CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5311

MEDICAL REVIEW(S)

Office of Hematology and Oncology Products
Division of Oncology Products 1

Supplemental BLA Containing Final Study Report in Fulfillment of Postmarketing Commitments #1 and #3

BLA Number: 103792
Supplement Number: 5311

Letter Date: November 25, 2013
Stamp Date: November 26, 2013
PDUFA Goal Date: May 28, 2014
Target Action Date: February 28, 2014

Clinical Reviewer: Julia A. Beaver, M.D.
Statistical Reviewer: Erik Bloomquist
Clinical Team Leader: Patricia Cortazar, M.D.
Review Completion Date: February 25, 2014

Established Name: Herceptin® (Trastuzumab)
Therapeutic Class: HER2 Monoclonal Antibody
Applicant: Genentech, Inc.

Dosing Regimen Adjuvant Treatment of HER2-Overexpressing Breast Cancer: "Initial dose of 4mg/kg over 90 minute IV infusion, then 2mg/kg over (b) (4) minute IV infusion weekly for 52 weeks. Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30-90 minutes IV infusion every three weeks for 52 weeks."

This sBLA incorporates the weekly dosing regimen.

Indication for Adjuvant Breast Cancer: "Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; with docetaxel and carboplatin; or as a single agent following multi-modality anthracycline based therapy."

This sBLA application addresses the adjuvant indication as part of a treatment regimen consisting of doxorubicin, cyclophosphamide and paclitaxel.

1. Summary

Herceptin is a HER2/neu receptor antagonist indicated for:

- the treatment of HER2 overexpressing breast cancer
- the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma

On November 16, 2006, Genentech's supplemental BLA (STN: BLA 103792/51500) was approved for the use of Herceptin® as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the treatment of patients with HER2-overexpressing, node-positive or high risk node-negative breast cancer. This approval in the adjuvant setting was based on the Disease-Free Survival (DFS) results from the joint analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study B-31 and the North Central Cancer Treatment Group (NCCTG) Study N9831.

The current submission addresses the following Postmarketing Commitments (PMCs) which are subject to reporting of 21 CFR 601.70:

PMC# 1: To provide a final study report at the time of the final analysis of overall survival (analysis based on 710 deaths) in accordance with the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The final study report should include the primary datasets and programs for generation of analyses and all subset analyses for the final analysis of overall survival and an updated analysis of disease-free survival, including exploratory analyses in subgroups based on the timing and type of hormonal treatment administered to patients.

PMC#3: To provide interim cardiac safety updates on an annual basis beginning on 30 September 2006, as the first cutoff date and ending with a final comprehensive cardiac safety analysis report submitted by 30 September 2012. Each annual cardiac safety update will include a detailed narrative summary of each new clinical event with associated radiologic reports and laboratory findings for all patients enrolled as of the termination of study enrollment in April 2005. The first annual cardiac safety update will be submitted by 28 April 2007. The final comprehensive cardiac safety analysis will be included in the final study report based on 710 deaths. In addition, the final comprehensive study report will contain primary datasets for the intent-to-treat (ITT) population and summary analyses that include, but are not limited to, the analyses described in the statistical analysis plan of April 2005.

This joint clinical and statistical review addresses the updated efficacy from the protocol-specified preplanned final Overall Survival (OS) analysis and the final cardiac safety analysis of results from Studies NSABP B31 and NCCTG N9831 in fulfillment of PMCs #1 and #3. This review also includes the proposed labeling changes. Genentech submitted the updated datasets with a final analysis of OS, an updated analysis of DFS and a final and comprehensive cardiac safety analysis. In fulfillment of PMC #1, Genentech submitted datasets from studies NSABP B-31 and NCCTG N9831 for the final analysis of overall survival and updated analysis of disease-free survival. In fulfillment of PMC #3, Genentech submitted final cardiac safety analysis of results from studies NSABP B-31 and NCCTG N9831.

2. Recommendation on Regulatory Action

We agree with Genentech's assessment of efficacy and safety. The 8.3-year follow-up data from the joint NSABP B-31 and NCCTG N9831 analysis contained in this study report represents the final efficacy and safety update mandated by the Subpart H postmarketing commitments #1 and #3. The efficacy results with mature OS continue to support the superiority of trastuzumab therapy in the adjuvant setting with no new safety signals. At 8.3 years of median follow-up [AC→TH], the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74) and the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm. The final OS analysis results indicate that the OS benefit was consistent across several subgroups (age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy).

We recommend fulfillment of both PMCs #1 and #3. FDA will update the label accordingly (see Section 4). Herceptin continues to demonstrate a positive risk-benefit for the adjuvant treatment of HER2 overexpressing breast cancer with respect to cardiovascular and other toxicities weighed against a clinically meaningful and significant DFS and OS benefit.

3. Clinical Studies

This application jointly analyzed two randomized Phase 3 studies: The National Surgical Adjuvant Breast and Bowel Cancer Project (NSABP) Study B-31 and the North Central Cancer Treatment Group (NCCTG) Study N9831. There were extensive discussions on the plan for a combined analysis of data from the two studies in order to get an earlier assessment of the efficacy of Herceptin for adjuvant treatment, and the FDA agreed with this joint analysis plan prior to the first planned analysis of either study. The studies were considered amenable for a joint analysis given that both contained comparable control and treatment arms and although the population in the studies differed slightly, both high-risk node-negative and node-positive patients are of high risk of recurrence and death. These two studies both incorporated chemotherapy regimens, Arm 1 of NSABP B-31 and Arm A of NCCTG N9831, of doxorubicin/cyclophosphamide (AC) followed by paclitaxel (T) (with slight frequency and dosing variations of the paclitaxel regimen) as the control regimen (AC→T). Both studies also contained arms, Arm 2 of NSABP B-31 and Arm C of NCCTG N9831, with Herceptin for one year beginning with T after AC treatment, (AC→TH). Thus Arm 1 and Arm A, and Arm 2 and Arm C from the two studies were combined for this analysis. Arm B (sequential therapy) from the NCCTG N9831 trial was not included because this treatment arm was not comparable to the treatment arms included in Study NSABP B31 and it would have been invalid to pool and analyze this data.

In both studies, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization or was required to be performed at a reference laboratory. The ITT population from the joint study population included 4063 patients at the protocol-specified final overall survival analysis; 2031 patients received Herceptin with median treatment duration of 51 weeks. Similar demographic and baseline characteristics were reported. The median age was 49 years (range 24-80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian. The primary endpoint of the joint analysis of the studies was DFS and safety with a secondary endpoint of OS. DFS was measured from the time of randomization until recurrence of local, regional, or

distant breast cancer, development of a contralateral breast cancer or other second primary cancer, or death from any cause. Patients who did not experience any DFS events were censored at the time of their last visit. OS was measured from the time of randomization until death from any cause. Patients not reported as deceased were censored at the time of their last visit. The joint study was set to have a final OS analysis at a protocol-specified number of deaths that occurred on June 30th, 2012 with 707 deaths.

3.1 NSABP B-31:

NSABP B-31 is entitled "A Randomized Trial Comparing the Safety and Efficacy of Adriamycin (doxorubicin) and Cyclophosphamide Followed by Taxol (paclitaxel),(AC→T), to that of Adriamycin and Cyclophosphamide Followed by Taxol Plus Herceptin, (AC→TH), in Node-Positive Breast Cancer Patients Who Have Tumors that Overexpress HER2". NSABP B-31 was a randomized open-label Phase 3 multicenter study conducted in the United States (US) and Canada, which enrolled 2119 node-positive, HER2+, early breast cancer patients. Patients were stratified by the number of positive nodes (1-3, 4-9, 10+), planned hormonal therapy (tamoxifen, anastrozole, neither), surgery/radiation therapy, institution, and intended frequency of paclitaxel administration. Patients were randomized 1:1 to receive four 21-day cycles of Doxorubicin 60mg/m2 IV concurrently with Cyclophosphamide 600mg/m2 on Day 1 followed by:

Arm 1: Paclitaxel 175 mg/m^2 for four cycles (3 weeks per cycle) or 80mg/m^2 for 12 cycles (1 week per cycle) as selected by the investigator prior to randomization.

Arm 2: Paclitaxel according to one of the above regimens concurrently with Herceptin loading dose (given on same day as first paclitaxel dose) at 4mg/kg followed by 2mg/kg IV to complete 52 weeks.

Patients completed chemotherapy and went on to complete appropriate radiation therapy as indicated. Patients with ER+ and/or PR+ tumors received tamoxifen or an aromatase inhibitor. In some cases patients continued on to receive an aromatase inhibitor after tamoxifen therapy.

3.2 NCCTG N9831:

NCCTG N9831 is entitled "Phase III Trial of Doxorubicin and Cyclophosphamide (AC) Followed by Weekly Paclitaxel with or without Trastuzumab as Adjuvant Treatment for Women with HER-2 Over-expressing or Amplified Node Positive or High-Risk Node Negative Breast Cancer." NCCTG N9831 was a randomized open-label Phase 3 multicenter study of AC→T vs. AC→TH in a population of node-positive or high-risk node-negative HER2+ early breast cancer patients conducted in the US, Canada and multiple other countries. High-risk node-negative disease was defined as a tumor size of >1cm with estrogen receptor (ER) and progesterone receptor (PR) negativity, or a tumor size >2cm regardless of hormone receptor status. Patients were stratified by cooperative group, nodal status, and receptor status. A total of 1944 patients were randomized 1:1:1 to receive four cycles of doxorubicin at 60mg/m^2 IV concurrently with cyclophosphamide at 600mg/m^2 IV on Day 1 every 21 days followed by one of three regimens:

Arm A: Paclitaxel 80mg/m^2 for 12 weeks given weekly.

Arm B: Paclitaxel 80mg/m^2 for 12 weeks given weekly followed by Herceptin weekly with a loading dose at 4mg/kg followed by 2mg/kg IV to complete 52 weeks.

Arm C: Paclitaxel 80mg/m^2 for 12 weeks given concurrently with Herceptin IV. Herceptin loading dose (given on same day as first paclitaxel dose) given at 4mg/kg followed by 2mg/kg IV to complete 52 weeks.

Arm B of this study was excluded from the joint analysis. Patients completed chemotherapy and went on to complete appropriate radiation therapy as indicated. Patients with ER+ and/or PR+ tumors received tamoxifen or an aromatase inhibitor. In some cases patients continued on to receive an aromatase inhibitor after tamoxifen therapy.

3.3 Summary of Efficacy Findings

3.3.1 2.0 Years of Median Follow-up:

NSABP B-31/NCCTG N9831:

The joint analysis demonstrated that the addition of Herceptin to adjuvant chemotherapy had a statistically significant improvement in DFS at 2.0 years of follow up. The ITT population included 3752 patients; 1872 patients received Herceptin and 133 (7.1%) experienced a DFS event compared to 261 (13.9%) of the 1880 patients not receiving Herceptin. The hazard ratio for the addition of Herceptin to chemotherapy relative to chemotherapy alone was 0.48 (95% CI 0.39, 0.59; $p<0.0001$). OS analysis at this time was not mature, as not enough OS events occurred. These DFS results supported the initial approval of Herceptin in the adjuvant setting.

3.3.2 8.3 Years of Median Follow-up:

NSABP B-31/NCCTG N9831:

The joint efficacy (ITT) population had a median duration of follow-up of 7.9 years (range: 0-12.2) for the control chemotherapy arm and 8.3 years (range 0.1-12.1) for the Herceptin containing arm.

Disease Free Survival:

The applicant submitted updated DFS data and demonstrated that at 8.3 years of median follow-up 1161 patients in the ITT population experienced a DFS event, 479 from the Herceptin arm and 682 from the control arm. Of note 24.8% of patients in the chemotherapy alone arm crossed over to receive some Herceptin. The hazard ratio for the Herceptin containing arm compared to the chemotherapy alone arm was 0.61 (95% CI 0.54, 0.69; log-rank p-value <0.0001). These results are consistent with the DFS findings at 2.0 years of median follow-up and remain statistically significant in demonstrating a benefit of the addition of Herceptin to the chemotherapy regimen in this setting. Table 1 summarizes DFS results. An absolute benefit of 11.2% (95% CI 8.3%, 14.2 %) was demonstrated with the DFS estimated at 74.2% in the AC→TH arm and 62.9% in the AC→T arm.

Table 1: 8.3-year efficacy DFS data (Applicant's Table)

	AC→T (n=2032)	AC→T + H (n=2031)
Patients with an event [a]	682 (33.6%)	479 (23.6%)
Distant recurrence	415	239
Local/regional recurrence	124	86
Contralateral breast cancer	43	45
Other second primary cancer	71	70
Death NED	29	39
Patients without an event	1350 (66.4%)	1552 (76.4%)
Stratified analysis		
Hazard ratio [b]	0.61	
95% CI	(0.54, 0.69)	
p-value (log-rank)	< 0.0001	
Events per 1000 woman years (95% CI)		
Entire study	52 (48, 56)	32 (29, 35)
Year 2	99 (85,115)	52 (42, 63)
Year 4	55 (44, 68)	31 (23, 40)
Year 6	39 (29, 51)	22 (15, 30)
Year 8	31 (21, 44)	32 (23, 44)
Year 10	22 (10, 42)	24 (13, 41)

A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; NED=no evidence of disease; T=paclitaxel.

[a] Earliest contributing event.

[b] Relative to the chemotherapy-alone arm. Estimated by Cox regression stratified by study, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

Survival:

The applicant submitted OS survival data for the joint analyses of NSABP B-31 and NCCTG N9831. OS was a secondary endpoint for the joint analysis and at the time of the initial DFS data at 2.0-year follow up was not yet mature. At the time of the current analysis with a follow-up of 8.3 years, there were 707 deaths with 289 deaths in the AC→TH arm and 418 deaths in the AC→T arm. The hazard ratio for Herceptin arm relative to the chemotherapy alone arm was 0.64 (95% CI 0.55, 0.74; p<0.0001). At 8.3 years of follow-up the OS rate was estimated to be 86.9% in the Herceptin arm and 79.4% in the chemotherapy alone arm yielding an absolute benefit of 7.4% (95% CI 4.9%, 10%). Table 2 and Figure 1 summarize the OS joint analysis results.

Multiple subgroup analyses were performed with respect to demographics, tumor characteristics, and additional treatment. In general, the OS benefit of the Herceptin containing arm was preserved across all subgroups. Table 3 shows subgroups of interest. Additional analyses examining HER2 overexpression/amplification by immunohistochemistry and FISH are also shown in Table 3.

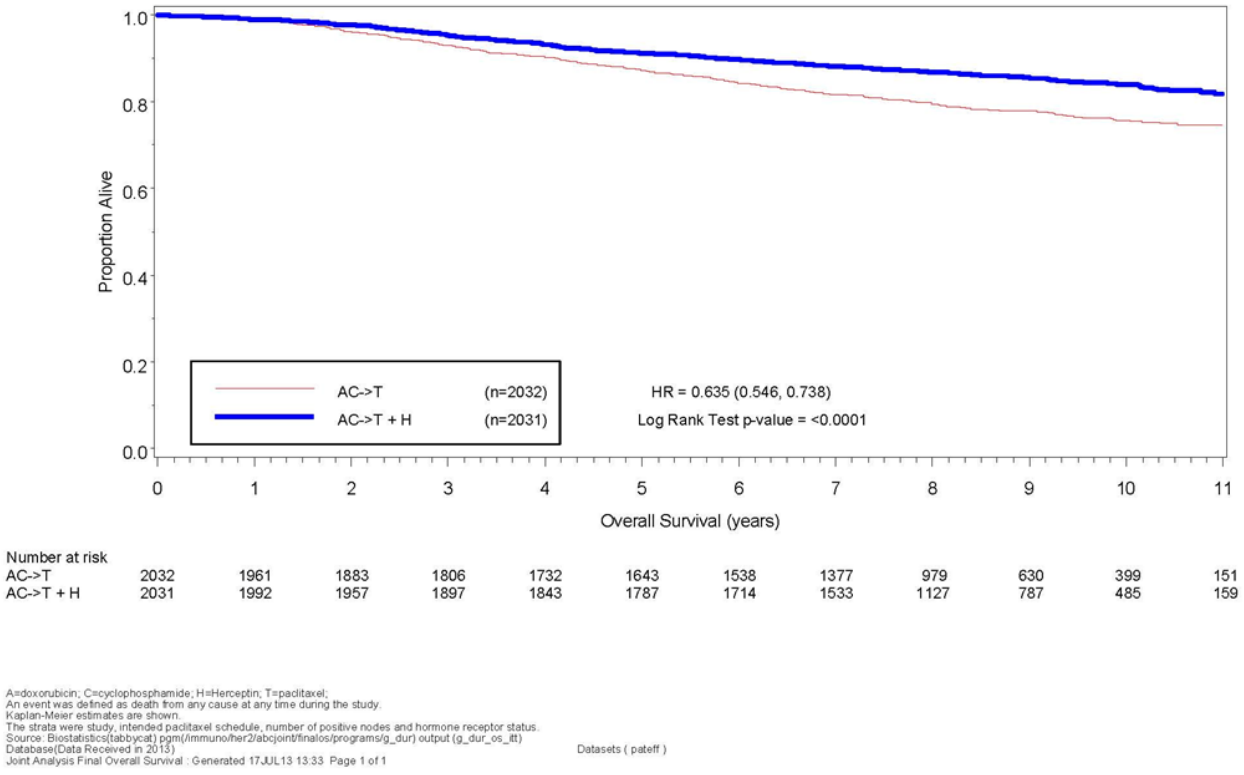
Table 2: 8.3-year efficacy OS data (Applicant's Table)

	AC→T (n=2032)	AC→T+H (n=2031)
Patients who died	418 (20.6%)	289 (14.2%)
Patients alive	1614 (79.4%)	1742 (85.8%)
Stratified analysis		
Hazard ratio [a]	0.635	
95% CI	(0.546, 0.738)	
p-value (log-rank)	< 0.0001	
Deaths per 1000 woman years (95% CI)		
Entire study	28 (25, 30)	18 (16, 20)
Year 2	31 (24, 40)	13 (8, 19)
Year 4	29 (22, 39)	22 (16, 30)
Year 6	35 (26, 46)	17 (11, 24)
Year 8	26 (18, 37)	14 (9, 22)
Year 10	28 (15, 47)	20 (10, 34)

A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; T=paclitaxel.

[a] Relative to the chemotherapy-alone arm. Estimated by Cox regression stratified by study, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

Figure 1: Duration of Overall Survival (Applicant's Figure)



A=doxorubicin; C=cyclophosphamide; H=Herceptin; T=paclitaxel;
An event was defined as death from any cause at any time during the study.
Kaplan-Meier estimates are shown.
The strata were study, intended paclitaxel schedule, number of positive nodes and hormone receptor status.
Source: Biostatistics(tabbycat) pgm(/immuno/her2/abcjoint/finalos/programs/g_dur) output (g_dur_os_itt)
Database(Data Received in 2013)
Joint Analysis Final Overall Survival : Generated 17JUL13 13:33 Page 1 of 1
Datasets (pateff)

Table 3: Overall Survival by Demographic and Tumor Characteristics (Applicant's Table):

Baseline Characteristics	AC→T Total n	AC→T Patients with an Event n	AC→T Events/ 1000 Women Years	AC→T+H Total n	AC→T+H Patients with an Event n	AC→T+H Events/ 1000 Women Years	Hazard Ratio	(95% CI)
Age at randomization (1)								
<= 50	1094	201	25	1103	143	16	0.65	(0.52, 0.81)
> 50	938	217	31	928	146	20	0.63	(0.51, 0.78)
Age at randomization (2)								
<= 39	334	65	26	322	45	17	0.66	(0.45, 0.97)
40-49	685	122	24	699	88	16	0.66	(0.50, 0.87)
50-59	664	127	25	653	91	17	0.69	(0.53, 0.91)
> 59	329	104	45	357	65	23	0.51	(0.37, 0.69)
Age at randomization (3)								
<= 65	1908	379	27	1890	256	17	0.63	(0.54, 0.74)
> 65	124	39	45	141	33	31	0.71	(0.45, 1.14)
Race/ethnicity								
Asian/Pacific Islander	73	16	33	82	7	10	0.36	(0.16, 0.94)
Black	150	28	25	147	21	18	0.69	(0.39, 1.23)
Hispanic	86	22	38	73	7	13	0.35	(0.15, 0.82)
White	1700	345	27	1694	252	19	0.68	(0.58, 0.80)
Other	17	4	32	23	1	5	0.18	(0.02, 1.76)

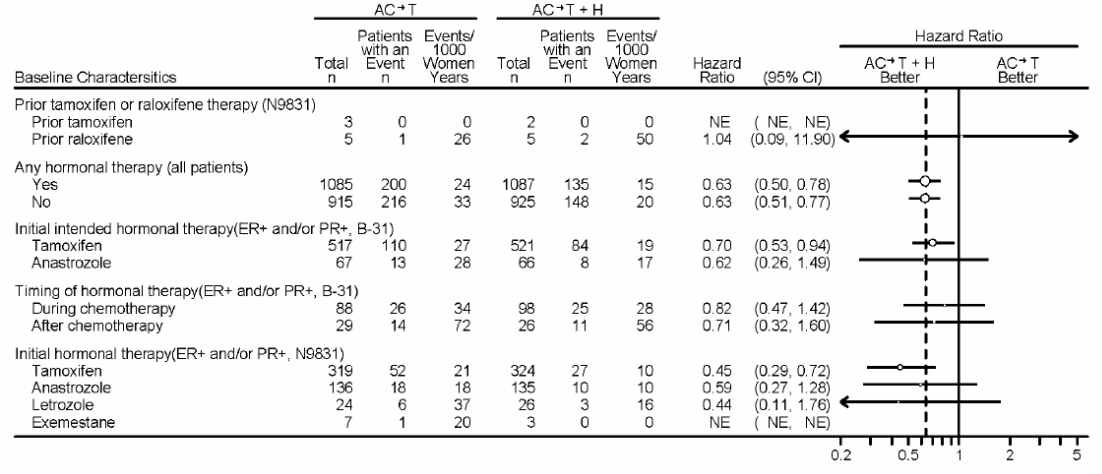
Hazard Ratio: AC→T+H Better / AC→T Better; 0.2, 0.5, 1, 2, 5

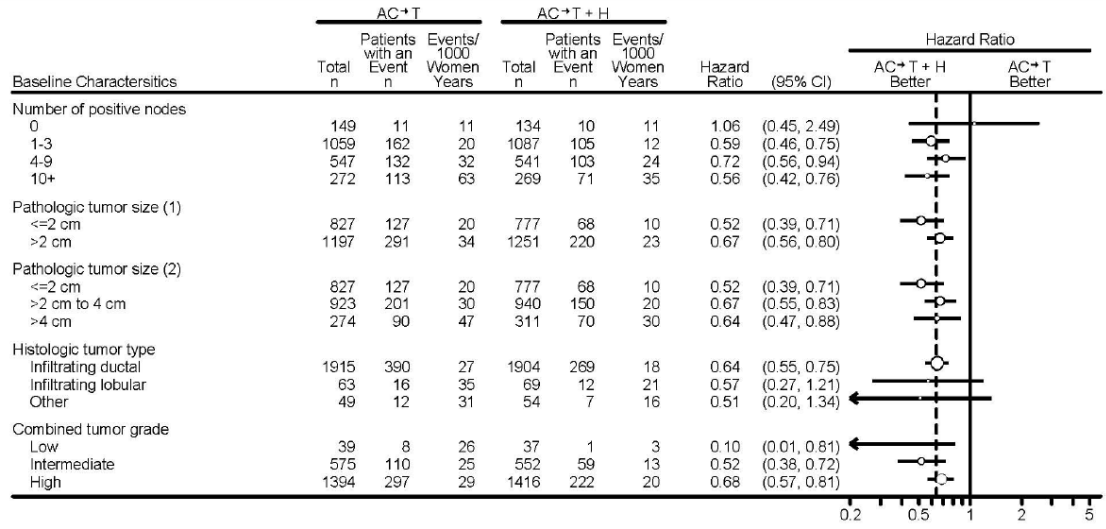
Baseline Characteristics	AC→T Total n	AC→T Patients with an Event n	AC→T Events/ 1000 Women Years	AC→T+H Total n	AC→T+H Patients with an Event n	AC→T+H Events/ 1000 Women Years	Hazard Ratio	(95% CI)
Country of residence								
Canada	42	8	27	42	9	31	1.06	(0.40, 2.82)
USA	1978	408	28	1982	277	17	0.62	(0.54, 0.73)
Other	12	2	24	7	3	75	2.23	(0.37, 13.36)
Performance Status (B-31)								
0 - Karnofsky 90-100	979	222	30	990	155	19	0.64	(0.52, 0.78)
1 - Karnofsky 70-80	82	26	46	67	10	19	0.42	(0.20, 0.87)
2+- Karnofsky <= 60	0	0	0	1	1	102	NE	(NE, NE)
Menopausal status (N9831)								
Premenopausal	434	63	20	413	46	14	0.70	(0.48, 1.03)
Postmenopausal	275	54	28	253	36	18	0.66	(0.43, 1.00)
Other, < 50 years	91	10	15	94	11	16	1.03	(0.44, 2.43)
Other, >= 50 years	171	43	36	213	30	19	0.52	(0.33, 0.83)
Enrollment period (N9831)								
Enrolled before Arm C closed	279	61	26	278	52	20	0.78	(0.54, 1.13)
Enrolled after Arm C reopened	692	109	23	695	71	14	0.61	(0.45, 0.82)

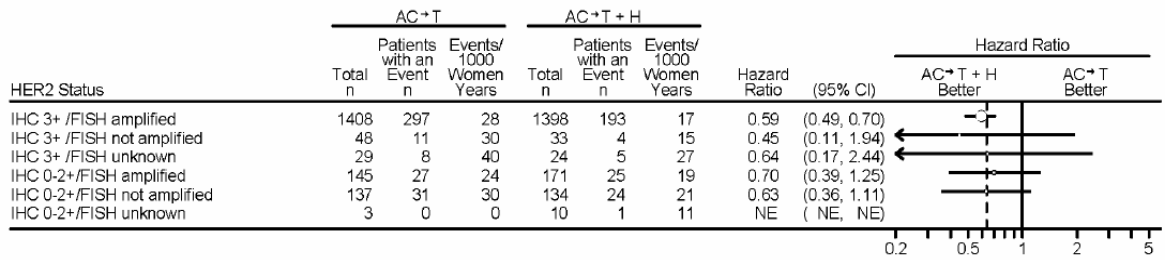
Hazard Ratio: AC→T+H Better / AC→T Better; 0.2, 0.5, 1, 2, 5

Baseline Characteristics	AC→T Total n	AC→T Patients with an Event n	AC→T Events/ 1000 Women Years	AC→T+H Total n	AC→T+H Patients with an Event n	AC→T+H Events/ 1000 Women Years	Hazard Ratio	(95% CI)
Estrogen receptor status								
ER+	1057	192	24	1040	130	15	0.63	(0.51, 0.79)
ER-	969	226	32	990	159	21	0.64	(0.52, 0.78)
Progesterone receptor status								
PR+	813	140	22	784	94	14	0.64	(0.49, 0.83)
PR-	1210	277	32	1242	194	20	0.63	(0.52, 0.76)
Hormone receptor status								
ER+ and/or PR+	1111	206	24	1112	140	15	0.63	(0.51, 0.78)
ER- and PR-	914	212	32	918	148	21	0.64	(0.52, 0.80)
ER+ and PR-	296	65	30	326	46	18	0.59	(0.40, 0.86)
ER- and PR+	54	14	35	72	10	17	0.49	(0.21, 1.11)
Surgery/radiation therapy								
Lumpectomy+radiation therapy	740	120	21	736	76	12	0.59	(0.44, 0.79)
Mastectomy w/o radiation therapy	465	82	23	479	57	15	0.63	(0.45, 0.88)
Mastectomy+radiation therapy	709	191	36	737	135	23	0.63	(0.51, 0.79)
Lumpectomy, radiation therapy unknown	37	8	45	25	5	42	0.94	(0.31, 2.87)
Mastectomy, radiation therapy unknown	66	15	54	43	14	68	1.24	(0.60, 2.58)
Pathologic node positive								
Yes (all patients)	1878	407	29	1897	279	18	0.63	(0.54, 0.73)
Yes (N9831)	822	159	27	839	113	17	0.64	(0.50, 0.82)
No (N9831)	149	11	11	134	10	11	1.06	(0.45, 2.49)

Hazard Ratio: AC→T+H Better / AC→T Better; 0.2, 0.5, 1, 2, 5







A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; t=paclitaxel; NE=not estimable.
Dashed line represents hazard ratio for OS for all patients in the ITT Population.
An event was defined as death from any cause.
Hazard ratio was estimated by Cox regression stratified by Study and intended paclitaxel schedule.

Reviewer Comments:

DFS in the Herceptin arm was statistically superior to the control chemotherapy arm at 8.3 years of median follow-up. These results are consistent with the 2.0 years of median follow-up efficacy data. FDA verified the DFS results with the applicant's submitted datasets using a stratified log-rank test. The absolute benefit of improvement in DFS of 11.8% (95% CI 8.9%, 14.6%) is clinically meaningful and statistically significant.

The OS analysis at 8.3 years of median follow-up demonstrates a statistically significant

and clinically meaningful benefit of the addition of Herceptin to chemotherapy. FDA analyzed the efficacy endpoint of OS with the applicant's datasets using a stratified log-rank test in the combined ITT patient population from both studies. FDA agrees with the applicant's updated 8.3 years of follow-up data. Efficacy results of DFS and OS at 2.0 years and 8.3 years of median follow-up as confirmed by FDA are shown in Table 4.

Table 4: Efficacy Results DFS and OS at 2.0 years and 8.3 years of Median Follow-up

Efficacy Endpoint	**AC→T**	**AC→TH**
2.0 Years		
Disease-free survival at 2 yrs	**(n= 1880)**	**(n= 1872)**
Patients with an event	261 (13.9%)	133 (7.1%)
Patients without an event	1619 (86.1%)	1739 (92.9%)
Stratified analysis		
Hazard ratio [a]	0.48	
95% CI	(0.39, 0.59)	
p-value (stratified log rank)	<0.0001	
Overall survival at 2 yrs	**(n= 1880)**	**(n= 1872)**
Patients who died	92 (4.9%)	62 (3.3%)
Patients alive	1788 (95.1%)	1810 (96.7%)
Stratified analysis		
Hazard ratio [a]	0.67	
95% CI		
p-value (log rank)	Non-significant	
8.3 Years		
Disease-free survival at 8 yrs	**(n=2032)**	**(n=2031)**
Patients with an event	682 (33.6%)	479 (23.6%)
Patients without an event	1350 (66.4%)	1552 (76.4%)
Stratified analysis		
Hazard ratio [a]	0.61	
95% CI	(0.54, 0.69)	
p-value (log rank)	<0.0001	
Overall survival at 8 yrs	**(n=2032)**	**(n=2031)**
Patients who died	418 (20.6%)	289 (14.2%)
Patients alive	1614 (79.4%)	1742 (85.8%)
Stratified analysis		
Hazard ratio [a]	0.64	
95% CI	(0.55, 0.74)	
p-value (log rank)	<0.0001	

A= doxorubicin; C= cyclophosphamide; CI= confidence interval; H= Herceptin; T= paclitaxel

[a] Relative to AC→T arm. Estimated by Cox regression stratified by study, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

Across multiple subgroups including tumor characteristics, additional therapies and demographics, the OS benefit of the Herceptin containing arm was preserved. The only exceptions were in cases where the number of events was small. These findings were also

verified with the submitted datasets. Interestingly, even with limited events, there appeared to be a trend towards benefit in HER2 negative populations. Secondary to these findings, cooperative groups have launched trials examining the role of Herceptin in the HER2- population.

3.4 Summary of Safety Findings

Updated safety results indicated no change in the risk profile of Herceptin and are consistent with prior safety reports. Although NSABP B-31 and NCCTG N9831 were analyzed jointly for this supplement, the adverse events (AEs) were recorded differently and thus AE safety data submitted was for individual studies. In addition, patients who received Herceptin at any point for added adjuvant therapy after chemotherapy treatment (regardless of if they were randomized to Arm 1, 2, A, or C) were analyzed as a separate sequential arm (AC→T→H). Table 5 shows an overview of safety.

Table 5: Overview of Safety (Applicant's Table)

	AC→T	AC→T+H	AC→T→H
Any AE [a]			
Study B-31	688/821 (83.8%)	912/1030 (88.5%)	136/170 (80.0%)
Study N9831	292/648 (45.1%)	557/967 (57.6%)	107/187 (57.2%)
Grade ≥3 AEs [a]			
Study B-31	327/821 (39.8%)	447/1030 (43.4%)	49/170 (28.8%)
Study N9831	128/648 (19.8%)	222/967 (23.0%)	42/187 (22.5%)
Grade 5 AEs [a]			
Study B-31	1/821 (0.1%)	1/1030 (0.1%)	0%
Study N9831	1/648 (0.2%)	2/967 (0.2%)	0%
SAE [b]	NA	NA	NA
Deaths [c]	353/1462 (24.1%)	255/1994 (12.8%)	30/350 (8.6%)
Withdrawals from treatment due to toxicity	59/1655 (3.6%)	160/2000 (8.0%)	23/364 (8.2%)
Other Significant AEs			
Hematologic toxicities [a]			
Study B-31	136/821 (16.6%)	247/1030 (24.0%)	30/170 (17.6%)
Study N9831	5/648 (0.8%)	18/967 (1.9%)	3/187 (1.6%)
Pulmonary events [a]			
Study B-31	44/821 (5.4%)	147/1030 (14.3%)	14/170 (8.2%)
Study N9831	6/648 (0.9%)	33/967 (3.4%)	4/187 (2.1%)
Thrombosis			
Study B-31	12/821 (1.5%)	27/1030 (2.6%)	0/170 (0%)
Study N9831	22/648 (3.4%)	27/967 (2.8%)	3/187 (1.6%)
Acute toxicities related to radiation therapy (Study N9831 only) [a,d]	417/467 (89.3%)	605/690 (87.7%)	120/136 (88.2%)
Cardiac-related AEs [e]	68/1469 (4.6%)	322/1997 (16.1%)	33/357 (9.2%)
Grade ≥3 cardiac-related AEs	19/1469 (1.3%)	72/1997 (3.6%)	6/357 (1.7%)
Pregnancy [f]	0/1655 (0%)	4/2000 (0.2%)	0/364 (0%)

AE=adverse event; A=doxorubicin; C=cyclophosphamide; H=Herceptin; NA=not applicable; SAE=serious adverse event; T=paclitaxel.

Note: Periods 2–4 is defined as any time following the initiation of paclitaxel therapy.

Mortality:

The primary cause of mortality in all three treatment groups was metastatic breast cancer. The rate of non-breast cancer related deaths counted from the initiation of paclitaxel at 8.3 years of median follow-up were similar among the different treatment arms (3.6% AC→TH, 2.9% AC→T→H, and 4% AC→T). The overall death rates in the different treatment arms demonstrated an improvement in the arms containing Herceptin (12.8% AC→TH, 8.5% AC→T→H, and 25.6% AC→T) with the majority of deaths occurring from metastatic breast cancer.

Adverse Events:

Adverse events (AEs) after the initiation of paclitaxel occurred in 88.5% of patients in the AC→TH group, 80% of the AC→T→H group, and 83.8% of the AC→T group in the NSABP B-31 study. In the NCCTG N9831 study, AEs during this time period occurred in 57.6% in the AC→TH group, 57.2% of the AC→T→H group, and 45.1% of the AC→T group. Neither study specifically assessed if adverse events resulted in study treatment withdrawal or discontinuation. In addition, neither study assessed AEs as serious or non-serious. Grade $\geq$ 3 AEs occurred in 43.4% and 23% for the AC→TH group, 28.8% and 22.5% for the AC→T→H group, and 39.8% and 19.8% for the AC→T group respectively in the NSABP B-31 and the NCCTG N9831 studies as recorded after the initiation of paclitaxel. AEs in the updated safety analysis were similar with respect to severity and rate to prior safety reports.

Pregnancy:

While the studies did not prospectively collect pregnancy data, there were four reports of pregnancies for patients enrolled in NSABP B-31. Of those four patients, one patient's data is unknown, one electively terminated in the first trimester while on Herceptin, one patient had a healthy baby five years after trastuzumab treatment, and one patient on Herceptin for 6 months was found to have severe oligohydramnios at 23 weeks pregnant and after subsequent cessation of Herceptin delivered a full-term healthy infant.

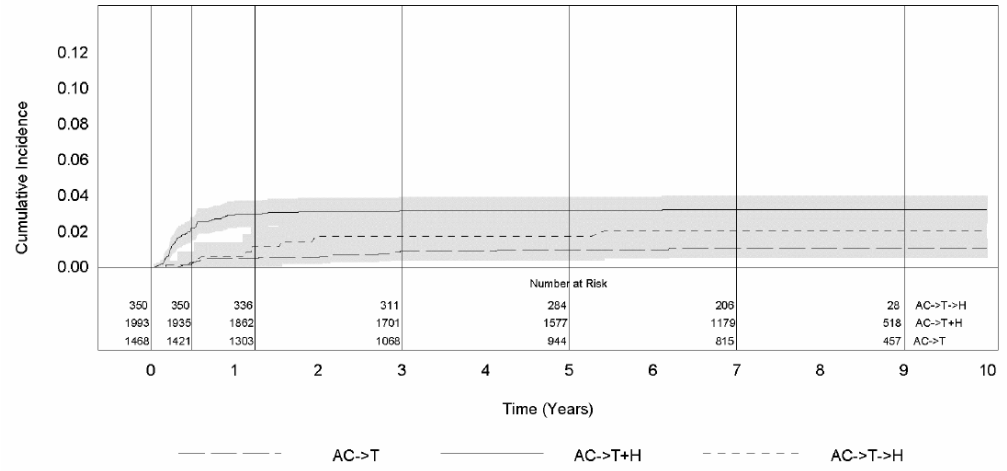
Cardiac Toxicity:

As cardiac toxicity is a known effect of Herceptin, the applicant and FDA placed specific interest on cardiac toxicity data related to symptomatic and asymptomatic left ventricular dysfunction per PMC #3. Overall, cardiac-related adverse events occurred at rates of 16.1% in the AC→TH group, 9.2% in the AC→T→H group, and 4.6% of patients in the AC→T group as recorded after the initiation of paclitaxel. The applicant reported left ventricular dysfunction in 13.1% of patients in the AC→TH group, 7.6% in the AC→T→H group, and 1.9% of patients in the AC→T group during the reporting period beginning with the initiation of paclitaxel. Grade $\geq$ 3 cardiac LV dysfunction occurred in 2.1% of patients in the AC→TH group, 0.8% in the AC→T→H group, and 0.1% of patients in the AC→T group.

Patients who developed symptomatic CHF typically exhibited left ventricular (LVEF) dysfunction reversibility with 64.5% of patients becoming asymptomatic and 90.3% demonstrating partial or full LVEF recovery at time of latest follow-up. 8.5% of patients discontinued Herceptin prior to the completion of the 52 weeks most commonly for decrease in LVEF. The applicant reported that the majority of cardiac events occurred in the first 15 months from initiation of Herceptin therapy as shown in Table 6. After 15 months, the incidence plateaus for all treatment groups. For these reasons, this safety update at 8.3 years did not demonstrate

major changes in the cardiac safety signal of Herceptin.

Table 6: Cumulative Incidence of Time to First Cardiac Event (Applicant's Table):



Deaths from cardiac causes were also reviewed. Patient narratives demonstrated there were seven deaths with cause of death listed as cardiac death, sudden cardiac death, or CHF in the AC→TH group of the combined studies. All but one of these deaths occurred approximately six to ten years after the initiation of Herceptin therapy. This one case occurred during therapy and was clearly related to CHF (Patient ID 2123 in the NCCTG N9831 study). This patient was 33 at the time of her enrollment, had a Left Ventricular Ejection Fraction (EF) of 58% after AC therapy, and was found after approximately ten weeks of Herceptin to have symptoms of CHF with an EF of 10%. She subsequently developed cardiac failure requiring significant medical therapy however approximately eight weeks later died of cardiomyopathy. Autopsy reported the cause of death as related to anthracyline use. Per the applicant's definition of death from cardiac events this single case was the only case in the AC→TH group that met the full definition (death clearly being related to CHF, MI or primary arrhythmia). However, the applicant also included a patient with sudden death presumed cardiac death (Patient ID 710209925 from the NSABP B-31 study) into the cardiac event category bringing the total deaths related to cardiac events in the AC→TH group to two. In the AC→T→H group one patient died a definite cardiac death from myocardial infarction (MI). There was also one death in the AC→T→H group in a patient with unresolved CHF that occurred approximately 2 years 10 months after Herceptin therapy; however, the death was attributed to causes unknown. In the AC→T group there were five deaths from cardiac events.

Reviewer Comments:

The updated results of the safety data with 8.3 years of median follow up were reviewed and do not significantly differ from the safety profile of Herceptin as previously reported in the joint analysis clinical study report and addendum (2/4/2006 and 7/23/2008). FDA reviewed the cardiac death patient narratives and verified the causes as described above. While the percentage of cardiovascular events is increased from prior reports so are the events in the chemotherapy alone arm and the difference remains similar, as does the comparison to other Herceptin cardiac data. FDA also examined and verified the numbers of reversibility of cardiac toxicity after discontinuation of Herceptin and concurred that the majority of events occurred within the first

15 months after Herceptin therapy with most CHF events being reversible.

4. Labeling Changes

In order to reflect the updated safety and efficacy results, FDA and the applicant incorporated changes into the label. As ado-trastuzumab emtansine is now approved, a statement was added in order to draw providers attention to the differences in the drugs. In the Warnings and Precautions section under Cardiomyopathy, updated data from the jointly analyzed studies was added to update the safety information in the label. The Clinical Trial Experience section was also updated to include the new percentage of adverse events according to toxicity; the percentage change in adverse events from the prior label was minimal. Cardiomyopathy information regarding reversibility of left ventricular dysfunction was also added to this Clinical Trial Experience section as described in the review document above. Efficacy information regarding overall survival and subgroup analysis was added to the Clinical Studies section and tables with the new data described above were added.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA A BEAVER
02/25/2014

PATRICIA CORTAZAR
02/25/2014

ERIK W BLOOMQUIST
02/27/2014

SHENGHUI TANG
02/27/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 103792/5311 **Applicant:** Genentech, Inc **Stamp Date:** 11/26/13

Drug Name: Herceptin **NDA/BLA Type:** sBLA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	✓			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?				
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	✓			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	✓			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: NSABP B-31, NCCTG N9831 Sample Size: (b) (4) Arms: Location in submission:	✓			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 NSABP B-31 / NCCTG N9831 Indication: Breast Cancer	✓			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			✓	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			✓	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			✓	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	✓			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			✓	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	✓			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	✓			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			✓	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			✓	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✓	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			✓	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
34.	Are all datasets to support the critical safety analyses available and complete?	✓			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	✓			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			✓	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer	Date 1/23/14
Clinical Team Leader	Date 1/23/14

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA A BEAVER
01/24/2014