patricia Cortazar will lead on 5189 supplement. Until issues arise, supplements will be reviewed together (including labeling). Patricia Cortazar needs access to RMS-BLA.

2. ODAC- Will go to ODAC?

   Discussion: No

3. Consults required for this application?

   a. Will DSI Inspections be required?

      Discussion: probably no need for DSI inspections.

   b. Would you like to request a formal consult for OSE reviewer (Bob Pratt manages Herceptin)? Do we have specific questions for OSE?

      Discussion: No need for OSE reviewer as just finished Hera approval

   c. SEALD consults will be requested will be invited to the Filing and Mid-Cycle meeting and will be invited to all Labeling Meetings as they are scheduled.

      Discussion: Also request DDMAC consult.

4. Discuss any issues that have been identified during the review to date or need to request additional information:

   a. CMC

      Discussion: Need to confirm source information for Herceptin material used in the supporting trials. CMC will do categorical exclusion.

   b. Clinical

Discussion: Request Sponsor to map our raw text terms to MEDRA.

c. Statistical

d. Clinical Pharmacology

Discussion: No clinical pharmacology in supplement, so no PK reviewer needed.

5. Any other issues related to this application that requires discussion?

Discussion: None.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 05/05/08

From: Erik Laughner, DBOP/OODP/CDER

Subject: Internal Memo regarding 041807 pre-sBLA meeting STN 103792 (BCIRG)

FDA did not generate minutes to this meeting. FDA edited Genentech's provided minutes.