s 22

From: s 47F
Sent: Thursday, 2 January 2020 8:55 PM
To: s 22
Cc: s 22
Subject: RE: FW: s 47E [SEC=OFFICIAL]
Attachments: 1342.5 - Draft PSD +technical subsection s 22 docx

HI s 22 ,
Updated PSD looks great – just found one minor typo but otherwise fine.
Other comments below.
s 47F

From: s 22
Sent: Thursday, 2 January 2020 4:17 PM
To: s 47F
Cc: s 22
Subject: RE: FW: s 47E) [SEC=OFFICIAL]

s 47F

Happy New Year to you! I hope you got to celebrate something of New Year's Eve!

I confirm that the PSD has not been shared with the applicant, and won't be shared until it is fully ratified.

Please see the attached version of the PSD for your further review:
s 47E

s 47E s 47C, s 47E

s 47E

Once you are happy with this latest version of the PSD (plus any further modifications from you), I suggest that I circulate it on your behalf for one last opportunity for comment from s 47E s 47F with a time limit of say a week in case s 47E are on leave). s 47E

s 47E

s 22
Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 47F
Sent: Tuesday, 31 December 2019 7:22 PM
To: s 22
Cc: s 22
Subject: RE: FW: s 47E [SEC=OFFICIAL]

Hi s 22
s 47E

s 47F
s 47E
PPS – happy new year to everyone and sorry again that I have been so tardy on this one.

From: s 22
Sent: Monday, 16 December 2019 6:33 PM
To: s 47F
Cc: s 22
Subject: FW: FW: s 47E) [SEC=OFFICIAL]

s 47F

FYI below and attached. s 47C

47
F

s 47G

s 22
Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 47F
Sent: Monday, 16 December 2019 6:25 PM
To: s 22
Cc: s 22
Subject: Re: FW: FW: Request for statistical advice (MSAC) [SEC=OFFICIAL]

Thanks s 22 My responses in red in the attached.

Again, let me know if anything is unclear.

s 47F

On Mon, Dec 9, 2019 at 4:48 AM s 22 wrote:

s 47F

s 47C, s 47E

s 47C, s 47E

Please let me know if I have been unclear in this follow-up email. Otherwise, I look forward to hearing further from you, on I am hoping is a more straightforward request.

Thanks again for all your input. It is greatly appreciated.

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

From: s 47F
Sent: Friday, 6 December 2019 6:27 PM
To: s 22
Cc:
Subject: Re: FW: s 47E [SEC=OFFICIAL]

s 22

s 47E

s 47F

On Fri, Dec 6, 2019 at 8:26 AM s 22 wrote:

s 47F

s 22

s 47E

Thanks again.

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

From: s 47F
Sent: Thursday, 5 December 2019 7:14 PM
To: s 22

Cc: s 22
Subject: Re: FW: s 47E [SEC=OFFICIAL]

Hi s 22

Please find attached my comments. I've appended these to the s 47C - hopefully this makes things easier to follow.

s 22

s 47F

On Thu, Nov 21, 2019 at 11:56 PM Mitchell, s 22 wrote:

s 47F

s 47E

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

From: s 22
Sent: Friday, 15 November 2019 4:10 PM
To: s 47F
Cc: s 22
Subject: s 47E) [SEC=OFFICIAL]

s 47F

s 22

I am attaching:

- Draft minutes/Public Summary Document (PSD) of MSAC's most recent consideration of Oncotype DX, with heavy reliance on TAILORx s 47E
- The 2018 primary publication of TAILORx
- The supplementary analyses to this publication
- A 2019 secondary publication from TAILORx also referred to by MSAC

s 47E

s 47C

I trust that these arrangements are all satisfactory for you. Please let me know if you have any concerns.

s 22

s 47E

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

From: s 47F
Sent: Wednesday, 13 November 2019 8:33 AM
To: s 22
Cc: s 22
Subject: s 47E) [SEC=OFFICIAL]

Thanks s 22 . s 47E . s 22

s 47F

On Tue, Nov 12, 2019 at 9:06 AM s 22 wrote:

s 47F

s 47E

s 47E

Thanks again.

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

From: s 22
Sent: Monday, 11 November 2019 9:54 AM
To: s 47F
Cc: s 22
Subject: s 47E [SEC=OFFICIAL]

s 47F

s 47E

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

From: s 47F
Sent: Saturday, 9 November 2019 8:01 AM
To: s 22
Cc: s 22
Subject: Re: s 47E [SEC=OFFICIAL]

Hi s 22 - great to hear from you!

Happy to help on this one.

Let me know how you want to go about it.

s 47F

On Fri, Nov 8, 2019 at 6:13 AM s 22 wrote:

s 47F

s 22

s 47E

s 47E

s 47G

Please let me know what you think about all this.

Thanks

s 22

Office of HTA/Technology Assessment and Access Division

Department of Health

s 22

GPO Box 9848, Canberra ACT 2601

s 22

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Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1342.5 Gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Applicant: **Specialised Therapeutics Australia Pty Ltd**

Date of MSAC consideration: **MSAC 76th Meeting, 1-2 August 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission seeking public funding for the gene expression profiling (GEP) test using the real-time reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes (Oncotype DX®) in women with newly diagnosed stage I or II breast cancer, who are oestrogen receptor positive (ER-positive) or progesterone receptor positive (PR-positive), Human Epidermal Growth Factor Receptor 2 negative (*HER2*-negative), and lymph node negative (LN-negative), was received from Specialised Therapeutics by the Department of Health.

2. MSAC's advice to the Minister - August 2019

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for this gene expression profiling test for patients with breast cancer primarily because its ability to identify those who could safely be spared the addition of chemotherapy to endocrine therapy was not demonstrated by the new trial. The re-analysis of previously provided evidence was also insufficient to change the previous conclusion that the test could not satisfactorily identify those intermediate-risk patients who would benefit from the addition of chemotherapy to endocrine therapy.

3. Summary of consideration and rationale for MSAC's advice

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

4. Background

The original application (Application 1345) was considered by MSAC at its July 2013 meeting, subsequent resubmissions were then considered in April 2014, November 2015, July 2016 and July 2017. The PSDs for these applications can be viewed on the MSAC website.

At its July 2017 meeting, MSAC did not support Oncotype DX breast cancer assay due to the uncertainty of the incremental benefit of the Oncotype DX breast cancer assay over optimal care (Application 1342.4 Public Summary Document (PSD) 2017, p2). MSAC noted that data from ongoing trials like the TAILORx trial, if suitable, may be useful in addressing this uncertainty (PSD, p3).

5. Prerequisites to implementation of any funding advice

The Oncotype DX Breast Cancer Assay test is performed in a single laboratory in the United States by Genomic Health Inc. Therefore, the test would not be subject to approval or regulation by the Therapeutic Goods Administration (TGA). A November 2015 report by the US Food and Drug Administration (FDA) raised concerns about the current lack of regulation within the US for assays that are 'Laboratory Developed Tests' (LDTs), such as Oncotype DX.

MSAC previously raised concerns about the reliance on a single laboratory performing the test located in the US outside Australian standards maintained through the TGA or the National Association of Testing Authorities (NATA). MSAC also previously noted that a number of complex implementation issues would need to be considered by Government if this test was supported for listing in Australia.

6. Proposal for public funding

The proposal for public funding was changed since the previous resubmission (1342.4), and is presented in Table 2 (applicant-highlighted changes with the previous submission are in red text). The resubmission requested a fee of $5,085 per service, and did not request any confidential pricing or fee arrangement.

Table 2 Proposal for public funding; changes from previous submission annotated (in red)

Gene expression profiling of tumour samples (surgical resection preferably or core biopsy) by reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes in breast cancer tissue.

See Note for information on how results should be interpreted.

Previous submissions did not include a note on how results should be interpreted.

May only be used to test samples from patients with all of the following characteristics as determined by the referring clinician:

- early invasive breast cancer (stages I-II)

No substantial change.

- oestrogen receptor positive or progesterone receptor positive as determined by immunohistochemistry at an approved Australian pathology laboratory

No substantial change.

- HER2 negative as determined by immunohistochemistry and/or in situ hybridisation at an approved Australian pathology laboratory

No substantial change.

- node negative

Previous submissions allowed for node positivity. Public funding no longer requested for node positive patients.

- tumour size >= 10 mm and < 50 mm, or tumour size >= 5 mm and < 10 mm with unfavourable histological features (intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion)

The minimum tumour size of 2 mm has increased to 10 mm (or 5 mm with unfavourable histology).

There was previously no maximum tumour size.

Eligibility was also previously determined by the presence of 1 or 2 negative prognostic risk factors.

- suitable for hormone therapy
- suitable for adjuvant chemotherapy (ECOG performance status 0-2)
- may only be used once per new primary breast cancer

No substantial change.

Fee: $5,085

Note:

Chemotherapy decisions are guided by a patient's Recurrence Score (RS). Patients with RS <26 are recommended endocrine therapy and patients with RS ≥26 are recommended adjuvant chemotherapy according to Oncotype DX. There is some evidence that there may be a chemotherapy benefit in patients aged ≤ 50 years, with RS 16-25.

Previous submissions did not include a note on how results should be interpreted.

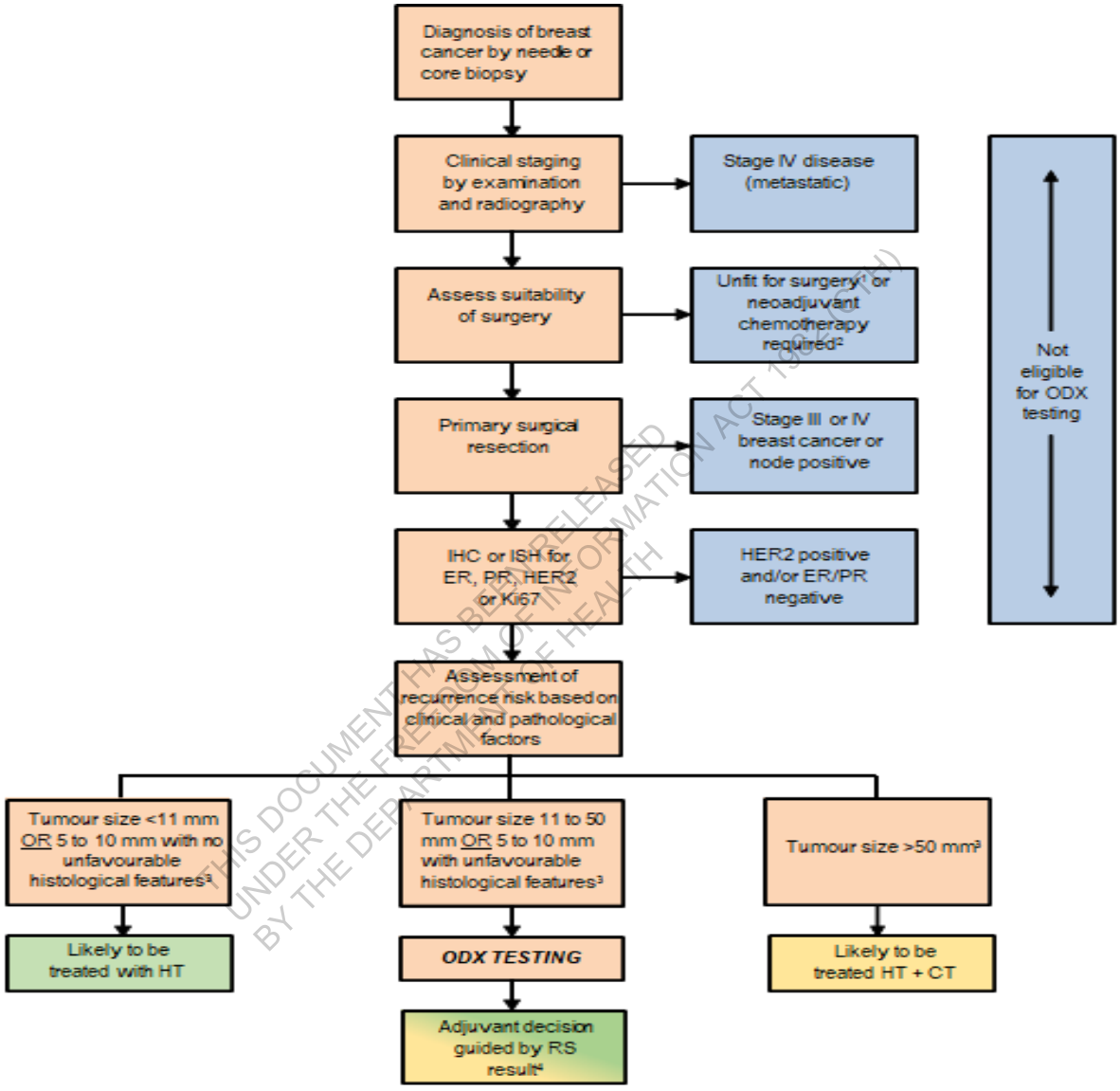
7. Summary of Public Consultation Feedback/Consumer Issues

See Application 1342.4 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

The resubmission's proposed clinical management algorithm (Figure 1) differed from that presented in earlier MSAC applications for Oncotype DX in that it excluded node positive patients, and the process used to exclude patients with very high or low clinical risk was based on the approach applied in TAILORx. In addition, the algorithm included a footnote to clarify how recurrence score (RS) results should be interpreted and used to guide chemotherapy decisions.

Figure 1 Clinical management algorithm for the use of Oncotype DX in Australian clinical practice



[1] ODX is only appropriate for post-surgical patients
[2] Patients who have received neo-adjuvant chemotherapy would continue with chemotherapy and Oncotype DX has not been validated for patients who have undergone neoadjuvant therapy
[3] Tumour size and grade parameters are based on eligibility for the TAILORx trial (Sparano, 2018)
[4] Chemotherapy decisions are guided by a patient's Recurrence Score (RS). Patients with RS<26 are recommended endocrine therapy and patients with RS≥26 are recommended adjuvant chemotherapy according to Oncotype DX; there is some evidence that there may be a chemotherapy benefit in patients aged ≤ 50 years, with RS 16-25.
Abbreviations: CT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HT, hormone therapy; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; ODX, Oncotype DX, RS, Recurrence Score

9. Comparator

The comparator for the resubmission remained the same as that for the previous submissions - usual care. MSAC has previously accepted the comparator as usual care, defined as optimised subjective assessment of various clinical and pathological factors to estimate the risk of recurrence; which are likely combined using formal algorithms.

10. Comparative safety

The resubmission did not present a specific assessment of comparative safety. The Critique stated that the safety concerns remain as those outlined by MSAC previously and quoted in the resubmission. "MSAC previously noted that although the test is procedurally safe because it relies on samples already taken for other purposes, there is a degree of risk in the misallocation of patients to risk categories, which would affect the outcomes of the therapy subsequently selected" (PSD for MSAC Application 1342, November 2013).

11. Comparative effectiveness

The resubmission was based on one prospective randomised trial and one re-analysis of a retrospective cohort study:

- The TAILORx trial was a prospective trial (N=10,273; registered population), that used a patient's recurrence score only to guide treatment. Women with intermediate RS (11-25) were randomised to endocrine therapy (ET) alone or ET+ chemotherapy (CT) (n=6,907; Arms B and C); and those with low (0-10; n=1,629; Arm A) or high (≥26; n=1,737; Arm D) RS were treated with ET alone or ET+CT, respectively (Sparano et al. NEJM, 2018). Results were provided for the 'main analysis set' or 'intention-to-treat (ITT) population' (n=9,719 across all four arms), and some results were also provided for the per protocol population ('as treated population'), which the Critique stated was an important comparison for demonstrating non-inferiority of ET alone vs. ET+CT. In addition, Sparano et al. stated comparisons of ITT population, stratified by randomisation, could still be biased because of differences in the group refusing chemotherapy (Arm C) and the group receiving chemotherapy (Arm B).
- Geyer et al. (2018) was a retrospective re-analysis of the NSABP B-20 study (Fisher et al. 1997; Paik et al. 2006, previously considered by MSAC); a re-analysis of this study based on the recurrence scores used in the TAILORx trial and removing patients who were *HER2*-positive (Geyer et al. 2018).

TAILORx

The Critique presented forest plots for the primary outcome- invasive disease-free survival (iDFS) (Figure 2) and secondary outcome- freedom from recurrence at a distant site or distant recurrence-free interval (DRFI) (Figure 3).

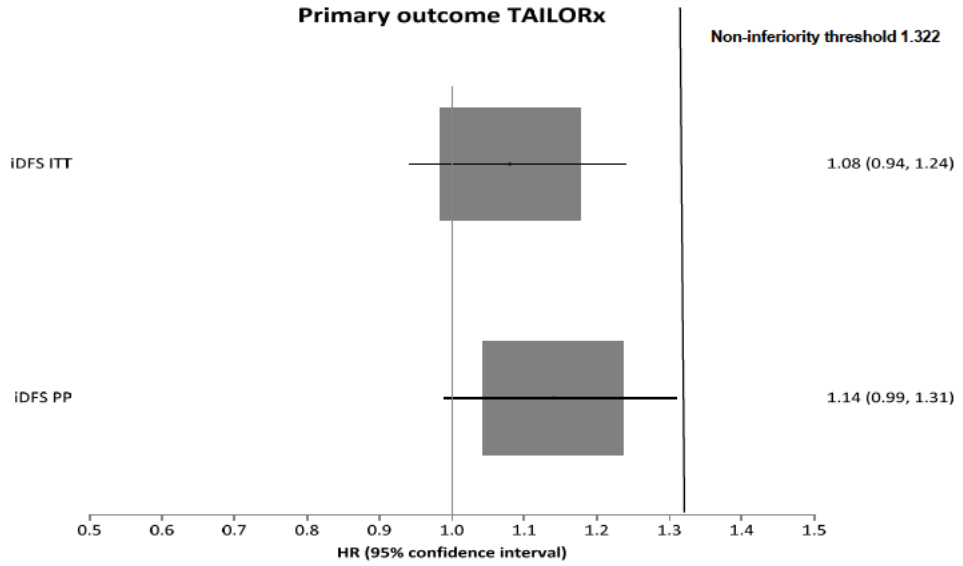


Figure 2 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as-treated' (PP) populations, with the non-inferiority threshold for invasive disease-free survival (iDFS)

The primary analysis to support the claim of no difference between the treatment arms - endocrine therapy alone compared to endocrine therapy plus chemotherapy - met the prespecified non-inferiority threshold. However, the Critique outlined the following issues to consider:

- For the ITT population, the prespecified non-inferiority margin of 32.2% decrease in invasive disease-free survival for endocrine therapy alone compared to endocrine therapy plus chemotherapy appears to be quite large and not supported by the references cited in the trial report.
- Results for the 'as treated' population are close to rejecting the null hypothesis of no difference between the treatment arms.
- The 'as-treated' population baseline characteristics were statistically significantly different for important baseline prognostic variables such as age, menopausal status, tumour size and tumour grade (such that, on average, 'lower risk' women were randomised to ET alone and 'higher' risk women were randomised to ET+CT).
- The non-adherence to assigned therapy in the ET alone arm was 185/3458 = 5% but 608/3449 = 18% in the ET+CT arm, compared to only 89/1737 = 5% in the non-randomised high RS score chemotherapy arm.
- There was a high risk of bias in the trial design.
- There was significant loss to follow up which was deemed not important due to the lower than expected iDFS rate.
- There are four endocrine therapy regimens and nine chemotherapy regimens, which may introduce confounding to the extent that they are not equi-effective.

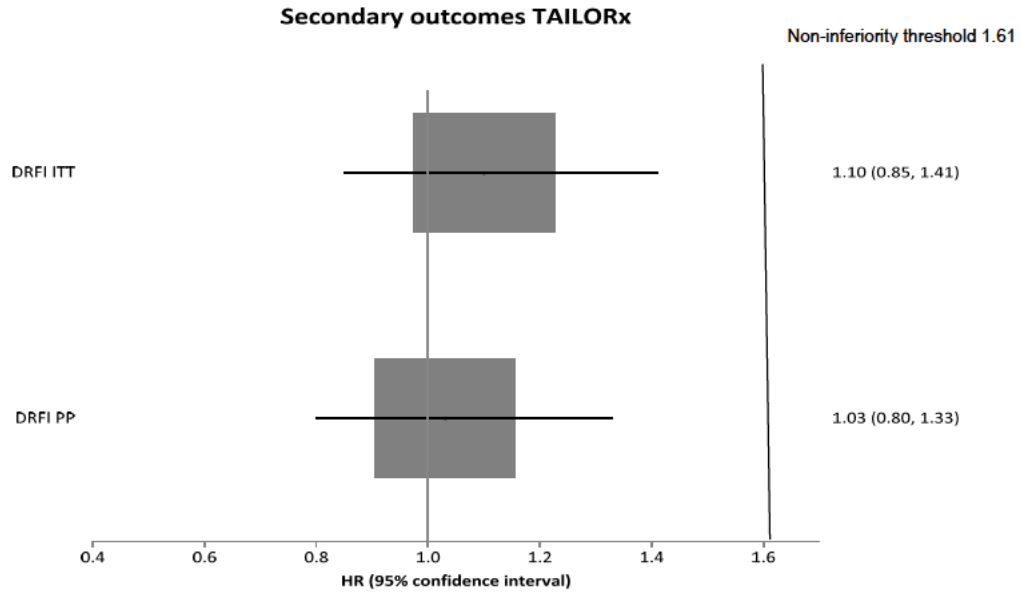


Figure 3 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as treated' (PP) populations with non-inferiority threshold for distant recurrence-free interval (DRFI)

The secondary analysis to support the claim of no difference between the treatment arms - endocrine therapy alone compared to endocrine therapy plus chemotherapy - also met the prespecified non-inferiority threshold. However, the Critique outlined issues to consider:

- For the ITT population, the non-inferiority margin of a 61% decrease in freedom from recurrence at a distant site for endocrine therapy alone compared to endocrine therapy plus chemotherapy appears to be quite large and not supported by the references cited in the trial report.
- Full statistical power to do this comparison was not achieved: the prespecified number of events of 284 was not reached, but only 199 events were recorded.

Table 3 presents the estimated survival rates according to recurrence scores and assigned treatment in the ITT population. The Critique stated that similar issues as identified above for the primary and secondary analyses also occurred; the number of events required for full statistical power was not achieved and the evidence to support the assumptions for the prespecified non-inferiority threshold of 1.46 was not provided in the resubmission or the trial report.

Table 3 Estimated survival rates according to RS and assigned treatment in the ITT population

End point and treatment group	Rate at 5 years (%)±SE	Rate at 9 years (%)±SE
Invasive disease-free survival		
Score of ≤10, endocrine therapy alone	94.0±0.6	84.0±1.3
Score of 11-25, endocrine therapy alone	92.8 ±0.5	83.3±0.9
Score of 11-25, chemotherapy + endocrine therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemotherapy + endocrine therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy alone	99.3±0.2	96.8±0.7
Score of 11-25, endocrine therapy alone	98.0±0.3	94.5±0.5
Score of 11-25, chemotherapy + endocrine therapy	98.2±0.2	95.0±0.5
Score of ≥26, chemotherapy + endocrine therapy	93.0±0.8	86.8±1.7

End point and treatment group	Rate at 5 years (%)±SE	Rate at 9 years (%)±SE
Freedom from recurrence of breast cancer at a distant or local-regional site		
Score of ≤10, endocrine therapy alone	98.8±0.3	95.0±0.8
Score of 11-25, endocrine therapy alone	96.9±0.3	92.2±0.6
Score of 11-25, chemotherapy + endocrine therapy	97.0±0.3	92.9±0.6
Score of ≥26, chemotherapy + endocrine therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, endocrine therapy alone	98.0±0.4	93.7±0.8
Score of 11-25, endocrine therapy alone	98.0±0.2	93.9±0.5
Score of 11-25, chemotherapy + endocrine therapy	98.1±0.2	93.8±0.5
Score of ≥26, chemotherapy + endocrine therapy	95.9±0.6	89.3±1.4

Source: Table 7 of the Critique.

Geyer et al. (2018)

The re-analysis of the Paik et al. (2006) study by Geyer et al. (2018), considering only *HER2*-negative women and applying the 'old' and 'new' RS thresholds applicable for the definition of low, intermediate and high risk of recurrence is presented in Table 4. The Critique stated that the issues previously identified by MSAC about the 2006 Paik 2006 study design remain.

Table 4 HR of adjuvant chemotherapy by RS subgroup, distant recurrence free survival (Geyer et al. 2018)

	N	Effect hazard ratio (95% CI)	P-value
Overall (without *HER2*+ patients)	569	0.59 (0.31, 1.04)	Log rank P=0.06
Original RS subgroup n=569*	569		
Chemotherapy in RS <18	347	1.19 (0.40, 3.49)	
Chemotherapy in RS 18-30	125	0.64 (0.23, 1.75)	
Chemotherapy in RS ≥31	97	0.18 (0.07*, 0.46);*	
Likelihood ratio test on interaction			0.023
TAILORx RS groupings	569		
Chemotherapy in RS ≤10	176	1.19 (0.41, 3.51)	
Chemotherapy in RS 11-25	271	0.61 (0.26, 1.35)	
Chemotherapy in RS >25	122	0.27 (0.12, 0.62)	
Likelihood ratio test on interaction			0.014

Source: Tables 2 & 3 Geyer et al. 2018, Table 42 of the resubmission. Cox proportional Hazards Regression Model adjusted for patient age (>50 years vs ≤50 years), clinical tumour size (>2.0 vs ≤2.0 cm), ER by ligand blinding assay (≥100 vs <100 fmol/mg), PR by ligand blinding assay (≥100 vs <100 fmol/mg), and tumour grade (well differentiated, moderately differentiated and poorly differentiated.

Clinical claim

The Critique summarised the clinical claims in the resubmission:

- A non-inferiority claim, for patients who the Oncotype DX test categorises into the intermediate recurrence group score, that endocrine therapy alone is no worse for the risk of distant recurrence free survival compared to endocrine therapy plus chemotherapy.
- A superiority claim, for patients who the Oncotype DX test categorises into the high recurrence group score, but usual care had determined treatment with endocrine therapy as sufficient, that the addition of chemotherapy would improve their disease free survival, risk of distant recurrence and overall survival.

The non-inferiority claim was based on the results from TAILORx, and the superiority claim was based on retrospective predictive data from the NSABP B-20 study (Paik et al. 2006; Geyer et al. 2018).

12. Economic evaluation

Table 5 summarises the economic evaluation.

Table 5 Summary of the economic evaluation

Perspective	Australian health care system
Comparator	Usual care, as defined by the MINDACT protocol used in TAILORx. Specifically, patients with low clinical risk do not receive adjuvant CT, patients with high clinical risk do receive adjuvant CT
Type of economic evaluation	Cost-utility analysis
Sources of evidence	TAILORx trial to determine allocation of CT in the usual care and Oncotype DX arms of the model NSABP B-20 Geyer et al. (2018) re-analysis to determine benefit of CT in patients who otherwise would not have received it
Time horizon	Lifetime
Outcomes	Life years gained, QALYs
Methods used to generate results	Markov cohort analysis
Health states	Free of disease recurrence • stratified by underlying Oncotype DX RS category and allocation to CT Disease recurrence Breast cancer death Other death
Cycle length	Annual
Discount rate	5% per annum
Software packages used	Microsoft Excel

The Critique stated that the model structure and modelling assumptions overwhelmingly favours Oncotype DX as all instances where Oncotype DX/RS score does not lead to optimal treatment were not considered, therefore the modelled economic evaluation presented is likely the most optimistic (and possibly implausible) scenario. The Critique presented the disaggregated incremental cost and effectiveness for "chemotherapy sparing" (Table 6) and "chemotherapy indicating" (Table 7) components of the model.

Table 6 Summary of disaggregated incremental cost and effectiveness in "chemotherapy sparing" only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,253.65	$3,116.03	-$1,862.38
Endocrine therapy	$3,160.85	$3,160.85	$0.00
Recurrent disease	$5,791.22	$5,791.22	$0.00
Total	**$15,290.72**	**$12,068.10**	**$3,222.62**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.6530**	**13.6530**	**0**
Disease-free	*13.4577*	*13.4577*	*0*
Post recurrence	*0.1953*	*0.1953*	*0*

Parameter	Oncotype DX	Usual care	Incremental
QALY	**13.4621**	**13.4575**	**0.0045**
Disease-free	*13.3066*	*13.3021*	*0.0045*
Post recurrence	*0.1554*	*0.1554*	*0*
		$ per life year gained	**$NA**
		$ per QALY gained	**$711,529**

Text in italics indicate values calculated for the Critique.
Source: 72 p155 of the resubmission; ODX_EconModel.xlsm.
[a] That is, moving any patients with RS ≤25 treated with ET+CT in the usual care arm to ET alone in the Oncotype DX arm.

Table 7 Summary of disaggregated incremental cost and effectiveness in "chemotherapy indicating" only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$3,672.22	$3,116.03	$556.19
Endocrine therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791.22	-$1,040.43
Total	**$16,683.36**	**$12,068.10**	**$4,615.26**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5752**	**13.4575**	**0.1177**
Disease-free	*13.4466*	*13.3021*	*0.1445*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	**$40,660**
		$ per QALY gained	**$39,217**

Text in italics indicate values calculated for the Critique.
Source: 72 p155 of the resubmission; ODX_EconModel.xlsm.
[a] That is, moving any patients with RS ≥26 treated with ET alone in the usual care arm to ET+CT in the Oncotype DX arm.

The overall base case ICER is presented in Table 8 (combining the "chemotherapy sparing" and "chemotherapy indicating" components).

Table 8 Summary of disaggregated incremental cost and effectiveness from base case

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,809.84	$3,116.03	-$1,306.19
Endocrine therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791.22	-$1,040.43
Total	**$14,820.98**	**$12,068.10**	**$2,752.88**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5798**	**13.4575**	**0.1222**
Disease-free	*13.4522*	*13.3021*	*0.1501*

Parameter	Oncotype DX	Usual care	Incremental
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	**$24,253**
		$ per QALY gained	**$22,525**

Text in italics indicate values calculated for the Critique.
Source: Table 69, p153, Tables 70 and 71 p154 of the resubmission; ODX_EconModel.xlsm.

The Critique highlighted that the base case ICER/QALY ($22,525) was driven by the "chemotherapy indicating" component (based on Geyer et al. 2018), contributing more benefit than the "chemotherapy sparing" component (incremental QALYs: 0.1177 *vs*. 0.0045, respectively); considered the "chemotherapy indicating" component was based on weaker evidence base, which MSAC had considered before when previously deciding not to support Oncotype DX.

The Critique's sensitivity analyses showed the modelled results were most sensitive to the effect of chemotherapy on absolute risk of recurrence in RS ≥26 patients and the model duration.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of the Oncotype DX test (Table 9).

Table 9 Net financial impact of Oncotype DX over five years by Commonwealth health budget and patient population

Summary	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)
Patients diagnosed with breast cancer [A]	17,210	17,530	17,850	18,170	18,490
Number of patients eligible for Oncotype DX [B]	4,652	4,739	4,825	4,912	4,998
Number of patients using Oncotype DX testing [C]	1,396	1,896	2,171	2,456	2,749
Total expenditure on Oncotype DX [D]	$6,980,873	$9,480,899	$10,860,713	$12,283,795	$13,750,143
Critique values (removed $83.40 co-pay)	*$6,942,488*	*$9,428,768*	*$10,800,995*	*$12,216,251*	*$13,674,537*
Change in expenditure due to Oncotype DX [E]	-$1,795,774	-$2,438,885	-$2,793,832	-$3,159,908	-$3,537,114
Critique values (removed $83.40 co-pay)	*-$1,640,985*	*-$2,228,663*	*-$2,553,015*	*-$2,887,537*	*-$3,232,229*
Net impact of Oncotype DX on expenditure	**$5,185,099**	**$7,042,014**	**$8,066,882**	**$9,123,887**	**$10,213,029**
Critique values (removed $83.40 co-pay)	***$5,301,503***	***$7,200,104***	***$8,247,980***	***$9,328,715***	***$10,442,308***

[A] AIHW Cancer incidence projections; [B] 27% of [A]; [C] After applying expected uptake rates of 30 to 55%; [D] $5085 per test less patient contribution of $83.40 per test; [E] Savings of $1287 per patient tested due to reduction in chemotherapy.

The Critique stated that sensitivity analysis indicated that the estimates of net cost to the Commonwealth health budget is heavily reliant on the assumed uptake of the Oncotype DX test and also, but to a lesser extent, assumptions around cost offsets to the PBS.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Recurrence Score® (RS) thresholds for categorising low, intermediate and high risk of distant recurrence appear to be arbitrary and subject to change	The RS thresholds were modified in the context of the TAILORx trial. It is not unreasonable to adjust parameters based on additional data, and the new threshold level of 26 appears safe based on the TAILORx and other supporting studies.
Population (as per the eligibility criteria into the TAILORx trial)	The eligible population should be specified as patients with newly diagnosed breast carcinomas; who are ER-positive, *HER*2-negative, lymph node-negative and post-surgical; and who have not received neoadjuvant therapy.
Proposed note defining eligibility for funding should be modified, as it suggests that patients with an RS ≥26 should receive chemotherapy only	TAILORx trial protocol specified that women with an RS ≥26 were assigned to receive chemotherapy plus endocrine therapy. Therefore, this should be reflected in the note.
Clinical need	There is a view among clinicians that knowledge of the genomic features of breast cancers is required to provide a higher level of evidence on which to base systemic treatment decisions. Multigene assays are being employed routinely by clinicians in the US.
Context	Oncotype DX represents one of the more rigorously developed gene assays with good quality control; NCCN preferred and 'strong' recommendation by ASCO.
Uncertain chemotherapy benefit – 26% or 15% or 20.5%?	20.5% may be an acceptable estimate.
Costs of adding chemotherapy may be underestimated	The cost of chemotherapy needs to be revisited – if it is higher, cost offsets would be higher.
Test is not registered for use in Australia and a single laboratory in the US performs the test and may not be eligible for listing on the MBS. Who will pay for this? What about out-of-pocket costs?	Since testing is done outside Australia, is it possible for MBS to pay the small pathology fee for collecting and preparing the sample to be sent, and then adopt a separate arrangement to reimburse the patient for the rest?
Different results from the modelled economic evaluation depending on accepting different sources of clinical evidence	Given MSAC's published views on the strength of the evidence available previously, it may be useful for MSAC to consider the disaggregated analyses of the non-inferiority (based on TAILORx) and effectiveness (based on re-analysing the previous retrospective predictive evidence) components of the model.

ESC discussion

Application 1342.5 is a resubmission seeking public funding for a gene expression profiling test, Oncotype DX®, for patients with breast cancer. The test generates a Recurrence Score® (RS) that is used to predict the likelihood of breast cancer recurrence and the potential benefit of also receiving adjuvant chemotherapy for surgically treated patients with early-stage invasive breast cancer receiving adjuvant endocrine therapy.

ESC noted the resubmission included two therapeutic claims:

1. Oncotype DX will identify patients who would not benefit from also receiving adjuvant chemotherapy, thus sparing them the adverse effects and other risks associated with chemotherapy (referred to as "chemotherapy sparing"; RS <26)

2. Oncotype DX will identify patients likely to benefit from also receiving adjuvant chemotherapy who would not have been identified through standard clinical practice; appropriate use of chemotherapy will result in improved disease-free survival (referred to as "chemotherapy indicating"; RS ≥26).

ESC noted MSAC's previous concerns about reliance on a single United States (US) laboratory performing the test. However, ESC considered that centralisation of testing could be seen as a significant strength of Oncotype DX in terms of reproducibility. It does not suffer from the same problems as other assays based on technologies that are difficult to standardise across different laboratories. Hence, there is no laboratory-based need for an Australian laboratory to implement new testing strategies.

ESC noted that the US Food and Drug Administration is currently obtaining guidance and feedback on its proposed oversight of laboratory-developed tests such as Oncotype DX, but new guidelines are not yet in place. The laboratory is accredited by the College of American Pathologists under the US Clinical Laboratory Improvement Amendment (CLIA) of 1988, which has parallels with accreditation by the National Association of Testing Authorities (NATA) in Australia.

ESC noted that the resubmission used the structure of an MBS item with descriptor, fee and note to frame its request for public funding. The note is intended to help interpret RS scores for making chemotherapy decisions. It states that patients with RS <26 are recommended endocrine therapy and patients with RS ≥26 are recommended adjuvant chemotherapy. However, ESC noted that the TAILORx trial protocol specified that women with RS ≥26 were assigned to receive adjuvant chemotherapy plus endocrine therapy. This should be reflected in the note.

ESC noted that the proposed fee of $5,085 per test service was higher than the confidential fee in previous submissions ($3,375). The resubmission proposed that $85 of the fee is for the Australian pathology laboratory retrieving and preparing the tissue.

ESC noted that some of the PICO criteria have changed since the previous MSAC considerations of this application, to align with the TAILORx trial:

- population – narrowed to include node negative-women with larger tumour size (the initial submission and first resubmission allowed for node positivity, while the second and third resubmissions excluded lymph node positivity but allowed smaller tumour sizes)
- intervention – RS threshold for decision-making with respect to recommending adjuvant chemotherapy as well as receiving adjuvant endocrine therapy is now 26 instead of 31
- comparator – usual care is now more clearly defined, and aligned with the MINDACT protocol used in TAILORx.

ESC considered that the eligible population should be specified as patients with newly diagnosed breast carcinomas ER-positive, *HER2*-negative, lymph node-negative who are post-surgical and who have not received neoadjuvant therapy. Restrictions might also include requesting by a specialist medical or surgical oncologist.

Although changing the RS threshold will change the consequences for the eligible population, ESC noted that the TAILORx trial was specifically designed to establish whether treating women with a mid-range RS of 11-25 with adjuvant endocrine therapy alone results in significantly worse breast cancer outcomes compared treating these women with both adjuvant chemotherapy and adjuvant endocrine therapy. This is the patient group for whom the decision around the use of adjuvant chemotherapy is not clear based on clinical-pathological factors such as tumour size and grade.

From the consumer point of view, ESC noted that genomics is becoming a part of better patient-centred care. There is considerable positive benefit for patients of better diagnoses leading to better treatment decisions, including patients being able to avoid chemotherapy if it is not required. ESC noted that equity of access issues arise from this test not being rendered in Australia.

ESC noted that Oncotype DX is a rigorously developed gene assay with good quality control. It is given a 'strong' recommendation in the American Society of Clinical Oncology (ASCO) guidelines, and the National Comprehensive Cancer Network (NCCN) has designated it as the preferred multigene panel assay.

ESC noted that other countries fund Oncotype DX. The National Institute for Health and Care Excellence (NICE) recommended it in 2013 for coverage under England's National Health Service (NHS), for use in early-stage ER-positive, *HER2*-negative, node-negative invasive breast cancer patients with 'intermediate risk'. Coverage was renewed in 2018 and expanded to include patients with micrometastases. Node-positive disease is not covered by England's NHS, but some patients are covered by private insurance.

Oncotype DX is publicly funded for almost all eligible patients in England, with no patient co-payment. Genomic Health Inc. estimated that 95% of the trusts serving breast cancer patients in the UK use the test, and over 22,000 women in the UK had undergone the test as of late 2018.

In Canada, all 10 provinces provide Oncotype DX under their public healthcare systems. Seven of the 10 provinces provide the test for node-negative and micrometastases patients; three provinces also provide, and one is considering providing, the test for node-positive patients.

In the USA, Oncotype DX is covered by Medicare (which covers people over 65 years of age) in all states except two, and by Medicaid (which covers people on low incomes) in all 50 states. The test is also covered by all major private insurers. Medicare and other public systems cover node-negative and node-positive patients; about half the private insurers cover node-positive patients.

ESC noted that there is an increasing view that clinicians should be using a higher level of evidence based on genomic subtyping of individual cancers (in addition to traditional histological features and immunohistochemical markers) to provide more specific and tailored treatments for breast cancer patients. Oncotype DX and other similar multigene assays are being increasingly used worldwide, and there is an increasing clinician-led demand for access to these types of assays. Assays like Oncotype DX are intended for use as an additional tool to guide decision-making, not to dictate treatment. ESC noted that clinicians and researchers are also currently using whole exome sequencing (WES) and whole genome sequencing (WGS) to investigate the genomic profile of breast cancers.

ESC considered that most clinicians would order the Oncotype DX assay selectively, particularly in instances when decision-making is complex. However, ESC considered that there is some risk of leakage. ESC noted that NICE guidance for Oncotype DX has recently been updated, which may inform concerns regarding leakage.

ESC noted the limitations of the current online prediction tools used to estimate the risk of recurrence and to make treatment decisions (Wazir et al. 2017):

- Adjuvant! Online tends to overestimate the number of patients at high risk; overestimate the survival rates of younger women with ER-positive breast cancer; overestimate the added value of chemotherapy for older patients; and *HER2* assessment is not included

- NHS Predict does not provide any estimate of local relapse; and does not consider mortality due to causes other than breast cancer. Some patients, particularly those with small, biologically aggressive cancers, may therefore not receive chemotherapy that would be of benefit.

ESC noted that the previously provided retrospective predictive data from the randomised NSABP B-20 study (Paik et al. 2006) was again relied on to support the clinical claim that Oncotype DX will identify patients likely to benefit from also receiving adjuvant chemotherapy who would not have been identified through standard clinical practice. The re-analysis of these data by Geyer et al. 2018 was relied on to demonstrate that also receiving adjuvant chemotherapy is superior to endocrine therapy alone in patients with RS ≥26.

ESC noted that the TAILORx trial provided NHMRC Level II evidence that adjuvant chemotherapy can be withheld in patients with an RS <26 without affecting the patient's risk of disease recurrence (Sparano et al. 2018). ESC also noted that exploratory analyses indicated that also receiving adjuvant chemotherapy was associated with some benefit for women aged ≤50 years with an RS of 16-25.

ESC noted that two Australian Decision Impact Studies (ADIS) previously presented to MSAC were used in the resubmission to characterise current patterns of care. These data were used to investigate the applicability of usual care in TAILORx to Australian practice. One of these studies (de Boer et al. 2013) found that the Oncotype DX RS changed the treatment recommendation in 24% of patients with node-negative tumours. In the other study (Chin-Lenn et al. 2018), the Oncotype DX RS changed treatment recommendations in 38% of patients, noting that the change in treatment recommendation could be in either direction: to include chemotherapy when it would have otherwise been excluded, or to exclude chemotherapy when it would otherwise have been included. However, ESC considered that the lack of proven clinical utility in the Australian context to be an ongoing issue. There is still no good description of current Australian practice as the ADIS studies are now several years old. It is likely to be different to practice in the US and UK, and it cannot be assumed that incremental clinical utility will be the same in Australia as in other countries.

ESC noted that the cost of adjuvant chemotherapy used in the model revised since the previous submission was recalculated by the applicant for its pre-ESC response using the Critique's assumption of four cycles rather than six. However, ESC noted the comment in the pre-ESC response that the revised cost is likely to be an underestimate of the true burden of this chemotherapy to the health care system. ESC commented that most adjuvant chemotherapy treatments go beyond four cycles so the cost might be underestimated, and noted that if this cost is higher, cost offsets would be higher.

ESC noted that the period of adjuvant chemotherapy treatment was based on six cycles; the pre-ESC response based this cost on four cycles, but did not change the disutility duration to reflect four cycles. ESC queried whether using four cycles would reduce the estimate of quality-adjusted life years gained from avoiding the toxicity of adjuvant chemotherapy.

ESC noted translation issues arising from uncertainty regarding the appropriate extent of benefit (i.e. reduction in absolute risk of disease recurrence) of receiving adjuvant chemotherapy as well as adjuvant endocrine therapy in patients with an RS ≥26. The resubmission originally used a value of 26% (based on Geyer et al.), but the Critique suggested 15% would be more appropriate in the Australian context. Instead, the pre-ESC response reduced the incremental benefit of chemotherapy from 26% in the base case to a mid-point of 20.5%. ESC advised that 20.5% may be acceptable.

ESC noted that the revised model used revised utility values, which were more in line with TAILORx.

ESC noted that the base case ICER/QALY from the revised combined model was sensitive to several assumptions, which varied this estimate within the range of $22,000–$50,000 (using a chemotherapy benefit of 20.5%). However, ESC noted that the ICER/QALY calculated using a chemotherapy benefit of 15% was more than $67,500.

ESC noted that although the modelled economic evaluation was structurally correct, it was basic. It included only univariate sensitivity analyses, but no probability sensitivity analyses or cost-effectiveness acceptability curves. The model included direct costs only; but not out-of-pocket costs. ESC queried whether the PBS cost of new chemotherapy drugs used in the TAILORx trial had been included in the cost offsets.

ESC noted that the analysis also gave two disaggregated results based on the two sources of clinical utility evidence: evidence for the non-inferiority claim is from the TAILORx randomised trial, but the modelled economic evaluation is driven by superiority claim from the retrospective predictive re-analysis from Paik/Geyer. ESC noted that it may be useful for MSAC to consider the disaggregated analyses of the non-inferiority and superiority components of the model (as well as the combined analysis).

ESC noted that the resubmission's revised financial analyses resulted in a modest increase in the net budgetary impact to $44.7 million over the first 5 years. The resubmission also provided a revised estimate incorporating updated (2017) breast cancer incidence data from the Australian Institute of Health Welfare of $50.3 million over the first 5 years. ESC considered these two estimates to be more realistic than the estimate of $51.6 million over 5 years using UK uptake data. However, ESC considered that the financial estimates remained subject to significant uncertainty due to low uptake rate assumptions and the fact that the TAILORx trial did not report important patient baseline characteristics, such as the percentage expression of ER or PR.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The MSAC Executive 3 February 2012 teleconference agreed for MSAC applicants to be given the opportunity to have a comment inserted in the final outcomes document – to be limited to one paragraph and/or a link to reference material

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1342.5 Gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Applicant: **Specialised Therapeutics Australia Pty Ltd**

Date of MSAC consideration: **MSAC 76th Meeting, 1-2 August 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission seeking public funding for the gene expression profiling (GEP) test using the real-time reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes (Oncotype DX® or ODX) in women with newly diagnosed stage I or II breast cancer, who are oestrogen receptor positive (ER-positive) or progesterone receptor positive (PR-positive), Human Epidermal Growth Factor Receptor 2 negative (HER2-negative), and lymph node negative (LN-negative), was received from Specialised Therapeutics by the Department of Health.

2. MSAC's advice to the Minister - August 2019

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for this gene expression profiling test for patients with breast cancer primarily because its ability to identify those who could safely be spared the addition of chemotherapy to endocrine therapy was not demonstrated by the new trial. The re-analysis of previously provided evidence was also insufficient to change the previous conclusion that the test could not satisfactorily identify those intermediate–risk patients who would benefit from the addition of chemotherapy to endocrine therapy.

3. Summary of consideration and rationale for MSAC's advice

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

4

s 47C, s 47E

5

s 47C, s 47E

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s 47C, s 47E

4. Background

The original application (Application 1345) was considered by MSAC at its July 2013 meeting, subsequent resubmissions were then considered in April 2014, November 2015, July 2016 and July 2017. The PSDs for these applications can be viewed on the MSAC website.

At its July 2017 meeting, MSAC did not support Oncotype DX breast cancer assay due to the uncertainty of the incremental benefit of the Oncotype DX breast cancer assay over optimal care (Application 1342.4 Public Summary Document (PSD) 2017, p2). MSAC noted that data from ongoing trials like the TAILORx trial, if suitable, may be useful in addressing this uncertainty (PSD, p3).

5. Prerequisites to implementation of any funding advice

The ODX Breast Cancer Assay test is performed in a single laboratory in the United States by Genomic Health Inc. Therefore, the test would not be subject to approval or regulation by the Therapeutic Goods Administration (TGA). A November 2015 report by the US Food and

Drug Administration (FDA) raised concerns about the current lack of regulation within the US for assays that are 'Laboratory Developed Tests' (LDTs), such as ODX.

MSAC previously raised concerns about the reliance on a single laboratory performing the test located in the US outside Australian standards maintained through the TGA or the National Association of Testing Authorities (NATA). MSAC also previously noted that a number of complex implementation issues would need to be considered by Government if this test was supported for listing in Australia.

6. Proposal for public funding

The proposal for public funding has changed since the previous resubmission (1342.4), and is presented in Table 2 (applicant highlighted changes with previous submission in red). The applicant has requested a fee of $5,085 per service, and the resubmission did not request any confidential pricing or fee arrangement.

Table 2 Proposal for public funding; changes from previous submission annotated (in red)

Gene expression profiling of tumour samples (surgical resection preferably or core biopsy) by reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes in breast cancer tissue.

See Note for information on how results should be interpreted.

Previous submissions did not include a note on how results should be interpreted.

May only be used to test samples from patients with all of the following characteristics as determined by the referring clinician:

- early invasive breast cancer (stages I-II)

No substantial change.

- oestrogen receptor positive or progesterone receptor positive as determined by immunohistochemistry at an approved Australian pathology laboratory

No substantial change.

- HER2 negative as determined by immunohistochemistry and/or in situ hybridisation at an approved Australian pathology laboratory

No substantial change.

- node negative

Previous submissions allowed for node positivity. Public funding no longer requested for node positive patients.

- tumour size >= 10 mm and < 50 mm, or tumour size >= 5 mm and < 10 mm with unfavourable histological features (intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion)

The minimum tumour size of 2 mm has increased to 10 mm (or 5 mm with unfavourable histology).

There was previously no maximum tumour size.

Eligibility was also previously determined by the presence of 1 or 2 negative prognostic risk factors.

- suitable for hormone therapy
- suitable for adjuvant chemotherapy (ECOG performance status 0-2)
- may only be used once per new primary breast cancer

No substantial change.

Fee: $5,085

Note:

Chemotherapy decisions are guided by a patient's Recurrence Score (RS). Patients with RS<26 are recommended endocrine therapy and patients with RS≥26 are recommended adjuvant chemotherapy according to Oncotype DX. There is some evidence that there may be a chemotherapy benefit in patients aged ≤ 50 years, with RS 16-25.

Previous submissions did not include a note on how results should be interpreted.

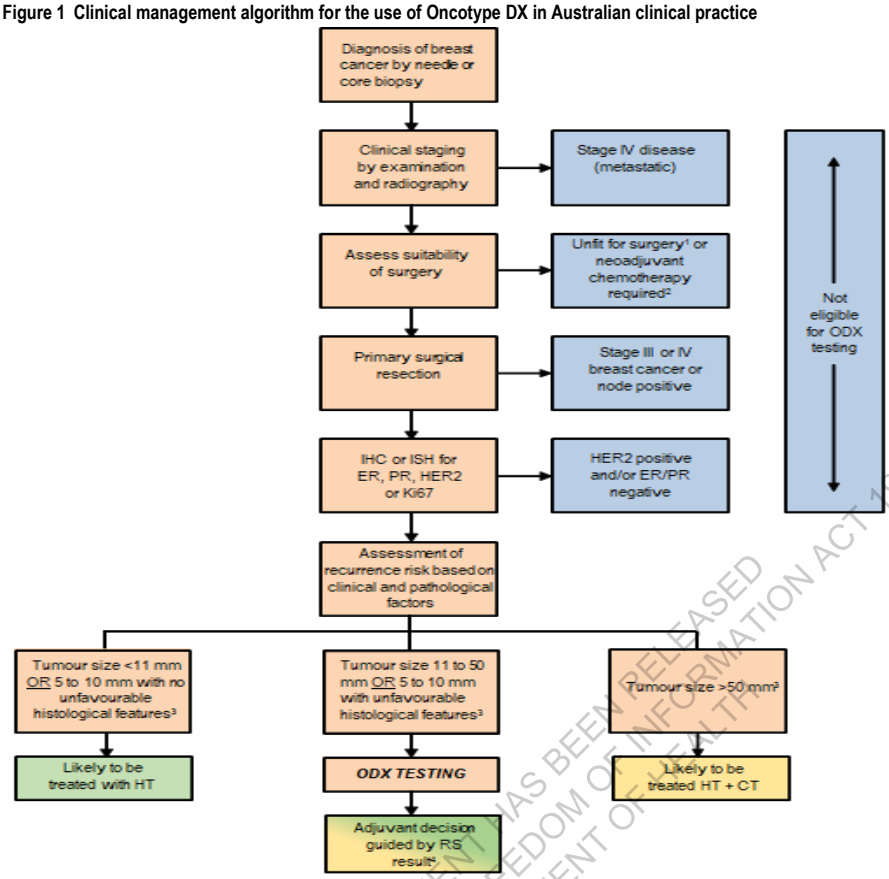
7. Summary of Public Consultation Feedback/Consumer Issues

See Application 1342.4 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

The resubmission proposed clinical management algorithm (Figure 1) differs from that presented in earlier MSAC applications for Oncotype DX in that it excludes node positive patients, and the process used to exclude patients with very high or low clinical risk is based on the approach applied in TAILORx. In addition, the algorithm includes a footnote to clarify how recurrence score (RS) results should be interpreted and used to guide chemotherapy decisions.

Figure 1 Clinical management algorithm for the use of Oncotype DX in Australian clinical practice



[1] ODX is only appropriate for post-surgical patients.
[2] Patients who have received neo-adjuvant chemotherapy would continue with chemotherapy and Oncotype DX has not been validated for patients who have undergone neoadjuvant therapy
[3]Tumour size and grade parameters are based on eligibility for the TAILORx trial (Sparano, 2018)
[4]Chemotherapy decisions are guided by a patient's Recurrence Score (RS). Patients with RS<26 are recommended endocrine therapy and patients with RS≥26 are recommended adjuvant chemotherapy according to Oncotype DX; there is some evidence that there may be a chemotherapy benefit in patients aged ≤ 50 years, with RS 16-25.
Abbreviations: CT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HT, hormone therapy; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; ODX, Oncotype DX, RS, Recurrence Score

9. Comparator

The comparator for the current resubmission remains the same as that for the previous submissions - usual care. MSAC has previously accepted the comparator as usual care, defined as optimised subjective assessment of various clinical and pathological factors to estimate the risk of recurrence; which are likely combined using formal algorithms.

10. Comparative safety

The resubmission did not present a specific assessment of comparative safety. The Critique stated that the safety concerns remain as those outlined by MSAC previously and quoted in

the resubmission. "MSAC previously noted that although the test is procedurally safe because it relies on samples already taken for other purposes, there is a degree of risk in the misallocation of patients to risk categories, which would affect the outcomes of the therapy subsequently selected" (PSD for MSAC Application 1342, November 2013).

11. Comparative effectiveness

The resubmission is based on one prospective randomised trial and one re-analysis of a retrospective cohort study:

- The TAILORx trial was a prospective trial (N=10,273; registered population), that used a patient's recurrence score only to guide treatment. Women with intermediate RS (11-25) were randomised to endocrine therapy (ET) alone or ET+ chemotherapy (CT) (n=6,907; Arms B and C); and those with low (0-10; n=1,629; Arm A) or high (≥26; n=1,737; Arm D) RS were treated with ET alone or ET+CT, respectively (Sparano et al. NEJM, 2018). Results were provided for the 'main analysis set' or 'intention-to-treat (ITT) population' (n=9,719 across all four arms), and some results were also provided for the per protocol population ('as treated population'), which the Critique stated was an important comparison for demonstrating non-inferiority of ET alone vs. ET+CT. In addition, Sparano et al. stated comparisons of ITT population, stratified by randomisation, could still be biased because of differences in the group refusing chemotherapy (Arm C) and the group receiving chemotherapy (Arm B).
- Geyer et al. (2018) was a retrospective re-analysis of the NSABP B-20 trial (Fisher et al. 1997; Paik et al. 2006, previously considered by MSAC); a re-analysis of this study based on the recurrence scores used in the TAILORx trial and removing patients who were HER2-positive (Geyer et al. 2018).

TAILORx

The Critique presented forest plots for the primary outcome- invasive disease-free survival (iDFS) (Figure 2) and secondary outcome- freedom from recurrence at a distant site or distant recurrence-free interval (DRFI) (Figure 3).

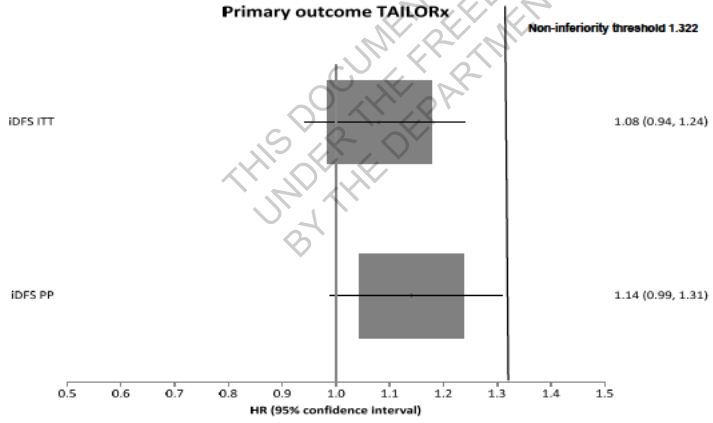


Figure 2 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as-treated' (PP) populations, with the non-inferiority threshold for invasive disease-free survival (iDFS)

The primary analysis to support the claim of no difference between the treatment arms - endocrine therapy alone compared to endocrine therapy plus chemotherapy - met the prespecified non-inferiority threshold. However, the Critique outlined the following issues to consider:

- For the ITT population, the prespecified non-inferiority margin of 32.2% decrease in invasive disease-free survival for endocrine therapy alone compared to endocrine therapy plus chemotherapy appears to be quite large and not supported by the references cited in the trial report.
- Results for the 'as treated' population are close to rejecting the null hypothesis of no difference between the treatment arms.
- The 'as-treated' population baseline characteristics were statistically significantly different for important baseline prognostic variables such as age, menopausal status, tumour size and tumour grade (such that, on average, 'lower risk' women were randomised to ET alone and 'higher' risk women were randomised to ET+CT).
- The non-adherence to assigned therapy in the ET alone arm was 185/3458 = 5% but 608/3449 = 18% in the ET+CT arm, compared to only 89/1737 = 5% in the non-randomised high RS score chemotherapy arm.
- There was a high risk of bias in the trial design.
- There was significant loss to follow up which was deemed not important due to the lower than expected iDFS rate.
- There are four endocrine therapy regimens and nine chemotherapy regimens, which may introduce confounding to the extent that they are not equi-effective.

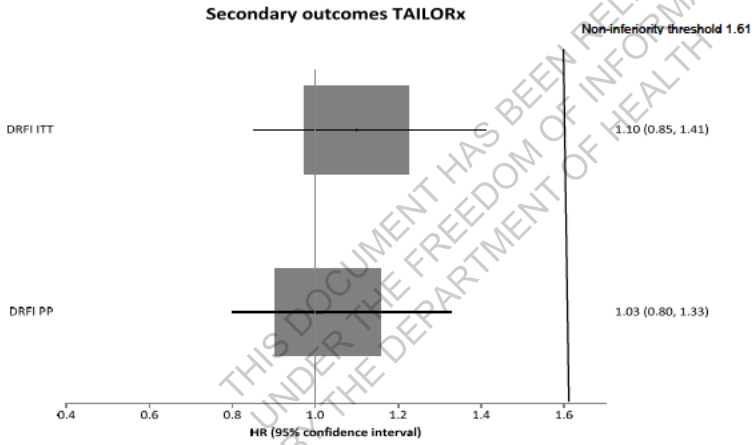


Figure 3 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as treated' (PP) populations with non-inferiority threshold for distant recurrence-free interval (DRFI)

The secondary analysis to support the claim of no difference between the treatment arms - endocrine therapy alone compared to endocrine therapy plus chemotherapy - also met the prespecified non-inferiority threshold. However, the Critique outlined issues to consider:

- For the ITT population, the non-inferiority margin of a 61% decrease in freedom from recurrence at a distant site for endocrine therapy alone compared to endocrine therapy plus chemotherapy appears to be quite large and not supported by the references cited in the trial report.

- Full statistical power to do this comparison was not achieved: the prespecified number of events of 284 was not reached, but only 199 events were recorded.

Table 3 presents the estimated survival rates according to recurrence scores and assigned treatment in the ITT population. The Critique stated that similar issues as identified above for the primary and secondary analyses also occurred; the number of events required for full statistical power was not achieved and the evidence to support the assumptions for the prespecified non-inferiority threshold of 1.46 was not provided in the SBA or the trial report.

Table 3 Estimated survival rates according to RS and assigned treatment in the ITT population

End point and treatment group	Rate at 5 years (%)±SE	Rate at 9 years (%)±SE
Invasive disease-free survival		
Score of ≤10, endocrine therapy alone	94.0±0.6	84.0±1.3
Score of 11-25, endocrine therapy alone	92.8 ±0.5	83.3±0.9
Score of 11-25, chemotherapy + endocrine therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemotherapy + endocrine therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy alone	99 3±0.2	96.8±0.7
Score of 11-25, endocrine therapy alone	98.0±0.3	94.5±0.5
Score of 11-25, chemotherapy + endocrine therapy	98 2±0.2	95.0±0.5
Score of ≥26, chemotherapy + endocrine therapy	93.0±0.8	86.8±1.7
Freedom from recurrence of breast cancer at a distant or local-regional site		
Score of ≤10, endocrine therapy alone	98.8±0.3	95.0±0.8
Score of 11-25, endocrine therapy alone	96 9±0.3	92.2±0.6
Score of 11-25, chemotherapy + endocrine therapy	97.0±0.3	92.9±0.6
Score of ≥26, chemotherapy + endocrine therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, endocrine therapy alone	98.0±0.4	93.7±0.8
Score of 11-25, endocrine therapy alone	98.0±0.2	93.9±0.5
Score of 11-25, chemotherapy + endocrine therapy	98.1±0.2	93.8±0.5
Score of ≥26, chemotherapy + endocrine therapy	95 9±0.6	89.3±1.4

Source: Table 7 of the Critique.

Geyer et al. (2018)

The re-analysis of the Paik et al. (2006) study by Geyer et al. (2018), considering only HER2-negative women and applying the 'old' and 'new' RS thresholds applicable for the definition of low, intermediate and high risk of recurrence is presented in Table 4. The Critique stated that the issues previously identified by MSAC about the 2006 Paik 2006 trial design remain.

Table 4 HR of adjuvant chemotherapy by RS subgroup, distant recurrence free survival (Geyer et al. 2018)

	N	Effect hazard ratio (95% CI)	P value
Overall (without HER2+ patients)	569	0 59 (0.31, 1.04)	Log rank P=0.06
Original RS subgroup n=569*	569		
Chemotherapy in RS <18	347	1.19 (0.40, 3.49)	
Chemotherapy in RS from 18-30	125	0.64 (0.23, 1.75)	
Chemotherapy in RS ≥31	97	0.18 (0.07, *0.46);*	
Likelihood ratio test on interaction			0.023
TAILORx RS groupings	569		
Chemotherapy in RS ≤10	176	1.19 (0.41, 3.51)	

	N	Effect hazard ratio (95% CI)	P value
Chemotherapy in RS 11-25	271	0.61 (0.26, 1 35)	
Chemotherapy in RS >25	122	0 27 (0.12, 0.62)	
Likelihood ratio test on interaction			0.014

Source: Tables 2 & 3 Geyer et al. 2018, Table 42 of the re-submission. Cox proportional Hazards Regression Model adjusted for patient age (>50 years vs ≤50 years), clinical tumour size (> 2.0 vs ≤2.0cm), ER by ligand blinding assay (≥100 vs <100 fmol/mg), PR by ligand blinding assay (≥100 vs <100 fmol/mg), and tumour grade (well differentiated, moderately differentiated and poorly differentiated.

Clinical claim

The Critique summarised the resubmission clinical claims:

- *A non-inferiority claim, for patients who the Oncotype DX test categorises into the intermediate recurrence group score, that endocrine therapy alone is no worse for the risk of distant recurrence free survival compared to endocrine therapy plus chemotherapy.*
- *A superiority claim, for patients who the Oncotype DX test categorises into the high recurrence group score, but usual care had determined treatment with endocrine therapy as sufficient, that the addition of chemotherapy would improve their disease free survival, risk of distant recurrence and overall survival.*

The non-inferiority claim is based on the results from TAILORx and the superiority claim is based on retrospective predictive data from the NSABP B-20 study (Paik et al. 2006; Geyer et al. 2018).

12. Economic evaluation

Table 5 summarises the economic evaluation.

Table 5 Summary of the economic evaluation

Perspective	Australian health care system
Comparator	Usual care, as defined by the M NDACT protocol used in TAILORx. Specifically, patients with low clinical risk do not receive adjuvant CT, patients with high clinical risk do receive adjuvant CT
Type of economic evaluation	Cost-utility analysis
Sources of evidence	TA LORx trial to determine allocation of CT in the usual care and Oncotype DX arms of the model NSABP B-20 Geyer et al. (2018) re-analysis to determine benefit of CT in patients who otherwise would not have received it
Time horizon	Lifetime
Outcomes	Life years gained, QALYs
Methods used to generate results	Markov cohort analysis
Health states	Free of disease recurrence • stratified by underlying Oncotype DX RS category and allocation to CT Disease recurrence Breast cancer death Other death
Cycle length	Annual
Discount rate	5% per annum
Software packages used	Microsoft Excel

The Critique stated that the model structure and modelling assumptions overwhelmingly favours Oncotype DX as all instances where Oncotype DX/RS score does not lead to optimal treatment were not considered, therefore the economic model presented is likely the most optimistic (and possibly implausible) scenario. The Critique presented the disaggregated incremental cost and effectiveness for "chemotherapy sparing" (Table 6) and "chemotherapy indicating" (Table 7) components of the model.

Table 6 Summary of disaggregated incremental cost and effectiveness in "chemotherapy sparing" only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,253.65	$3,116.03	-$1,862.38
Endocrine therapy	$3,160.85	$3,160.85	$0.00
Recurrent disease	$5,791.22	$5,791 22	$0.00
Total	**$15,290.72**	**$12,068.10**	**$3,222.62**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.6530**	**13.6530**	**0**
Disease-free	*13.4577*	*13.4577*	*0*
Post recurrence	*0.1953*	*0.1953*	*0*
QALY	**13.4621**	**13.4575**	**0.0045**
Disease-free	*13.3066*	*13.3021*	*0.0045*
Post recurrence	*0.1554*	*0.1554*	*0*
		$ per life year gained	**$NA**
		$ per QALY gained	**$711,529**

Text in italics indicate values calculated during the critique.
Source: 72 p155 of the SBA, ODX_EconModel xlsm.
[a] That is, moving any patients with RS ≤25 treated with ET+CT in the usual care arm to ET alone in the Oncotype DX arm.

Table 7 Summary of disaggregated incremental cost and effectiveness in "chemotherapy indicating" only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$3,672.22	$3,116.03	$556.19
Endocrine therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791 22	-$1,040.43
Total	**$16,683.36**	**$12,068.10**	**$4,615.26**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5752**	**13.4575**	**0.1177**
Disease-free	*13.4466*	*13.3021*	*0.1445*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	**$40,660**
		$ per QALY gained	**$39,217**

Text in italics indicate values calculated during the critique.
Source: 72 p155 of the SBA, ODX_EconModel xlsm.
[a] That is, moving any patients with RS ≥26 treated with ET alone in the usual care arm to ET+CT in the Oncotype DX arm.

The overall base case ICER is presented in Table 8 (combining the "chemotherapy sparing" and "chemotherapy indicating" components).

Table 8 Summary of disaggregated incremental cost and effectiveness from base case

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,809.84	$3,116.03	-$1,306.19
Endocrine therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791 22	-$1,040.43
Total	**$14,820.98**	**$12,068.10**	**$2,752.88**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5798**	**13.4575**	**0.1222**
Disease-free	*13.4522*	*13.3021*	*0.1501*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	**$24,253**
		$ per QALY gained	**$22,525**

Text in italics indicate values calculated during critique.
Source: Table 69, p153, Table 70 and 71 p154 of the SBA, ODX_EconModel xlsm.

The Critique highlighted that the base case ICER/QALY ($22,525) was driven by the "chemotherapy indicating" component (based on Geyer et al. 2018), contributing more benefit than the "chemotherapy sparing" component (incremental QALYs: 0.1177 *vs*. 0.0045, respectively); considered the "chemotherapy indicating" component was based on weaker evidence base, which MSAC had considered before when previously deciding not to support Oncotype DX.

The Critique's sensitivity analyses showed the modelled results were most sensitive to the effect of chemotherapy on absolute risk of recurrence in RS≥26 patients and the model duration.

13. Financial/budgetary impacts

An epidemiological approach has been used to estimate the financial implications of the introduction of the Oncotype DX test (Table 9).

Table 9 Net financial impact of Oncotype DX over five years by Commonwealth health budget and patient population

Summary	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)
Patients diagnosed with breast cancer [A]	17,210	17,530	17,850	18,170	18,490
Number of patients eligible for Oncotype DX [B]	4,652	4,739	4,825	4,912	4,998
Number of patients using Oncotype DX testing [C]	1,396	1,896	2,171	2,456	2,749
Total expenditure on Oncotype DX [D]	$6,980,873	$9,480,899	$10,860,713	$12,283,795	$13,750,143
Critique values (removed $83.40 co-pay)	*$6,942,488*	*$9,428,768*	*$10,800,995*	*$12,216,251*	*$13,674,537*

Change in expenditure due to Oncotype DX [E]	-$1,795,774	-$2,438,885	-$2,793,832	-$3,159,908	-$3,537,114
Critique values (removed $83.40 co-pay)	*-$1,640,985*	*-$2,228,663*	*-$2,553,015*	*-$2,887,537*	*-$3,232,229*
Net impact of Oncotype DX on expenditure	**$5,185,099**	**$7,042,014**	**$8,066,882**	**$9,123,887**	**$10,213,029**
Critique values (removed $83.40 co-pay)	***$5,301,503***	***$7,200,104***	***$8,247,980***	***$9,328,715***	***$10,442,308***

[A] AIHW Cancer incidence projections; [B] 27% of [A]; [C] After applying expected uptake rates of 30 to 55%; [D] $5085 per test less patient contribution of $83.40 per test; [E] Savings of $1287 per patient tested due to reduction in chemotherapy.

The Critique stated that sensitivity analysis indicated that the estimates of net cost to the Commonwealth health budget is heavily reliant on the assumed uptake of the Oncotype DX test and also, but to a lesser extent, assumptions around cost offsets to the PBS.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Recurrence Score® (RS) thresholds for categorising low, intermediate and high risk of distant recurrence appear to be arbitrary and subject to change	The RS thresholds were modified in the context of the TAILORx trial. It is not unreasonable to adjust parameters based on additional data, and the new threshold level of 26 appears safe based on the TA LORx and other supporting studies.
Population (as per the eligibility criteria into the TA LORx trial)	The eligible population should be specified as patients with newly diagnosed breast carcinomas; who are *ER*-positive, *HER2*-negative, lymph node-negative and post-surgical; and who have not received neoadjuvant therapy.
Proposed note defining eligibility for funding should be modified, as it suggests that patients with an RS ≥26 should receive chemotherapy only	TA LORx trial protocol specified that women with an RS score of ≥26 were assigned to receive chemotherapy plus endocrine therapy. Therefore, this should be reflected in the note.
Clinical need	There is a view among clinicians that knowledge of the genomic features of breast cancers is required to provide a higher level of evidence on which to base systemic treatment decisions. Multigene assays are being employed routinely by clinicians in the US.
Context	Oncotype DX represents one of the more rigorously developed gene assays with good quality control; NCCN preferred and 'strong' recommendation by ASCO.
Uncertain chemotherapy benefit – 26% or 15% or 20 5%?	20 5% may be an acceptable estimate.
Costs of adding chemotherapy may be underestimated	The cost of chemotherapy needs to be revisited – if it is higher, cost offsets would be higher.
Test is not registered for use in Australia and a single laboratory in the US performs the test and may not be eligible for listing on the MBS. Who will pay for this? What about out-of-pocket costs?	Since testing is done outside Australia, is it possible for MBS to pay the small pathology fee for collecting and preparing the sample to be sent, and then adopt a separate arrangement to reimburse the patient for the rest?
Different results from economic model depending on accepting different sources of clinical evidence	Given MSAC's published views on the strength of the evidence available previously, it may be useful for MSAC to consider the disaggregated analyses of the non-inferiority (based on TA LORx) and effectiveness (based on re-analysing the previous retrospective predictive evidence) components of the model.

ESC discussion

Application 1342.5 is a resubmission seeking public funding for a gene expression profiling test, Oncotype DX®, for patients with breast cancer. The test generates a Recurrence Score®

(RS) that is used to predict the likelihood of breast cancer recurrence and the potential benefit of also receiving adjuvant chemotherapy for surgically treated patients with early-stage invasive breast cancer receiving adjuvant endocrine therapy.

ESC noted the resubmission includes two therapeutic claims:

1. Oncotype DX will identify patients who would not benefit from also receiving adjuvant chemotherapy, thus sparing them the adverse effects and other risks associated with chemotherapy (referred to as "chemotherapy sparing"; RS <26)

2. Oncotype DX will identify patients likely to benefit from also receiving adjuvant chemotherapy who would not have been identified through standard clinical practice; appropriate use of chemotherapy will result in improved disease-free survival (referred to as "chemotherapy indicating"; RS ≥26).

ESC noted MSAC's previous concerns about reliance on a single United States (US) laboratory performing the test. However, ESC considered that centralisation of testing could be seen as a significant strength of Oncotype DX in terms of reproducibility. It does not suffer from the same problems as other assays based on technologies that are difficult to standardise across different laboratories. Hence, there is no laboratory-based need for an Australian laboratory to implement new testing strategies.

ESC noted that the US Food and Drug Administration is currently obtaining guidance and feedback on its proposed oversight of laboratory-developed tests such as Oncotype DX, but new guidelines are not yet in place. The laboratory is accredited by the College of American Pathologists under the US Clinical Laboratory Improvement Amendment (CLIA) of 1988, which has parallels with accreditation by the National Association of Testing Authorities (NATA) in Australia.

ESC noted that the resubmission used the structure of an MBS item with descriptor, fee and note to frame its request for public funding. The note is intended to help interpret RS scores for making chemotherapy decisions. It states that patients with RS<26 are recommended endocrine therapy and patients with RS≥26 are recommended adjuvant chemotherapy. However, ESC noted that the TAILORx trial protocol specified that women with a score of ≥26 were assigned to receive adjuvant chemotherapy plus endocrine therapy. This should be reflected in the note.

ESC noted that the proposed fee of $5,085 per test service is higher than the confidential fee in previous submissions ($3,375). The applicant has proposed that $85 of the fee is for the Australian pathology laboratory retrieving and preparing the tissue.

ESC noted that some of the PICO criteria have changed since the previous MSAC considerations of this application, to align with the TAILORx trial:

- population – narrowed to include node negative-women with larger tumour size (the initial submission and first resubmission allowed for node positivity, while the second and third resubmissions excluded lymph node positivity but allowed smaller tumour sizes)
- intervention – RS threshold for decision-making with respect to recommending adjuvant chemotherapy as well as receiving adjuvant endocrine therapy is now 26 instead of 31
- comparator – usual care is now more clearly defined, and aligned with the MINDACT protocol used in TAILORx.

ESC considered that the eligible population should be specified as patients with newly diagnosed breast carcinomas *ER+*, *HER2–*, lymph node-negative who are post-surgical and who have not received neoadjuvant therapy. Restrictions might also include requesting by a specialist medical or surgical oncologist.

Although changing the RS threshold will change the consequences for the eligible population, ESC noted that the TAILORx trial was specifically designed to establish whether treating women with a mid-range RS of 11–25 with adjuvant endocrine therapy alone results in significantly worse breast cancer outcomes compared treating these women with both adjuvant chemotherapy and adjuvant endocrine therapy. This is the patient group for whom the decision around the use of adjuvant chemotherapy is not clear based on clinical–pathological factors such as tumour size and grade.

From the consumer point of view, ESC noted that genomics is becoming a part of better patient-centred care. There is considerable positive benefit for patients of better diagnoses leading to better treatment decisions, including patients being able to avoid chemotherapy if it is not required. ESC noted that equity of access issues arise from this test not being rendered in Australia.

ESC noted that Oncotype DX is a rigorously developed gene assay with good quality control. It is given a 'strong' recommendation in the American Society of Clinical Oncology (ASCO) guidelines, and the National Comprehensive Cancer Network (NCCN) has designated it as the preferred multigene panel assay.

ESC noted that other countries fund Oncotype DX. The National Institute for Health and Care Excellence (NICE) recommended it in 2013 for coverage under the England's National Health Service (NHS), for use in early-stage *ER+*, *HER2–*, node-negative invasive breast cancer patients with 'intermediate risk'. Coverage was renewed in 2018 and expanded to include patients with micrometastases. Node-positive disease is not yet covered by the NHS, but some patients are covered by private insurance.

Oncotype DX is publicly funded for almost all eligible patients in England, with no patient co-payment. Genomic Health Inc. estimates that 95% of the trusts serving breast cancer patients in the UK use the test, and over 22,000 women in the UK had undergone the test as of late 2018.

In Canada, all 10 provinces provide Oncotype DX under their public healthcare systems. Seven of the 10 provinces provide the test for node-negative and micrometastases patients; three provinces also provide, and one is considering providing, the test for node-positive patients.

In the USA, Oncotype DX is covered by Medicare (which covers people over 65 years of age) in all states except two, and by Medicaid (which covers people on low incomes) in all 50 states. The test is also covered by all major private insurers. Medicare and other public systems cover node-negative and node-positive patients; about half the private insurers cover node-positive patients.

ESC noted that there is an increasing view that clinicians should be using a higher level of evidence based on genomic subtyping of individual cancers (in addition to traditional histological features and immunohistochemical markers) to provide more specific and tailored treatments for breast cancer patients. Oncotype DX and other similar multigene assays are being increasingly used worldwide, and there is an increasing clinician-led demand

for access to these types of assays. Assays like Oncotype DX are intended for use as an additional tool to guide decision-making, not to dictate treatment. ESC noted that clinicians and researchers are also currently using whole exome sequencing (WES) and whole genome sequencing (WGS) to investigate the genomic profile of breast cancers.

ESC considered that most clinicians would order the Oncotype DX assay selectively, particularly in instances when decision-making is complex. However, ESC considered that there is some risk of leakage. ESC noted that NICE guidance for Oncotype DX has recently been updated, which may inform concerns regarding leakage.

ESC noted the limitations of the current online prediction tools used to estimate the risk of recurrence and to make treatment decisions (Wazir et al. 2017):

- Adjuvant! Online tends to overestimate the number of patients at high risk; overestimate the survival rates of younger women with ER-positive breast cancer; overestimate the added value of chemotherapy for older patients; and *HER2* assessment is not included

- NHS Predict does not provide any estimate of local relapse; and does not consider mortality due to causes other than breast cancer. Some patients, particularly those with small, biologically aggressive cancers, may therefore not receive chemotherapy that would be of benefit.

ESC noted that the previously provided retrospective predictive data from the randomised NSABP B-20 study (Paik et al. 2006) is again relied on to support the clinical claim that Oncotype DX will identify patients likely to benefit from also receiving adjuvant chemotherapy who would not have been identified through standard clinical practice. The re-analysis of these data by Geyer et al. 2018 is relied on to demonstrate that also receiving adjuvant chemotherapy is superior to endocrine therapy alone in patients with RS ≥26.

ESC noted that the TAILORx trial provides NHMRC Level II evidence that adjuvant chemotherapy can be withheld in patients with an RS ≤26 without affecting the patient's risk of disease recurrence (Sparano et al. 2018). ESC also noted that exploratory analyses indicated that also receiving adjuvant chemotherapy was associated with some benefit for women aged ≤50 years with an RS of 16–25.

ESC noted that two Australian Decision Impact Studies (ADIS) previously presented to MSAC are used in the resubmission to characterise current patterns of care. These data are used to investigate the applicability of usual care in TAILORx to Australian practice. One of these studies (de Boer et al. 2013) found that the Oncotype DX RS changed the treatment recommendation in 24% of patients with node-negative tumours. In the other study (Chin-Lenn et al. 2018), the Oncotype DX RS changed treatment recommendations in 38% of patients, noting that the change in treatment recommendation could be in either direction: to include chemotherapy when it would have otherwise been excluded, or to exclude chemotherapy when it would otherwise have been included. However, ESC considered that the lack of proven clinical utility in the Australian context to be an ongoing issue. There is still no good description of current Australian practice as the ADIS studies are now several years old. It is likely to be different to practice in the US and UK, and it cannot be assumed that incremental clinical utility will be the same in Australia as in other countries.

ESC noted that the cost of adjuvant chemotherapy used in the model revised since the previous submission was recalculated by the applicant using the Critique's assumption of four cycles rather than six. However, ESC noted the applicant's comment in response that the

revised cost is likely to be an underestimate of the true burden of this chemotherapy to the health care system. ESC commented that most adjuvant chemotherapy treatments go beyond four cycles so the cost might be underestimated, and noted that if this cost is higher, cost offsets would be higher.

ESC noted that the period of adjuvant chemotherapy treatment was based on six cycles; the applicant agreed to base this cost on four cycles but did not change the disutility duration to reflect four cycles. ESC queried whether using four cycles would reduce the estimate of quality-adjusted life years gained from avoiding the toxicity of adjuvant chemotherapy.

ESC noted translation issues arising from uncertainty regarding the appropriate extent of benefit (i.e. reduction in absolute risk of disease recurrence) of receiving adjuvant chemotherapy as well as adjuvant endocrine therapy in patients with an RS ≥26. The applicant originally used a value of 26% (based on Geyer et al.), but the Critique suggested 15% would be more appropriate in the Australian context. Instead, the applicant reduced the incremental benefit of chemotherapy from 26% in the base case to a mid-point of 20.5%. ESC advised that 20.5% may be acceptable.

ESC noted that the revised model uses revised utility values, which are now more in line with TAILORx.

ESC noted that the base case ICER/QALY from the revised combined model is sensitive to several assumptions, which vary this estimate within the range of $22,000–$50,000 (using a chemotherapy benefit of 20.5%). However, ESC noted that the ICER/QALY calculated using a chemotherapy benefit of 15% was more than $67,500.

ESC noted that although the economic evaluation model is correct, it is basic. It includes only univariate sensitivity analyses, but no probability sensitivity analysis or cost-effectiveness acceptability curve. The model includes direct costs only; it does not include out-of-pocket costs. ESC queried whether the PBS cost of new chemotherapy drugs used in the TAILORx trial had been included in the cost offsets.

ESC noted that the analysis also gave two results based on the source of clinical utility evidence: evidence for the non-inferiority claim is from the TAILORx randomised trial, but the economic analysis is driven by superiority claim from the retrospective predictive re-analysis from Paik/Geyer. ESC noted that it may be useful for MSAC to consider the disaggregated analyses of the non-inferiority and superiority components of the model (as well as the combined analysis).

ESC noted that the applicant's revised financial analyses resulted in a modest increase in the net budgetary impact to $44.7 million over the first 5 years. The applicant also provided a revised estimate incorporating updated (2017) breast cancer incidence data from the Australian Institute of Health Welfare of $50.3 million over the first 5 years. ESC considered these two estimates to be more realistic than the estimate of $51.6 million over 5 years using UK uptake data. However, ESC considered that the financial estimates remained subject to significant uncertainty due to low uptake rate assumptions and the fact that the TAILORx trial did not report important patient baseline characteristics, such as the percentage expression of ER or PR.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The MSAC Executive 3 February 2012 teleconference agreed for MSAC applicants to be given the opportunity to have a comment inserted in the final outcomes document – to be limited to one paragraph and/or a link to reference material

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

s 47C, s 47E

s 47C, s 47E

Please let me know if I have been unclear in this follow-up email. s 47E

Thanks again for all your input. It is greatly appreciated.

s 22

From: s 22
Sent: Monday, 9 December 2019 2:50 PM
To: s 47F
Subject: FW: FW: s 47E [SEC=OFFICIAL]
Attachments: Fragility of phase 3 results.pdf; 2017 FDA neratinib 208051Orig1s000MultidisciplineReview_pp95-97.pdf

s 47F

FYI mostly, unless you disagree with my interpretation of s 47E advice (sent to you last Friday evening – 6 December 2019) as summarised in my first paragraph to s 47E below.

s 22
Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 22
Sent: Monday, 9 December 2019 2:47 PM
To: s 47F
Cc: s 22
Subject: RE: FW: FW: Request for statistical advice (MSAC) [SEC=OFFICIAL]

s 47F

s 47E

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208051Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208051
Priority or Standard	Standard
Submit Date(s)	July 19, 2016
Received Date(s)	July 19, 2016
PDUFA Goal Date	July 19, 2017
Division/Office	DOP1/OHOP/OND
Review Completion Date	July 12, 2017
Established Name	Neratinib maleate
(Proposed) Trade Name	NERLYNX
Pharmacologic Class	Kinase inhibitor
Code name	HKI-272
Applicant	Puma Biotechnology
Formulation(s)	40 mg Tablet
Dosing Regimen	240 mg (40 mg × 6 tablets) orally once daily with food, continuously for one year
Applicant Proposed Indication(s)/Population(s)	Extended adjuvant treatment of adult patients with early stage ERBB2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

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Reviewers of Multi-Disciplinary Review and Evaluation

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Nonclinical Team Leader	Todd Palmby, PhD
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Office of Clinical Pharmacology Team Leader(s)	Jingyu (Jerry) Yu, PhD; Qi Liu, PhD
Clinical Reviewer	Harpreet Singh, MD Amanda Walker, MD
Clinical Team Leader	Laleh Amiri-Kordestani, MD
Statistical Reviewer	Joyce Cheng, PhD
Statistical Team Leader	Shenghui Tang, PhD
Associate Director for Labeling	William Pierce, PharmD
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Division Director (OB)	Rajeshwari Sridhara, PhD
Division Director (Acting) (DOP1)	Julia Beaver, MD
Office Director (or designated signatory authority)	Richard Pazdur, MD

Additional Reviewers of Application

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Microbiology	Huiquan Wu
OPDP	Kevin Wright
OSI	Lauren Iacono-Conner
OSE/DEPI	Carolyn McCloskey
OSE/DMEPA	Tingting Gao
OSE/DRISK	Till Olickal
DMPP	Rowe Medina
DEPI	Carolyn McCloskey
DPV	Peter Waldron/Pritpal Singh

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Neratinib (NERLYNX) is a new molecular entity and an orally available small molecule kinase inhibitor. It irreversibly binds to Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4.

The Applicant's proposed indication at the time of NDA submission was:
NERLYNX as a single agent is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.

The recommended indication is:
NERLYNX is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

The recommended dose for neratinib is 240 mg (40 mg × 6 tablets) taken orally, once daily with food, continuously for one year.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for approval of neratinib, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is primarily based on the efficacy and safety data from a single trial (Study 3004, ExteNET), a multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in women with early stage HER2-positive breast cancer after adjuvant treatment with trastuzumab. A total of 2840 patients were randomized 1:1 to receive either neratinib (n=1420) or placebo (n=1420). The primary analysis demonstrated a statistically significant stratified hazard ratio of 0.66 (0.49, 0.90) with an estimated 2.3% absolute difference in invasive disease-free survival (iDFS) at two years (94.2% on the neratinib arm vs 91.9% on the placebo arm). FDA has accepted disease-free survival as an approval endpoint in the adjuvant setting for breast cancer as well as other tumor types. Most common adverse events (≥10% incidence) in Study 3004 were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, and muscle spasms. Diarrhea leading to severe dehydration, renal insufficiency, and electrolyte abnormalities is uncommon and reversible with treatment interruption and/or discontinuation. Results from ongoing Phase 2 Study 6201 suggest that antidiarrheal prophylaxis decreases the incidence and severity of diarrhea.

During the review of the neratinib application, there was some uncertainty in the magnitude of treatment effect due to unplanned adaptations from multiple amendments and changes of Sponsor control, imbalance of early dropouts, and incomplete extended follow-up data. An Oncology Drug Advisory Committee was convened on May 24, 2017, to discuss and provide advice on this NDA. The committee voted in favor of the benefit-risk profile for the neratinib for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed breast cancer who have received prior adjuvant trastuzumab-based therapy.

All disciplines were in agreement with approval of neratinib, or did not identify any outstanding issues that precluded approval. In summary, neratinib for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy demonstrates a favorable benefit-risk profile with enough evidence to recommend approval.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

The applicant submitted an NDA application of neratinib for the proposed indication of extended adjuvant treatment of patients with early-stage ERBB2-positive breast cancer who have received prior adjuvant-trastuzumab based therapy. Neratinib is an orally available small molecule, irreversible pan-ERBB inhibitor that inhibits ERBB1, ERBB2, and ERBB4 by binding at the intracellular tyrosine kinase domain of the receptor, a mechanism of action that is different from trastuzumab. Preclinical data suggest that neratinib has antitumor activity in ERBB1- and/or ERBB2-expressing carcinoma cell lines, with cellular IC50<100nM (Rabindran et al 2004).

Breast cancer is the most frequently diagnosed malignancy in women and is the leading cause of cancer mortality in women worldwide. HER2 (ERBB2) positive breast cancer comprises approximately 20 to 25% of the entire breast cancer population (Slamon et al, 2011). ERBB2 protein overexpression or ERBB2 gene amplification in breast cancer tumors is associated with more aggressive clinical disease and poorer prognosis (Slamon et al 1987). Current standard of care for patients with HER2-positive early breast cancer is one year of adjuvant trastuzumab (Piccart-Gebhart et al 2005). However up to 26% of patients will recur within 5 years after adjuvant therapy. There is currently no available therapy for patients in the extended adjuvant setting after completing one year or trastuzumab.

The ExteNET (Extended Adjuvant Treatment of Breast Cancer with Neratinib) study was a randomized, double-blind, placebo-controlled trial of neratinib after trastuzumab in women with early-stage HER2/neu overexpressed/amplified breast cancer. The primary endpoint was to compare invasive disease-free survival (iDFS) of women with early-stage ERBB2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting, receiving neratinib compared with that of women receiving placebo. However, a series of major amendments truncated the study design, decreasing follow-up time from 5 years to 2 years. In addition, the primary analysis was changed from event-driven to time-driven. The reported number of patients with an iDFS event that occurred within 2 years after randomization was 173; of these, 67 (4.7%) were in the neratinib arm and 106 (7.5%) were in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than in the placebo arm, 94.2% and 91.9%, respectively. Results from the Applicant's 5-year exploratory analysis with reconsent data from 74.5% of the ITT patients show that the initial 2-year difference seen in the primary analysis appears to be sustained for up to 5-years. Certain subgroup analyses demonstrate the potential for a difference in magnitude of benefit; however, no subgroups demonstrated a potential detriment, and these analyses were exploratory.

There appears to be no evidence of long-term sequelae after treatment with neratinib and the toxicities are generally manageable with dose interruptions, dose reductions, and/or standard medical care. Diarrhea was the most common adverse event in ExteNET study with a 39.9% incidence of Grade 3-4 diarrhea and represents the most common AE leading to treatment discontinuation (16.8% of patients in Study 3004). Other frequent adverse events (≥10% incidence) in ExteNET study were nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased

appetite, and muscle spasms. Other than diarrhea, neratinib is associated with a low incidence of severe AEs. Diarrhea leading to severe dehydration, renal insufficiency, and electrolyte abnormalities is uncommon and reversible with treatment interruption and/or discontinuation. Results from ongoing Phase 2 Study 6201 suggest that antidiarrheal prophylaxis with loperamide decreases the incidence and severity of diarrhea; however, there may be a trade-off in terms of toxicities with more constipation and nausea in the setting of loperamide prophylaxis, and approximately one-fourth to one-third of patients still discontinued treatment due to toxicity.

Overall, the benefit-risk profile of neratinib in the extended adjuvant setting must be carefully considered for each patient.

The key issues concerning this application were:

- Risk-benefit profile of neratinib for extended adjuvant therapy in an early and often curative disease setting.
- Is there uncertainty in the magnitude of treatment effect due to unplanned adaptations to multiple amendments and incomplete follow up data?
- The totality of evidence of neratinib's efficacy data in the context of other approvals in the adjuvant setting.

Given these uncertainties, the Division convened an Oncologic Drug Advisory Committee (ODAC) meeting on May 24, 2017, to advise and offer insight on the overall benefit-risk of neratinib in the proposed population. The committee voted 12-4 that the efficacy and safety results of ExteNET supports a positive benefit-risk assessment of neratinib for the proposed population.

In conclusion, neratinib demonstrated a statistically significant improvement in iDFS in a large, randomized, double-blind study. Despite immature OS data, the unplanned amendments, and potential uncertainty introduced with respect to the magnitude of the neratinib effect, the sensitivity analyses results appeared generally similar to the primary analysis results, supporting an effect of neratinib in the intended population studied in the trial. Although no male patients were enrolled on the clinical trial, the Sponsor provided information from males treated with neratinib as well as a scientific rationale; therefore, the indication reflects "adult patients." In addition, the results in the context of other FDA-approved adjuvant breast cancer therapies have demonstrated a similar rate of benefit when compared to previous adjuvant hormonal therapy approvals. As suggested by the ODAC, a detailed description of exploratory subgroup analyses is provided in labeling. The safety profile is acceptable in the intended population. Appropriate labeling for dose modification and inclusion of diarrhea and hepatotoxicity in Warnings and Precautions identifies these concerns to prescribers and assists with appropriate management. In summary, neratinib for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy, demonstrates a favorable benefit-risk profile with enough evidence to recommend approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Breast cancer is the most frequently diagnosed malignancy in women and is the leading cause of cancer mortality in women worldwide. • HER2-positive breast cancer comprises approximately 20 to 25% of the entire breast cancer population. • HER2 gene amplification or HER2 protein overexpression in breast cancer tumors is associated with more aggressive clinical disease and historically poorer prognosis. • Approximately 20% of patients with HER2-positive early breast cancer will recur within 5 years after adjuvant therapy.	**HER2-positive breast cancer is a serious disease. There is an unmet medical need to develop therapies for it to reduce the chance of recurrence. When it recurs, it is incurable. Recurrent HER2-positive breast cancer could be life-threatening when progressive.**
Current Treatment Options	• Current standard of care for patients with HER2-positive early breast cancer is chemotherapy and one year of adjuvant trastuzumab. There are currently no approved therapies which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting. • For patients with hormone-receptor positive disease, there are several approved hormonal therapies which patients would continue to take after completion of trastuzumab-based therapy in the adjuvant setting	**Despite treatment with adjuvant chemotherapy and trastuzumab, up to 20% of patients will have recurrent disease. Patients with more high-risk disease features are at greater risk for recurrence.**
Benefit	• The ExteNET study was a randomized, double-blind, placebo-controlled trial of neratinib after trastuzumab in women with early-stage HER2/neu overexpressed/amplified breast cancer. The primary endpoint was to compare invasive disease-free survival (iDFS) of women with early-stage ERBB2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting, receiving neratinib compared with that of women receiving placebo. • The primary analysis demonstrated a statistically significant stratified hazard ratio of 0.66 (0.49, 0.90) observed with an estimated 2.3% absolute difference in iDFS at two years (94.2% on the neratinib arm vs. 91.9% on the placebo arm). • Results from the Applicant's 5-year exploratory analysis with reconsent	**While it is uncertain which patients derive the greatest benefit from a year of extended adjuvant therapy with neratinib, the overall 2.3% improvement in iDFS at 2 years is considered clinically meaningful in carefully selected patients.** **Exploratory subgroup analyses suggest that patients with HR+ tumors, and those closer to completion of trastuzumab may derive greater benefit from treatment with neratinib and this information was included in labeling.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	data from 74.5% of the ITT patients, shows that the initial 2-year difference seen in the primary analysis appears to be sustained for up to 5-years. • There may be a difference in the magnitude of benefit based on hormone receptor status (HR-positive HR=0.49 [0.31, 0.75], HR-negative HR=0.93 [0.60, 1.43]), however this is an exploratory subgroup analysis.	
Risk	• Diarrhea was the most frequently reported adverse reaction in the neratinib arm with an overall incidence of 95% and 40% of patients experiencing at least one episode of Grade 3 diarrhea. • Twenty-eight percent of patients discontinued neratinib due to an adverse event (AE), and the most common AE leading to discontinuation was diarrhea. • Other common adverse reactions observed in 10% or more of patients taking neratinib were nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, and muscle spasms. • Nonfatal serious adverse events occurred in 7.3% of patients on the neratinib arm and 6.0% of patients on the placebo arm in Study 3004. • The most frequent treatment-related SAE was diarrhea, reported in 22 patients on the neratinib arm and 1 patient on the placebo arm.	**Results from an ongoing Phase 2 study (PUMA-NER-6201) suggest that antidiarrheal prophylaxis decreases the incidence and severity of diarrhea in patients treated with neratinib.** **All treatment-related SAEs in the neratinib arm were reversible after discontinuation of study drug.** **The safety profile of neratinib is acceptable for the intended population.**
Risk Management	• There is no proposal for a formal risk management plan.	**The safe use of neratinib can be managed through accurate labeling and routine oncology care. No REMS is indicated.**

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Breast cancer is the most frequently diagnosed malignancy in women and is the leading cause of cancer mortality in women worldwide. HER2 (ERBB2)-positive breast cancer comprises approximately 20 to 25% of the entire breast cancer population (Slamon et al, N Engl J Med. 2011). ERBB2 protein overexpression or ERBB2 gene amplification in breast cancer tumors is associated with more aggressive clinical disease and poorer prognosis (Slamon et al, Science. 1987). Current standard of care for patients with HER2-positive early breast cancer is chemotherapy and one year of adjuvant trastuzumab (Piccart-Gebhart et al, N Engl J Med. 2005). Pertuzumab is also used in combination with trastuzumab and docetaxel as neoadjuvant treatment for selected patients. Approximately 20% of patients with HER2-positive early breast cancer will recur within 5 years after adjuvant therapy (Goldhirsch A et al, Lancet. 2013).

Trastuzumab (Herceptin), a humanized erbB-2 directed monoclonal antibody, is approved for the treatment of erbB-2 overexpressing breast cancer, both in the metastatic and the adjuvant settings.

- U.S. indication: trastuzumab is indicated for adjuvant treatment of erbB-2 overexpressing node positive or node negative (estrogen receptor/progesterone receptor [ER/PgR] negative or with one high risk feature) breast cancer.

Trastuzumab is administered either after chemotherapy or initially concurrent with taxane chemotherapy (neoadjuvant or adjuvant) and as single agent thereafter for up to 1 year. It can be given weekly or every 3 weeks. While there is a reduction in recurrence and a survival advantage after trastuzumab, there remains an unmet clinical need for further improvement in outcome due to ongoing recurrences at all possible sites of the disease. Limitations of antibody directed erbB-2 therapy might be overcome by small molecule pan-erbB tyrosine kinase inhibitors such as neratinib or lapatinib that inhibit not just erB-2 but also EGFR.

Women with erbB-2 positive early stage breast cancer treated with adjuvant chemotherapy and trastuzumab (begun concurrently with the chemotherapy) have an 85.9% 4-year disease free survival (DFS), or a hazard ratio of 3.8% per year, per the North American combined analysis. In the HERA trial, the 3-year DFS rate is 80.6%, or a hazard rate of 7.2% per year, for patients treated with trastuzumab (after adjuvant chemotherapy). In the BCIRG 006 study, the average 4-year DFS rate of 2 trastuzumab-containing arms is 82.5%, or a hazard rate of 4.9% per year (trastuzumab began concurrently with the chemotherapy). A precedent has been set for the investigation of anti-erbB-2 therapy remote from diagnosis in an adjuvant trial with lapatinib (the TEACH trial). Women who are trastuzumab naïve (did not or could not receive trastuzumab) and disease free anytime any time in follow-up from primary diagnosis have been

randomized to lapatinib or placebo for 1 year.

Extended adjuvant therapy with aromatase inhibitors has a substantial impact on disease free and overall survival, supporting such a trial design with other compounds such as erbB inhibitors.

2.2. Analysis of Current Treatment Options

There are currently no approved therapies which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting. Extended adjuvant treatment was studied in the HERA trial, which randomized 5102 women with HER2-positive early stage breast cancer to one year of trastuzumab vs two years vs observation with DFS and OS as endpoints. The study was event-driven and showed no difference in either DFS or OS for one year of trastuzumab vs two. However, when evaluating the Kaplan-Meier curves at the two-year time point, it appears that two years of trastuzumab may improve DFS. With extended follow up, this perceived benefit disappears.

For patients with hormone-receptor positive disease, there are several approved hormonal therapies that patients would continue to take after completion of trastuzumab-based therapy in the adjuvant setting. A summary of these therapies is included in Table 1.

Table 1: FDA Approved Hormonal Adjuvant Breast Cancer Therapies Since 1999[1]

FDA Approval Drug and Year	Treatment Arms	N DFS Events	Median Follow up (months)	Absolute Difference in DFS Event Rate	Hazard Ratio
Placebo controlled					
Letrozole 2004[2,3]	Letrozole	N=2582 122 (4.7%)	28	2.8%	0.62
	Placebo	N = 2586 193 (7.5%)			
	CMF	N=360 169 (47%)			
Tamoxifen 1999	Approval based on overview of adjuvant therapy of 10-year outcome data (N=36, 689), 55 randomized trials 10 year OS: 61.4% Tamoxifen vs. 50.5% control Recurrence-free rate at 10 years: 79.2% Tamoxifen vs. 64.3% control				
Exemestane 2005	Tamoxifen	N=2372 307 (13%)	35	4%	0.69
	Exemestane	N=2352 213 (9%)			
Anastrozole 2005	Tamoxifen	N=3116 651 (21%)	68	3%	0.87
	Anastrozole	N=3125 575 (18%)			
Letrozole[3] 2005	Tamoxifen	N=4007 369 (9.2%)	26	1.8%	0.79
	Letrozole	N= 4003 296 (7.4%)			

[1]- At the time of approval, some drugs also demonstrated an improvement in OS
[2]– Approval in extended adjuvant setting after 5 years of tamoxifen
[3]– Accelerated approval later converted to regular approval with additional follow-up data

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Neratinib is a new molecular entity (NME) and not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

- On June 30, 2003, Wyeth submitted an IND for the treatment of HER2+ metastatic breast cancer and tumors overexpressing HER2.
- One June 10, 2009, the ExteNET study 3004 protocol was submitted to the IND.
- In 2009, Wyeth transferred IND sponsorship to Pfizer (Wyeth was maintained as wholly owned subsidiary of Pfizer).
- On April 24, 2014, Pfizer transferred sponsorship of the IND to Puma.
- On November 14, 2014, the FDA acknowledged Puma's plan to request a full waiver from Pediatric Research Equity Act requirements based on their agreed upon Initial Pediatric Study Plan (iPSP) dated October 13, 2014.
- On November 25, 2014, a Type C meeting was held to discuss carcinogenicity studies.
- On March 10, 2015, and June 9, 2015, the executive carcinogenesis assessment committee recommended 2-year rate and 6 month Tg mouse carcinogenicity studies, respectively.
- On April 24, 2015, a Type C meeting was held to discuss data presentation and format, as well as the Statistical Analysis Plan.
- On March 21, 2016, a Type B, pre-NDA meeting was held.
- On July 8, 2016, the Agency provided a written response to a Type A non-clinical meeting, confirming that a 1 year rat carcinogenicity study will support NDA submission.
- On July 16, 2016, the NDA was submitted electronically.
- An Oncology Drug Advisory Committee meeting was held on May 24, 2017.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigations (OSI) audit was requested for this NDA. See Clinical Inspection Summary written by Lauren Iacono-Connors, Ph.D., Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI. The OSI inspected four of the highest accruing sites as well as the Applicant. A summary of the site inspections is provided in Table 2.

Table 2: Summary of OSI Site Inspections

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #1: Arlene Chan (Site 1360) 101 Monash Ave., Nedlands Western Australia 6009 Australia	Protocol: 3144A2-3004-WW Subjects: 46	October 31, 2016 – November 4, 2016	Preliminary classification VAI
CI #2: Beth Hellerstedt (Site 1526) 6204 Balcones Drive Austin, TX 78731	Protocol: 3144A2-3004-WW Subjects: 70	January 9-13, 2017	Preliminary Classification NAI
CI #3: Neelima Denduluri (Site 1804) 8503 Arlington Boulevard, Suite 400 Fairfax, VA 22031	Protocol: 3144A2-3004-WW Subjects: 29	December 5-6, 2016	Preliminary Classification NAI
CI #4: Zorica Tomasevic (Site 1191) Belgrade 11 000 Serbia	Protocol: 3144A2-3004-WW Subjects: 22	November 14-18, 2016	Preliminary classification VAI
Sponsor: Puma Biotechnology Inc. 10880 West Wilshire Blvd Suite 2150 Los Angeles, CA 90024-4800	Protocol: 3144A2-3004-WW Site Numbers: 1526, 1804, 1360, 1191, 1189, and 1860	March 15-17, 2017	Preliminary classification NAI

NAI: No deviations from regulations. VAI: Deviation(s) from regulations.

1. Site 1360 (Professor Arlene Chan)

The inspection revealed no significant deficiencies. The primary efficacy endpoint, iDFS, was verifiable with the source records generated at the site. There was no evidence of underreporting of AEs. However, the drug dispensing records were not always an accurate accounting of drug use by study subjects. Specifically, at the Month 1 study visit, February 24, 2010, Subject 12831 was dispensed IP kits 506396 and 506398. The subject would run out of study drug prior to the month 3 visit and therefore, required a resupply before the visit. Source documentation indicated that the site received a verbal assignment on May 4, 2010, from the IVRS (ICON) system kit 505971 to be dispensed to the subject. An email dated May 4, 2010, shows kit 505974 was manually assigned by the IVRS system to be dispensed to the subject. An email dated May 4, 2010 system for kit 505971 was manually assigned by the IVRS system to be dispensed to the subject. The drug accountability log shows kit 505971 was dispensed to this subject on May 4, 2010. Kit 505974 was never dispensed and was logged as destroyed at the time of study close per site guidelines on September 20, 2011.

<u>Reviewer comment:</u> In a written response dated November 15, 2016, to the Form FDA 483 inspection operations, Professor Chan acknowledged that investigational drug disposition records were not adequate and that the IVRS system was non-functional at the time. A corrective action plan, to include a new SOP, "Management of Centrally Allocated Trial Medication," should mitigate the inspectional finding moving forward.
This inspectional observation should have no impact on study outcomes or have placed the subject at undue risk.

4. Site 1191 (Dr. Zorica Tomasevic)

The inspection revealed no significant deficiencies. The primary endpoint, iDFS, was verifiable with the source records generated at the site. With a few exceptions, there was no evidence of under-reporting of AEs. Briefly, there were three subjects who had reported AEs in their diary that were not included in the subjects' eCRFs or the data listings submitted to the application.

Dr. Tomasevic stated in a written response to the Form FDA 483 inspectional observations, dated December 7, 2016, that at the time of subject visits, the Principal Investigator would review all diary entries with the subject. Potential AEs were discussed and documented in the source notes according to the instructions provided in the study protocol. Dr. Tomasevic acknowledged that all AEs discussed with the subject should have been reported to the sponsor per protocol requirements. She has since developed new processes that are being implemented that should minimize these inspectional observations moving forward. As part of the corrective action plan, Dr. Tomasevic reviewed the medical charts from all subjects and confirmed the safety of study subjects was not compromised. These inspectional observations should not importantly impact study outcomes or have placed subjects at undue risk.

Finally, the site did not maintain CT and MRI imaging used to determine (in part) disease

progression. However, the reports from the ultrasounds, CT scans, and MRIs for all subjects are included in the subject charts. Dr. Tomasevic responded in a written response to the From FDA 483 inspectional observations, dated December 7, 2016, that the clinical investigators at this site are not certified to read medical imaging scans; therefore, the site procedure requires that a local radiologist perform the scan, read the scan, and complete and return a signed clinical report to the clinical site. These signed radiology reports are maintained as source documentation in the subject charts and study records. As part of a corrective action, copies of all CT/MRI images performed at the Institute for Oncology and Radiology have since been retrieved and placed in the study files. Starting in December 2016, the site modified their process to obtain a copy of all medical imaging scans to include in the study file together with the radiology report.

Reviewer comment: ***The inspectional observation should not impact study outcomes or have placed subjects at risk.***

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

Two process-related impurities, [redacted] (b) (4), were identified in the drug product. These impurities were qualified in a 14-day toxicity nonclinical study in rats. Impurity [redacted] (b) (4) has been qualified up to [redacted] (b) (4)% and impurity [redacted] (b) (4) has been qualified up to [redacted] (b) (4)%. These impurities were also negative in the standard battery of genetox assays.

4.3. Clinical Microbiology

See the FDA product quality review for details.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Neratinib inhibited the kinase activity of EGFR, HER2, and HER4 in vitro at clinically relevant concentrations. Neratinib inhibited cell proliferation, HER2, and EGFR receptor phosphorylation; downstream MAPK and AKT signal transduction pathway activity and cell cycle regulatory pathway activities in HER2- and EGFR-dependent cancer cell lines. Inhibition of HER2 and EGFR by neratinib is irreversible, potentially due to covalent interaction at the cysteine residue of the adenosine triphosphate binding site of HER2. In vivo, neratinib inhibited the growth of tumors that express mutated HER2 oncogene or overexpress HER2 or EGFR, but did not inhibit tumor growth of human breast tumor cells that have low levels of HER2 or EGFR expression in mouse xenograft studies. The approved Established Pharmacologic Class (EPC) of "kinase inhibitor" is both clinically meaningful and scientifically valid for neratinib based on its pharmacological activity.

Based on in vitro screening assays, neratinib and its metabolites are not expected to have off-target activity for other receptors, enzymes, or ion channels at clinically relevant concentrations.

Single oral doses of neratinib at 5, 25, or 100 mg/kg to male rats did not have any effects on respiratory and CNS functions. Neratinib was a low potency hERG blocker in vitro, and single oral doses of neratinib at 5 or 10 mg/kg to male and female beagle dogs did not produce any remarkable effects on heart rate, arterial blood pressure, or electrocardiograms.

The brain-to-plasma exposure (AUC_{0-24}) ratios were low in CD-1 mice, suggesting poor penetration through the blood brain barrier.

The four metabolites identified in human plasma at the highest concentrations following oral neratinib administration are M3 (pyridine N-oxide), M6 (*N*-desmethyl), M7 (dimethylamine N-oxide) and M11 (bis-N-oxide). The steady-state % of total AUC of neratinib plus metabolites in human plasma for neratinib, M3, M6, M7 and M11 were 56.8, 8.5, 19.3, 12.2, and 3.3 %, respectively. The potency of the four metabolites was less than or equal to neratinib in binding or kinase inhibition of EGFR, HER2 and HER4. M3 was formed in rats, dogs and humans, and was further characterized in rats. Administration of M3 daily for 14 days resulted in no adverse effects in a repeat-dose toxicology study in rats up to a dose that was approximately equivalent to the amount of this metabolite formed in humans. M6 and M7 were formed by rats, dogs and humans at similar levels. M11 is a unique human metabolite, but is only present at 3.3% of total neratinib plus metabolites in human plasma, so no further toxicity characterization is warranted.

Repeat-dose, GLP, general toxicology studies with neratinib were conducted in rats and dogs for 26 and 39 weeks, respectively. Four neratinib-related deaths occurred in rats at ≥ 10 mg/kg/day prior to the scheduled necropsy. Clinical signs in these animals in the 30 mg/kg

group included fecal alterations, thin appearance, piloerection, and red pigment around nose/mouth. Necropsy findings in early decedents included lymphoid atrophy of the spleen and thymus. In surviving animals, clinical signs were similar to early decedents at 30 mg/kg/day; however, clonic convulsions were observed in a male at 10 mg/kg/day and a female at 30 mg/kg/day. One male dog receiving 2 mg/kg/day was found dead on day 230 (week 33) with a cause of death of cardiopulmonary thromboembolism secondary to renal membranous glomerulonephritis. Clinical signs included liquid/soft feces and decreased bodyweight. Decreased body weights and gains were observed at 30 mg/kg/day.

Neratinib-related increases in WBC and differentials, platelets and fibrinogen were observed at doses ≥ 3 mg/kg/day in rats and 2 mg/kg/day in dogs and correlated with microscopic findings of inflammation. Target organ toxicities were observed in the liver, lymph nodes, skin, gastrointestinal system, and mammary gland in males. Tubular basophilia in the kidney was also observed in dogs. Findings were either completely reversed or there was a trend of recovery after 28 days of non-dosing. These findings were consistent with the clinical adverse reactions reported in clinical trials, the majority of which (e.g., GI disorders and skin) are likely related the pharmacological inhibition of EGFR, HER2, or HER4. The AUC in rats and dogs in these studies were less than the AUC in patients receiving the recommended dose of 240 mg/day.

Diarrhea is the most common adverse event that occurs in patients treated with neratinib. A study was conducted in a rat model of neratinib-induced diarrhea to investigate pharmacokinetics and the effect on GI toxicity in the presence of therapeutic interventions. Budesonide was the most effective intervention of those tested in this model against neratinib-induced diarrhea, which was likely mediated by inhibiting mucosal inflammation and bile acid malabsorption. The results of this study may guide future clinical studies aimed at testing mitigation strategies for neratinib-induced diarrhea.

Neratinib and its metabolites (M3, M6, M7, & M11) were not mutagenic in the *in vitro* bacterial reverse mutation assay and not clastogenic in the *in vitro* human peripheral blood lymphocyte chromosome aberration assay. Neratinib was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

Neratinib was not carcinogenic in a 6-month study in Tg.rasH2 transgenic mice when administered daily by oral gavage at doses up to 50 mg/kg/day in males and 125 mg/kg/day in females. A 2-year carcinogenicity study in rats with oral neratinib is ongoing at this time and will be completed as a post-marketing requirement. No neratinib-related neoplastic findings were observed in rats in this study in groups receiving only 1 year of administration at doses up to 10 mg/kg/day.

Neratinib administration did not affect fertility in male or female rats at doses lower than the recommended dose of 240 mg/day in patients based on body surface area (mg/m^2). In the 39-week repeat-dose toxicity study in dogs, tubular hypoplasia of the testes was reported at exposures (AUC) that were lower than exposures in patients receiving the recommended dose of 240 mg/day, suggesting the potential for effects on male fertility.

In an embryo-fetal development study in rabbits, administration of oral neratinib to pregnant females during organogenesis resulted in maternal toxicity, abortions and embryo-fetal death (increased resorptions). Increased incidences of fetal gross external (domed head), soft tissue (dilation of the brain ventricles and ventricular septal defect), and skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities were observed. These findings occurred at AUCs below the AUC in patients receiving 240 mg/day. The package insert includes recommendations for contraception use during treatment and for 1 month after the last dose in females of reproductive potential and for 3 months after the last dose in males with female partners of reproductive potential. Current recommendations for contraception duration are 1 month for females and 3 months for males for a teratogenic and non-genotoxic drug with a plasma half-life of 17 hours, such as neratinib.

In a peri- and postnatal development study in rats, oral administration of neratinib from gestation day 7 until lactation day 20 resulted in maternal toxicity including decreased body weight gains and food consumption at AUCs lower than the AUC in patients receiving 240 mg/day. Effects on long-term memory were observed in male offspring at maternal doses that were lower than the recommended dose of 240 mg/day in patients based on mg/m^2. Due to the potential for serious adverse reactions in a breastfed infant, lactating women are advised in the package insert not to breast feed while taking Nerlynx and for 1 month following the last dose, since this duration exceeds 5 plasma half-lives for neratinib in patients (up to 17 hours) and is consistent with the recommendation for contraceptive use in females of reproductive potential.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

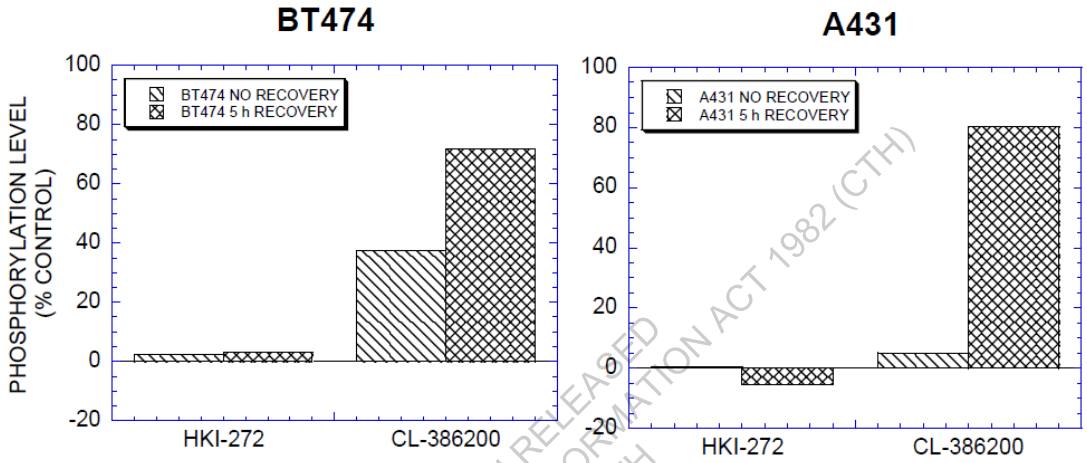
Primary pharmacology

Neratinib inhibited the kinase activity of HER2 and EGFR at IC_{50} values of 59 nM and 92 nM, respectively, in studies conducted by the Applicant. In another study reported in the literature, neratinib inhibited the activity of HER2 (IC_{50} = 39 nM), EGFR (IC_{50} =12 nM) and HER4 (IC_{50} = 19 nM) in a phosphorylation assay (Davis, Hunt, et al. 2011[1]). The kinase activity of neratinib was evaluated using a panel of recombinant serine-threonine kinases (Akt, cyclin D1/cdk4, cyclin E/cdk2, cyclin B1/cdk1, IKK-2, MK-2, PDK1, c-Raf, Tpl-2) or cMET. The results show that neratinib inhibited HER2 and EGFR phosphorylation at IC_{50} values of 59 nM and 92nM, respectively. Further, neratinib did not inhibit or caused weak inhibition of other tyrosine kinases (IC_{50}'s ≥ 8 fold over EGFR), suggesting specificity of neratinib for HER2 and EGFR.

The irreversible binding of neratinib to HER2 and EGFR receptors was determined in HER2 and EGFR overexpressing cell lines. BT474 (breast cancer) and A431 (squamous carcinoma) cells were incubated with 1 µM of neratinib (HKI-272) or CL-386200 for 3 hr. CL-386200 was included

because it lacks the Michael acceptor functional group and is a reversible binding inhibitor. Receptor phosphorylation in cells was measured immediately after or 5 hr after the removal of neratinib from the medium. If binding is irreversible, the inhibitor will remain bound to the kinase, and continue to block phosphorylation of the receptor after withdrawal of drug. The results show that neratinib inhibited HER2 and EGFR receptor phosphorylation by 98% and >99%, respectively compared to controls. No increase in phosphorylation was observed 5 hr after removal of neratinib (% inhibition was 97% for BT474 cells and 105% for A431 cells).

Figure 1. Irreversible Binding of Neratinib (HKI-272) to ERBB2



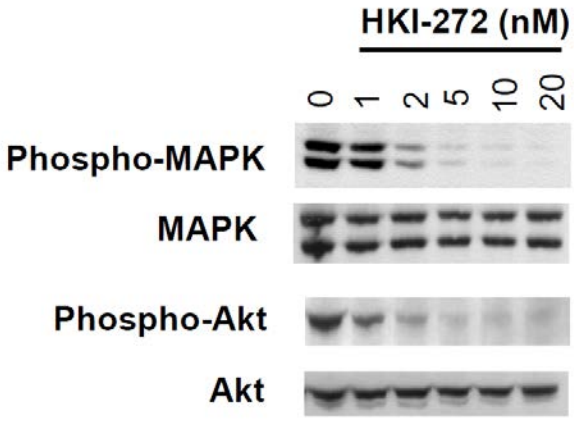
(Excerpted from Applicant's submission)

The Applicant evaluated the covalent interactions between neratinib and HER2. The results show that the irreversible binding of neratinib to HER2 is likely due to the covalent interactions of neratinib with the cysteine residue of the adenosine triphosphate binding site of HER2.

The effects of neratinib on target receptor function were determined by measuring receptor autophosphorylation in BT474 (breast cancer) and A431 (squamous carcinoma) human cells that overexpress HER2 and EGFR, respectively. The results show that neratinib inhibited HER2 ligand-independent receptor phosphorylation in BT474 cells and EGFR-dependent receptor phosphorylation in A431 cells at IC_{50}'s of 5 and 3 nM, respectively.

The effects of neratinib on downstream signaling transduction markers and cell cycle regulators were determined. The results show that neratinib reduced the phosphorylation of Akt and MAP kinase in BT474 cells at an IC_{50} of 2nM.

Figure 2. Effects of Neratinib on Map Kinase and Akt Activation



(Excerpted from Applicant's submission)

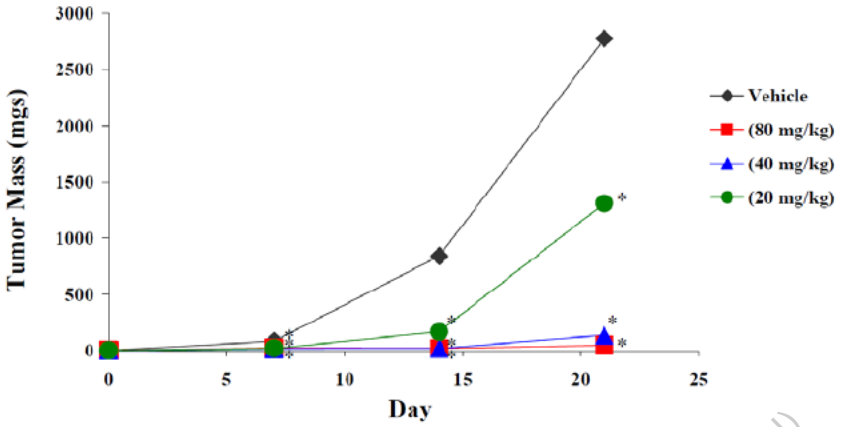
The effect of neratinib on HER2 signaling pathways and cell regulatory proteins and cell cycle phase transitions was examined. The results show that neratinib reduced cyclin D1 expression by 50% at an IC_{50} of 9 nM in BT474 cells. Further, neratinib caused a 50% decrease in the number of cells in the S (DNA synthesis) phase of the cell cycle at an IC_{50} of 2 nM.

The Applicant examined the effect of neratinib on cell cycle regulatory proteins and cell cycle transitions. Neratinib reduced the phosphorylation of cyclin D1 and retinoblastoma gene product (RB) at 5 nM. A corresponding increase in p27 (inhibitor of cell cycle progression) was also observed. Neratinib blocked cell cycle progression, causing a G1/S arrest. This was evidenced by an increase in the number of cells in G1 phase following addition of neratinib and 5-bromodeoxyuridine.

The ability of neratinib to inhibit cell proliferation was evaluated in a panel of cell lines (3T3, 3T3/*neu*, A431, SKBr-3, BT474, MDA-MB-435, and SW620) with varying levels of expression for EGFR and/or HER2. Neratinib reduced or inhibited the proliferation of 3T3/neu (IC_{50} = 3 nM HER2 oncogene); SK-BR-3 and BT474 (IC_{50}=2 nM; HER2 overexpressing); and A431 (IC_{50}=81 nM; EGFR overexpressing).

The inhibitory activity of neratinib on HER2 expressing tumors was evaluated in vivo. Neratinib was administered to athymic nu/nu female mice with tumors that expressed varying levels of HER2 or EGFR for 10 (3T3/neu) or 20 (BT-474, SK-OV-3, A431, MCF7, MX-1) consecutive days post tumor cell implantation. Tumor mass was determined every 7 days for up to 43 days and the percent tumor growth inhibition of the treated groups as compared to the control group. Neratinib inhibited tumor growth in a dose-dependent manner in multiple cell lines expressing HER2 or EGFR. Results in 3T3/neu cells were representative of effects in other cell lines.

Figure 3. Effect of Neratinib (HKI-272) on the growth of 3T3/neu in nude mice



Groups of 10 female nu/nu mice were injected with 2 x 106 3T3/Neu cells. Beginning the day after tumor cell implantation, mice were treated PO for 10 consecutive days with vehicle or HKI-272 at the doses indicated. Tumor mass was determined every 7 days for a period of 21 days. * P< 0.05 by one tailed Student's t-test.

(Excerpted from Applicant's submission)

The four metabolites identified in human plasma at the highest concentrations following oral neratinib administration are M3 (pyridine N-oxide; WYE-121529), M6 (N-desmethyl; WAY-193575), M7 (dimethylamine N-oxide; WYE-121592), and M11 (bis-N-oxide). The steady-state % of total AUC of neratinib plus metabolites in human plasma for neratinib, M3, M6, M7 and M11 were 56.8, 8.5, 19.3, 12.2, and 3.3 %, respectively. The % of AUC of neratinib (i.e., parent) in human plasma for M3, M6, M7, and M11 were 15, 33, 22, and 4%, respectively.

Neratinib, M3, M7, and M11 metabolites were evaluated in vitro for kinase inhibition activity against EGFR, HER2, and HER4 in binding and cell-based assays. Neratinib and M7 inhibited EGFR kinase activity similarly (IC_{50} values of 2.7 and 4.4 nM, respectively), while M3 and M11 were less active (IC_{50} values of 10 and 19 nM, respectively). Neratinib and M3 inhibited HER2 kinase activity similarly (IC_{50} values of 17 and 32 nM, respectively), while M7 and M11 had ≤ 10-fold the activity (IC_{50} values of 330 and 560 nM, respectively). All three metabolites, M3, M7, and M11, inhibited HER4 with IC_{50} values of 5.7, 3.8 and 4 nM, respectively. Neratinib inhibition of HER4 was not evaluated in this study.

The applicant evaluated the kinase activity of metabolite M6 (N-desmethyl) compared to neratinib in autophosphorylation assays. M6 also inhibited HER2, EGFR, and HER4 kinase activity in vitro at IC_{50} values of 21, 7, and 13 nM, respectively, to similar levels to neratinib (IC_{50} values of 39, 12 and 19, respectively). Metabolite M6 had similar potency as neratinib in cell proliferation assays in cells that overexpress HER2 or EGFR. M6 had activity that was less than or equal to neratinib in cell proliferation assays. Unlike neratinib, metabolite M6 did not reduce tumor growth in 3T3/*neu* or BT 474 xenograft mouse tumor models.

Secondary Pharmacology

Type of Study	Major Findings
Selectivity	
Study Title: Antitumor activity of HKI-272 (WAY-179272), an inhibitor of the Her-2 tyrosine kinase III: (b) (4) **Study No.:** RPT-49659 In vitro: Neratinib (0.001, 0.1 or 10 µM) was screened against a panel of 65 receptor targets including neurotransmitters, ion channels, prostaglandins, growth factors, steroids, second messengers, peptides, and various enzymes. Results were reported as percent inhibition of specific binding.	At 10 µM, neratinib inhibition was detected in the following: Adrenergic Alpha 1 (77%), Histamine H2 (104%), Histamine H3 (86%), Muscarinic M1 (91%), Muscarinic M2 (61%), Calcium Channel Type L (57%), Sodium Site 2 (53%), Neuronal-Binding (54%), Oxytocin (71%), Platelet Activating Factor (72%), Neurokinin NK1 (81%), Neurokinin NK2 (91%), Neurokinin NK3 (77%) and Vasopressin 1 (80%)
Study Title: *In Vitro* Pharmacology Study of One Compound **Study No.:** 100023347 In vitro: Neratinib (30 - 100 µM) was evaluated for radioligand binding activity in a series of binding assays to determine the binding inhibition for each target.	Neratinib IC_{50} values for the following targets: Ca^{2+} channel (L, dihydropyridine site): 11 µM α1 (non-selective): 16 µM; Histamine (H20): 4.5 µM; Histamine (H3): 12 µM; Muscarinic (M1): 1.0 µM; Muscarinic (M2): 9.0 µM; Na+ channel (site2): 5.4 µM; Neurokinin (NK1): 0.83 µM; Neurokinin (NK2): 4.1 µM; Neurokinin (NK3): 31 µM; Oxytocin: 3.6 µM; PAF: 15 µM; Vasopressin 1a: 1.1 µM

Neratinib metabolites M3, M6, M7, and M11 were studied in binding, enzyme, and uptake, and cellular and nuclear receptor functional assay screens to identify any potential off-target activity. The metabolites inhibited similar targets as neratinib with no apparent new targets that were only inhibited by the metabolites. With the calculated IC_{50} values in these assays, inhibition of these targets at clinically relevant concentrations in patients is not expected, given that the IC_{50} values in vitro were approximately ≥ 8-fold higher than the C_{max} in patients receiving the recommended dose of 240 mg/day.

Due to the severity of diarrhea that occurs in a large proportion of patients treated with neratinib, an in vitro study was conducted with neratinib to determine if it inhibits the cystic fibrosis transmebrane conductance regulator (CFTR). The CFTR is a major cyclic adenosine monophosphate (cAMP)-regulated chloride channel that is involved in intestinal fluid secretion and homeostasis. CFTR can cause excessive fluid secretion and secretory diarrhea if hyperactivated by drugs that interfere with CFTR-containing macromolecular complexes in intestinal epithelium which typically regulate its chloride channel function. At concentrations of

0.03, 0.3, 3, 10, and 30 µM in a patch-clamp study, neratinib had no effect on the CFTR chloride current. This suggests that neratinib mediated diarrhea is not through the CFTR channel.

Study title/ number: A rat model to investigate neratinib-induced diarrhea: pharmacokinetics and interventions (RPT-PUMA-0001)

Key Study Findings

- Budesonide appears to be effective in this model against neratinib-induced diarrhea by inhibiting mucosal inflammation and bile acid malabsorption.

Conducting laboratory and location: (b) (4)

GLP compliance: No

Methods

Frequency of dosing:	Daily for 28 consecutive days
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% HPMC
Species/Strain:	Crl:WI(Han) rats
Age:	7-9 weeks

Observations and Results: changes from control

Table 3. Diarrhea Rat Model Study Design

Group number	Dose (mg/kg/day)	Concentration (mg/ml)	Number /Sex
PU1			
1. Control	0		6M
2. Neratinib	15	3	3M
3. Neratinib	30	6	3M
4. Neratinib	50	10	6M
PU2			
1. Control	0		16M
2. Neratinib	50	10	16M
3. Neratinib + Crofemeler	50 + 25	10 + 5	16M
4. Neratinib + Loperamide	50 + 0.4	5 + 0.4	16M
PU3			
1. Control	0		4F
2. Neratinib	50	10	8F
PU4			
1. Control	0		4M
2. Neratinib	50	10	4M
3. Neratinib + Crofelemer	50 + 25	10 + 5	4M
4. Neratinib + Loperamide	50 + 0.4	10 + 0.4	4M
PU5			
1. Control	0		16M
2. Neratinib	50	10	16M
3. Neratinib + VSL3	50 + 4.0 x10^8 cfu	10 + 4.0 x10^8	16M
4. Neratinib + Budesonide	50 + 1	10 + 0.2	16M
5. Neratinib + Dexamethasone	50 + 0.1	10 + 0.02	16M
6. Neratinib + Naproxen	50 + 3 (twice daily)	10 + 0.6	16M
7. Neratinib + Colesevelam	50 + 300	10 + 40	16M

(Excerpted from Applicant's submission)

PU1:

- The 50 mg/kg dose caused the most consistent diarrhea and was associated with microscopic changes in the GI.

PU2:

- Neratinib concentration increased with co-administration of loperamide.
- Crofelemer decreased mean diarrhea severity score while loperamide increased mean diarrhea score.
- Five rats were removed due to toxicity associated with loperamide administration. Dose was reduced to 0.4 mg/kg.
- A decrease in baseline short circuit conductance (Cl^- secretion) in the ileum in all treatment groups, indicating that crofelemer decreases chloride secretion (-47%, -32% and -51% change from controls for neratinib, neratinib + crofelemer and neratinib + loperamide, respectively).

PU3:

- Neratinib caused more severe diarrhea in female compared to male rats.

PU4: Blood samples were taken at 0, 1, 3, 6, 9, 12, and 24 hr.

- Neratinib concentration increased with co-administration of loperamide compared to neratinib only.
- Neratinib concentration decrease with co-administration of crofelemer compared to neratinib only.

PU5:

- Co-administration of dexamethasone and budesonide increased neratinib concentration.
- ↓ mean number of days with moderate diarrhea, the daily proportion of rats with moderate diarrhea from treatment day 21, mean diarrhea severity score from day 23, prevented neratinib-induced apoptosis was prevented.
- Budesonide and dexamethasone co-treatment were associated with substantial inhibition of growth.
- ↓ urate (at 28 days only), ↓ albumin, ↓total protein, ↓ ALT and ↓ AST.
- Budesonide prevented the neratinib-related increase number of crypt goblet cells and reduced villus goblet in the ileum.
- Budesonide prevented the neratinib-related increase apoptosis in crypts of the proximal colon (1.4-fold (neratinib) & -37% (neratinib + budesonide) change from control).
- Apoptosis in the ileum was significantly decreased with neratinib & budesonide intervention (-30% & -66% change from control for neratinib & neratinib + budesonide, respectively).
- ErbB1 expression was decreased in the ileum in groups treated with neratinib and Neratinib + budesonide (-42% & -38% change from control for neratinib & neratinib + budesonide, respectively.
- ErbB2 expression was decreased in the ileum at 28 days by neratinib treatment (-25% change from control), which was prevented by budesonide (+25% change from control).

- Budesonide and dexamethasone co-treatment were associated with increased ErbB1 expression in the ileum and colon via western blot analysis compared to controls and neratinib-alone.
- Relative Phosphorylated ErbB2 Y1248 expression in the distal ileum and proximal colon was reduced in neratinib-treated rats, which was partially prevented by budesonide.

Safety Pharmacology

Study Title: HKI-272: Single Dose Oral (Gavage) Respiratory Safety Pharmacology Study in Male Rats

Study No.: RPT-47595

The effect of neratinib on respiratory function was evaluated in rats at single oral doses of 5, 25, and 100 mg/kg or vehicle control. There were no neratinib-related effects on mortality, clinical signs, and respiratory function, under the conditions tested.

Study Title: HKI-272: Single Dose Oral (Gavage) Central Nervous System Safety Pharmacology Study in Male Rats

Study No.: RPT-47592

The effect of neratinib on central nervous system (CNS) function was evaluated in rats at single oral doses of 5, 25, and 100 mg/kg or vehicle control. There were no neratinib-related effects on mortality, clinical signs, and CNS function, under the conditions tested.

Study Title: HKI-272: Effects on Cloned HERG Channels Expressed in Mammalian Cells

Study No.: RPT-59094

The effect of neratinib on the hERG (human ether-a-go-go-related gene) channel current was evaluated. Human embryonic kidney (HEK293) cells stably expressing the hERG potassium channel were exposed to HKI-272 at concentrations of 0.3 µM (0.2 µg/mL), 1 µM (0.7 µg/mL), 3 µM (2 µg/mL), and 10µM (6.8 µg/mL). Neratinib inhibited hERG potassium current at 4.9% (n = 3) at 0.3 µM, 34.2% (n = 3) at 1 µM, 61.4% (n = 3) at 3 µM, and 90.1% (n = 3) at 10 µM. Neratinib caused a concentration-dependent inhibition of hERG current at an IC_{50} of 1.9 µM (1.3 µg/mL). Therefore, neratinib has the potential inhibit the hERG channel in vitro under the conditions tested, although it is a low potency blocker.

Study Title: HKI-272: A Single Oral Dose Crossover Cardiovascular Study in Beagle Dogs

Study No.: RPT-48164

In this GLP study, the cardiovascular effects of neratinib after a single oral were evaluated in Beagle dogs. Dogs (n=4) were dosed at 5, 10, and 20 mg/kg neratinib or vehicle. All animals survived during this study. Clinical signs of emesis were observed in all dose groups. No remarkable changes in heart rate or arterial blood pressure were observed. PR, QRS, and QTc intervals of neratinib treated animals were comparable to the vehicle control group.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Study Title: HKI-272: Multiple (10 days) Dose Oral (Gavage) Pharmacokinetic Study in Male and Female Rats **Study No.:** RPT-75988	Neratinib and metabolite M7 exposure was lower in male rats compared to female rats following multiple doses of neratinib. No gender differences in metabolite M6 exposure were observed in rats. The T_{max} for HKI-272 and metabolites M6 and M7 ranged from 3 – 4 hr. The elimination half-life ($T_{1/2}$) of neratinib and metabolite M6 were 3.9 hr for male rats and 3.5 hr for female rats. The elimination half-life ($T_{1/2}$) of metabolite M7 was 7.7 hr for female rats. $T_{1/2}$ for male rats was not determined.
Study Title: HKI-272: Multiple (10 days) Dose Oral (Gavage) Pharmacokinetic Study in Male and Female Dogs **Study No.:** RPT-75987	No gender differences in neratinib and metabolite M7 exposure were observed in dogs. Metabolite M6 exposure was lower in males compared to females. The T_{max} for neratinib and metabolites M6 and M7 ranged from 1 to 6 hr in males and females, respectively. Following a single dose, the elimination half-life ($T_{1/2}$) of metabolites M6 & M7 were 10 hr for male dogs and 13 hr for female dogs. The elimination half-life ($T_{1/2}$) of neratinib was ~ 15 hr following multiple oral doses.
Distribution	
Study Title: HKI-272: In Vitro Protein Binding of HKI-272 in Male Mouse, Rat, Rabbit, Dog, and Human Plasma **Study No.:** RPT-61718	The overall mean percentages of neratinib bound to mouse, rat, rabbit, and dog plasma proteins were 99.8%, 99.9%, 98.8%, and 99.2%, respectively. Neratinib was not stable in human plasma under the conditions of the study. Plasma binding was determined indirectly by binding to HSA or AAG. Binding to HSA was 99.1% and AAG was 98.5%. Human plasma protein binding was estimated to be > 99%.
Study Title: HKI-272: Tissue Distribution Following a Single Oral 10 mg/kg Administration of [^{14}C]HKI-272 in Male Albino Sprague-Dawley and Pigmented Long-Evans Rats **Study No.:** RPT-71617	Radiolabeled neratinib was observed at 4 hr post-dose and was eliminated with a $t_{1/2}$ of ~3.9 and ~69 hr in plasma and whole blood, respectively. Radiolabeled neratinib-derived radioactivity was observed in all tissues evaluated, except for the eye and brain.
Study Title: HKI-272: Single and Multiple (7 Days) Dose Oral (Gavage) Pharmacokinetic and Brain Penetration Study in Male Mice	Brain-to-plasma exposure (AUC_{0-24}) ratios were 0.079 and 0.052 on day 1 and day 7, respectively, indicating poor penetration of neratinib in the mouse brain.

Type of Study	Major Findings
Study No.: RPT-77053	
Metabolism	
Study Title: HKI-272: Metabolism of ^{14}C-HKI-272 in Nude Mouse, Rat, Dog, and Human Liver Microsomes and LC-MS/MS Characterization of Metabolites **Study No.:** RPT-49166	- In the presence of NADPH and UDPGA, the main metabolites observed in all species were M6 (*N*-desmethyl) and M7 (*N*-oxide). - Similar for all species, except more of the M6 metabolite in dog. - M2 was observed in all species except dog. - M3 was observed in the nude mouse and human (addition of oxygen to neratinib). - No glucuronide conjugates detected. - When incubated with glutathione, M5 was observed in all species (glutathione conjugate). - In the presence of all three cofactors, the main metabolites were M4 (glutathione conjugate of M6) and M5. - M7 was observed in all species. - M1 was human specific and identified as the addition of oxygen and glutathione to HKI-272.
Study Title: HKI-272: Metabolism of ^{14}C-HKI-272 in Rats and Dogs and LC-MS/MS Characterization of Metabolites **Study No.:** RPT-49167	- Neratinib was the major circulating entity in rat and dog plasma at 56-80% and 44-73%, respectively. - M4 and M5 were detected in rat plasma (6-15%) and feces (5-10%). - Metabolites 6 and 7 were detected in dog plasma (12-19%).
Excretion	
Study Title: HKI-272: Single ^{14}C Oral Dose Mass Balance Study in Male Rats **Study No.:** RPT-47937 **Study Title:** HKI-272: Single ^{14}C Oral Dose Mass Balance Study in Male Dogs **Study No.:** RPT-48403	The major excretion route for neratinib was the feces in rats (90.7%) and dogs (66.2%). In rats and dogs, 89% and 60% was excreted within 48 hr of administration, respectively.
TK data from general toxicology studies <u>Rat: 26-week repeat-dose toxicology study</u> • Dosed once daily for 26 weeks • Dose levels: 3, 10, and 30 mg/kg at 10 mL/kg	<u>$T_{1/2}$</u>: 3.4 to 7.1 hours (males); 2.1 to 7.1 hours (females) <u>T_{max}</u>: 3 – 8 hours <u>Dose proportionality</u>: Plasma exposure ($AUC_{0\text{-}24h}$ and C_{max}) increased in a dose-proportional manner in males and more than dose proportional manner in females.

Type of Study

- Blood sample were collected on Day 176 at 1, 3, 4, 8, 12 and 24 hr post-dose

Major Findings

Day	Sex	Dose (mg/kg)	Cmax (µg/mL)	AUC_{0-t} (ng.hr/ml)	AUC/ Dose
176	M	3	0.468	5.29	1.76
		10	1.44	15.6	1.56
		30	2.45	33.0	1.10
	F	3	0.705	5.91	1.97
		10	3.22	38.9	3.89
		30	5.80	88.6	2.95

$T_{1/2}$: 2 – 7 hours
T_{max}: 1 – 8.5 hours
Accumulation: low
Dose proportionality: C_{max} and AUC increased dose-proportionally between all doses for males and females at Day 1 and males at Day 179; less than dose-proportionally between 2 and 6 mg/kg in females.

Dog: repeat-dose toxicology study (No. 66466)

- Dosed once daily for 39 weeks
- Dose levels: 0.5, 2, and 6 mg/kg at 5 mL/kg
- Blood samples were collected on Days 1 and 179 at 1, 2, 4, 7, 10 and 24 hr post-dose

Day	Sex	Dose (mg/kg)	Cmax (µg/mL)	AUC_{0-t} (ng.hr/ml)	AUC/ Dose
1	M	0.5	8.94	48.3	116
		2	33.5	211	118
		6	105	799	143
	F	0.5	8.7	34.4	76.9
		2	37.6	194	103
		6	94.3	801	139
179	M	0.5	6.89	59.2	118
		2	35.1	323	162
		6	77.3	870	145
	F	0.5	6.59	60.6	121
		2	38.4	512	256
		6	68.9	575	95.9

TK data from reproductive toxicology studies

Study title: An Embryo-Fetal Development Study of PB272 (Neratinib Maleate) by Oral Gavage in Rats
Study No.: 20065668

Rat

Species	Dose (mg/kg/day)	Dose (mg/m^2)	AUC (ng.hr/ml)	Human AUC_{ss} at clinical dose of 240 mg/dose	Ratio (Animal AUC/Human AUC)
Pregnant rat (GD17)	5	30	5320	939 (ng.hr/ml)	5.7
	10	60	8080		8.6
	15	90	14400		15.3

Study title: An Embryo-Fetal Development Study of PB272 (Neratinib Maleate) by Oral Gavage (Stomach Tube) in Rabbits
Study No.: 20065669

Rabbit

Species	Dose (mg/kg/day)	Dose (mg/m^2)	AUC (ng.hr/ml)	Human AUC_{ss} at clinical dose of 240 mg/dose	Ratio (Animal AUC/Human AUC)
Pregnant rabbit (GD19)	3	36	162	939 (ng.hr/ml)	0.2
	6	72	502		0.5
	9	108	787		0.8

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: HKI-272: Twenty-six Week Oral (gavage) Toxicity Study in Rats With a 4-Week Recovery (RPT-65714)

Key Study Findings

- 4 neratinib-related deaths: 1 (M) at 10 mg/kg/day & 3 (2M/1F) at 30 mg/kg/day. Clinical signs at 30 mg/kg included fecal alterations, thin appearance, piloerection, and red pigment around nose/mouth; necropsy findings included lymphoid atrophy of the spleen and thymus.
- Clonic convulsions in 1 (M) at 10 mg/kg/day and 1 (F) at 30 mg/kg/day
- Decreased body weights at 30 mg/kg/day, and increased WBC and differentials, and fibrinogen at ≥ 3 mg/kg/day (suggesting inflammation); Target organs: liver (biliary epithelial cell vacuolation), ileum (luminal dilatation), mandibular lymph node (plasmacytosis), mesenteric lymph nodes (sinus histiocytosis), skin (inflammation/serocellular crust), GI: cecum/ileum (inflammation), mammary gland (atrophy) (males only).

Conducting laboratory and location: Wyeth European DSM Research Center; Catania, Italy
GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	0, 3, 10, and 30 mg/kg/day; Daily for 6 months
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% methylcellulose (4000 cps) and 0.5% polysorbate 80, NF, in distilled water
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	25/sex/group
Age:	6 weeks
Satellite groups/ unique design:	TK; n = 3
Deviation from study protocol affecting interpretation of results:	**No**

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality (related to neratinib)</td><td>
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day of moribund sacrificed</th><th>Sex (animal #)</th><th>Prior to Death and Necropsy Findings</th></tr>
<tr><td>10</td><td>158</td><td>M (102)</td><td>No clinical signs prior to death</td></tr>
<tr><td>30</td><td>62</td><td>M (141)</td><td>Abnormal feces, thin appearance, piloerection, and red pigment around eyes, nose, mouth, bodyweight loss, distended abdomen</td></tr>
<tr><td>30</td><td>114</td><td>M (149)</td><td>Abnormal feces, thin appearance, piloerection, and red pigment around eyes, nose, mouth, ptosis, distended abdomen</td></tr>
<tr><td>30</td><td>49</td><td>F (163)</td><td>Abnormal feces, thin appearance, piloerection, and red pigment around nose/mouth</td></tr>
</table>
</td></tr>
<tr><td>Clinical Signs</td><td>MD: clonic convulsion (1 M)
HD: soft liquid feces, feces adhered to fur, thin appearance abrasion around nose/mouth, red pigment around nose/mouth, clonic convulsion (1 F), piloerection</td></tr>
<tr><td>Body Weights</td><td>HD: -11% at week 13 and -13% at week 26 in males; -21% for males and -18% for females for body weight gain</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Findings at week 26
LD: +13%/+66% WBCs (M/F), +16% LYM (M), +27%/+36% MON (M/F), +13% EOS (M)
MD: +19%/+11 WBCs (M/F), +12% LYM (M), +62%/+54 NEU (M/F) , +52%/+36% MON (M/F), +13%/+25% EOS (M/F), +25% LUC (M)
HD: +71%/+1-fold WBCs (M/F) , +29%/+28% LYM (M/F), +3.3-fold%/3.2-fold% NEU (M/F), +1.6-fold%/+1.3-fold% MON (M/F), +33%/+1.3-fold% EOS (M/F), +67%/+42% LUC (M/F), +13%/+17% FIB (M/F)
Recovery: all findings were completely or partially reversed</td></tr>
<tr><td>Clinical Chemistry</td><td>Findings at week 26
LD: +35% ALT (F)
MD: +45% ALT (F), +24 AST (F), +18% ALP (F)
HD: +32%/+43% ALT (M/F) , +33%/+52% AST (M/F), +36% ALP (F), -14%/-15% ALB (M/F), +21%/+26% GLOB (M/F), +21%/+16% BUN (M/F), -19% CHOL (M), -30%/-30 (M/F)
Recovery: all findings were completely or partially reversed</td></tr>
<tr><td>Gross Pathology</td><td>Ileum: distended (HD); lymph node, mandibular: enlarged (LD, MD, HD); lymph node, mesenteric: enlarged (HD, F); discolored (HD); Skin: crust (HD)</td></tr>
<tr><td>Organ Weights</td><td>HD: Kidney: +11%/+14% (M/F); Liver: +21% (F); Thyroid: +15%/+13% (M/F)
Recovery: all findings were completely or partially reversed</td></tr>
<tr><td>Histopathology
Adequate battery: Yes
Signed Pathology Report: Yes
Peer Reviewed: Yes</td><td>
<table>
<tr><th>Sex</th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th>Dose (mg/kg)</th><th>0</th><th>3</th><th>10</th><th>30</th><th>0</th><th>3</th><th>10</th><th>30</th></tr>
<tr><th>No. of animals</th><th>20</th><th>19</th><th>19</th><th>18</th><th>20</th><th>20</th><th>20</th><th>19</th></tr>
<tr><td>Ileum
Luminal dilatation
slight
mild</td><td></td><td></td><td></td><td>
5</td><td></td><td></td><td></td><td>
4
2</td></tr>
<tr><td>Atrophy, villous
slight
mild</td><td></td><td></td><td></td><td>
3
1</td><td></td><td></td><td></td><td>
3</td></tr>
</table>
</td></tr>
</table>

Cecum									
Inflammation									
slight			1	6			1	8
mild			1	6			2	4
Crypt abscess, slight				1			2	1
Colon									
Inflammation, slight				5			1	4
LN, mesenteric									
Plasmacytosis									
slight	3	2		1	9	2		1
mild	8	11	9	6	5	12	8	5
moderate	2	2	10	8	2	6	12	8
marked				3				5
LN, mandibular									
Plasmacytosis									
slight	8	10	12	6	12	9	6	6
mild	1			12			1	12
moderate								1
Bone Marrow									
Myeloid hyperplasia									
slight				1				3
mild				4				6
moderate				1				
Liver									
Vacuolation, biliary epithelial cell									
slight								9
mild								3
moderate								1
Skin									
Inflammation									
slight				2	1			3
mild				2				7
moderate				1				1
marked				2				3
Crust, serocellular									
slight								6
mild								3
moderate								2
Mammary Gland									
Atrophy									
slight		1	3					
mild		1	6	1				
moderate		2	2	8				
marked				6				
Kidney									
Hyaline droplet, tubular									
slight			6	10				
mild			2	3				
Lung									
Alveolar macrophages									
slight	3	8	4	16		2	9	9
mild				1				4
moderate								2

	Brain Iatrogenic unilateral axonal degeneration, slight				1					

Recovery: all findings were completely or partially reversed

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control. +: indicates increase in parameters compared to control.

Study title/ number: HKI-272: Thirty-nine Week Oral (gavage) Toxicity Study in Dogs (RPT-66466)

Key Study Findings

- One male dog found dead on Day 230: cause of death was cardiopulmonary thromboembolism secondary to renal membranous glomerulonephritis. Necropsy: kidney – glomerulonephritis (glomerular capillary basement membrane thickened, eosinophilic deposition, periodic acid schiff (PAS) positive material); heart (multifocal mural thrombosis in the right atrium, ventricle and atrioventricular valve, multifocal occlusive thrombosis, hemorrhagic necrosis)
- Liquid/soft feces and decreased bodyweight.
- Increased WBC and differentials, platelets, and fibrinogen observed at doses ≥ 2 mg/kg/day (suggesting inflammation); Target organs: gall bladder and salivary gland (lymphohistiocytic inflammation), lymph nodes (sinus erythrocytosis), testes (tubular hyperplasia), kidney (tubular basophilia).

Conducting laboratory and location: Wyeth European DSM Research Center; Catania, Italy
GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	0, 0.5, 6, and 6 mg/kg/day; Daily for 9 months
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% methylcellulose (4000 cps) and 0.5% polysorbate 80, NF, in distilled water
Species/Strain:	Beagle dogs
Number/Sex/Group:	4/sex/group
Age:	9-11 months
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day of Death</th><th>Sex (animal #)</th><th>Prior to Death and Necropsy Findings</th></tr>
<tr><td rowspan="2">2</td><td rowspan="2">230 (week 33)</td><td rowspan="2">M (18)</td><td>Clinical findings: Liquid/soft feces, decreased body weight, increases in platelets, fibrinogen, and amylase and decreases in total protein, albumin, A/G, and calcium.</td></tr>
<tr><td>Macroscopic findings: dark discoloration of the endocardium, lungs and mediastinal lymph nodes, and red fluid in the abdominal cavity
Microscopic findings: <u>kidney</u> – glomerulonephritis (glomerular capillary basement membrane thickened, eosinophilic deposition, periodic acid schiff (PAS) positive material); <u>heart</u> (multifocal mural thrombosis in the right atrium, ventricle and atrioventricular valve, multifocal occlusive thrombosis, hemorrhagic necrosis); <u>lung</u> (multifocal intra-alveolar fibrinous material); <u>mediastinal lymph node</u> – multifocal thrombosis
Cause of death: Cardiopulmonary thromboembolism; renal membranous glomerulonephritis</td></tr>
</table>
</td></tr>
<tr><td>Clinical Signs</td><td>Liquid and soft feces at all doses tested</td></tr>
<tr><td>Body Weights
Body weight gain:</td><td><u>HD</u>: -5%/-10% at week 19 and -9%/-12.5% at week 39 (M/F);
HD: -69%/-1-fold% from day 0 (M/F)</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>Hematology
<u>Findings at week 26</u></td><td><u>MD</u>: +23% WBCs (M), +33%/+17% NEU (M/F) , +24%/+11% MON (M/F), +13%/+15% PLT (M/F), +10%/+15 FIB (M/F)
<u>HD</u>: +62%/+54% WBCs (M/F) , +11%/+18% LYM (M/F), +76%/+67% NEU (M/F), +79%/+69% MON (M/F), +54%/+22% PLT (M/F), +49%/+31% FIB (M/F)</td></tr>
<tr><td>Clinical Chemistry
<u>Findings at week 26</u></td><td><u>LD</u>: -15% TG (M), -29% CHOL (F)
<u>MD</u>: +23%/+14% AMY (M/F), -37%/-20% ALP (M/F), -19% CHOL (F), -19%/-10% TG (M/F)
<u>HD</u>: +33%/+16% AMY (M/F), -35%/-10% ALP (M/F), -21%/-25% TP, (M/F), -31%/-32% ALB (M/F), +21%/+26% A/G (M/F), -30%/-52% CHOL (M/F), -18%/-22% TG (M/F), -13%/-15% Ca (M/F)</td></tr>
<tr><td>Gross Pathology</td><td>Lymph node, mesenteric: discolored (MD, HD)</td></tr>
<tr><td>Organ Weights</td><td>Thyroid: up to 85% (M) and 28% (F) increase from controls</td></tr>
<tr><td>Histopathology
Adequate battery: <u>Yes</u>
Signed Pathology Report: <u>Yes</u>
Peer Reviewed: <u>Yes</u></td><td>
<table>
<tr><th>Sex</th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>0.5</th><th>2</th><th>6</th><th>0</th><th>0.5</th><th>2</th><th>6</th></tr>
<tr><th>No. of animals</th><th>4</th><th>4</th><th>4</th><th>4</th><th>4</th><th>4</th><th>4</th><th>4</th></tr>
<tr><td>LN, Mesenteric
Sinus erythrocytosis
slight
mild</td><td>3</td><td>4</td><td>3</td><td>2
2</td><td>3</td><td>4</td><td>4</td><td>1</td></tr>
<tr><td>LN, mandibular Sinus erythrocytosis
slight</td><td></td><td>1</td><td>1</td><td>2</td><td></td><td></td><td></td><td>1</td></tr>
</table>
</td></tr>
</table>

		Duodenum Histiocytosis slight mild				1 3				4
		Gall bladder Mucinous hyperplasia slight mild	1		2	1 2			1	1 2
		Lymphohistiocytic inflammation slight mild moderate	2	2	1 1	1 1 1	2	2 1	2	1 2
		Colon Lymphohistiocytic inflammation, slight				1				
		Kidney Tubular basophilia, slight		1	1	1				
		Pancreas Zymogen depletion								1
		Salivary gland Lymphohistiocytic inflammation slight		1	1	2			1	1
		Testes Tubular hypoplasia mild slight		1	1 1	1 1	-	-	-	-

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
+: indicates increase in parameters compared to control.
Recovery not done

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: WAY-179272: Bacterial Reverse Mutation Test with Salmonella typhimurium and Escherichia coli (RPT-47493)

Key Study Findings:

- Neratinib was not mutagenic under the conditions tested.

GLP compliance: **Yes**

Test system: *Salmonella strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA (up to 5000 ug/plate; +/- S9)*

Study is valid: **Yes**

In Vitro Assays in Mammalian Cells

Study title/ number: WAY-179272: In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes (RPT-47795)

Key Study Findings: *[12 bullets only]*

- Under the conditions tested, neratinib was negative for the induction of structural chromosome aberrations.

GLP compliance: **Yes**

Test system: H*uman peripheral blood lymphocytes; up to 15 µg/mL (-S9); up to 30 µg/mL (+S9)*
Study is valid: **Yes**

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: HKI-272 single dose oral (gavage) Bone Marrow Micronucleus Study in Mice (RPT-48593)

Key Study Findings: *[12 bullets only]*

- HKI-272 was not clastogenic, under the conditions tested.

GLP compliance: **Yes**
Test system: CD-1 mice, bone marrow micronuclei; up to 2000 mg/kg single oral dose
Study is valid: **Yes**

Other Genetic Toxicity Studies

Metabolites

Study title/ number: WAY-121529: Bacterial Reverse Mutation Test with Salmonella typhimurium and Escherichia coli (RPT-78796, M3)

Key Study Findings:

- Metabolite, M3, was not mutagenic under the conditions tested.

GLP compliance: **Yes**
Test system: Salmonella strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA (up to 5000 ug/plate; +/- S9)
Study is valid: **Yes**

Study title/ number: HKI-272: In Vitro Mammalian Chromosome Aberration Test of M3 Metabolite in Human Peripheral Blood Lymphocytes (RPT-75469)

Key Study Findings:

- Metabolite, M3, was negative for the induction of structural chromosome aberrations under the conditions tested.

GLP compliance: **Yes**
Test system: Human peripheral blood lymphocytes; up to 40 µg/mL (-S9); up to 10 µg/mL (+S9)
Study is valid: **Yes**

Study title/ number: HKI-272 (Neratinib Maleate) Metabolites Bacterial Reverse Mutation Test in Salmonella typhimurium and Escherichia coli (9601138 (M6), 9601137 (M7), 9601139 (M11))

Key Study Findings:

- Metabolites, M6, M7, & M11 were not mutagenic under the conditions tested.

GLP compliance: **Yes**
Test system: Salmonella strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA (up to 5000 ug/plate; +/- S9)
Study is valid: **Yes**

Study Title: HKI-272 (Neratinib Maleate) Metabolites In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes (9601141 (M6), 9601140 (M7), 9601142 (M8)

Key Study Findings:

- Metabolites, M6, M7, & M11 were negative for the induction of structural chromosome aberrations under the conditions tested.

GLP compliance: **Yes**

Test system: Human peripheral blood lymphocytes; M6: 1, 2, 4, 8 µg/mL (-S9); 8, 16, 32 µg/mL (+S9); M7: up to 500 µg/mL (+/-S9); M11: up to 64 µg/mL (+/-S9)

Study is valid: **Yes**

Impurities

Study Title: (b) (4)

Key Study Findings:

- Neratinib (Spiked batch MB3307) was not mutagenic under the conditions tested.

GLP compliance: **Yes**

Test system: *Salmonella strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA*; Spiked batch MB3307 contained the impurities (b) (4) %, respectively. Up to 5000 µg/mL (+/-S9)

Study is valid: **Yes**

Study Title: (b) (4)

Key Study Findings:

- Under the conditions tested, neratinib (impurity spiked batch MB3307) was negative for the induction of structural chromosome aberrations.

GLP compliance: **Yes**

Test system: Human peripheral blood lymphocytes; up to 5000 µg/mL (+/-S9). Spiked batch MB3307 contained the impurities (b) (4) %, respectively. Up to 5000 µg/mL (+/-S9)

Study is valid: **Yes**

5.5.3. Carcinogenicity

Study title/ number: A 6-month Oral Carcinogenicity Study of Neratinib Maleate in CByB6F1/Tg rasH2 Hemizygous Mice (20065514)

Key Study Findings

- Under the conditions tested, neratinib was not carcinogenic in CByB6F1/Tg rasH2 transgenic mice following 6-months of oral daily administration.

Methods

Dose and frequency of dosing: Males: 0, 8, 20, 50 mg/kg/day
Females: 0, 20, 50, 125 mg/kg/day

Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF; 0.5% methylcellulose (4000 cps) (final concentrations) and purified (Type I) water
Species/Strain:	CByB6F1/Tg rasH2 transgenic mice
Number/Sex/Group:	25/sex/group
Age:	9 weeks
Satellite groups/ unique design:	Positive control, N-Nitrosomethylurea (NMU), was administered once on Day 1 via IP injection (n=15/sex/group)
Deviation from study protocol affecting interpretation of results:	No
ECAC concurrence:	Yes, for male doses; no, for female doses (Exec. CAC meeting of 6/9/2015)

Observations and Results:
Survival was adequate for analysis and there was no difference in survival amongst neratinib-treated mice compared to controls. There were decreased body weights in the 20 and 50 mg/kg/day-treated males and in 125 mg/kg/day-treated females. Clinical signs included decreased activity, hunched posture, thin appearance, tremors, ungroomed fur, changes in respiration (labored, shallow, and/or increased), apparent hypothermia (cold to touch), dehydration, and/or decreased feces. Mild incidences of cellularity or inflammation were observed at 50 mg/kg in males and 125 mg/kg in females. No drug-related neoplasms were identified in this study following daily oral administration of neratinib.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: HKI-272 Oral (Gavage) Fertility Dose Range Finding Study in Rats (RPT-67699)

Key Study Findings

- NOAEL for maternal toxicity and embryo-fetal toxicity was 5 mg/kg/day; NOAEL for paternal toxicity was 15 mg/kg/day.
- NOAEL for mating and fertility for male or female rats was 15 mg/kg/day.
- At 15 mg/kg/day, maternal toxicity (decreased body weight gain and irregular estrous cycles) and embryonic death (increased resorptions, post-implantation loss) was observed.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 5, 15, 45 mg/kg/day. Once daily to males for 6 weeks (4 weeks prior

	to cohabitation with untreated cohort females until 1 day prior to scheduled euthanasia), and to females for approximately 3 to 4 weeks, depending on day of mating (2 weeks prior to cohabitation with breeder males until GD 7).
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, 0.5% methylcellulose (4000 cps), and purified (Type I) water
Species/Strain:	Crl:CD(SD) rat
Number/Sex/Group:	10/sex/group
Satellite groups:	None
Study design:	Males and females were cohabited for up to 14 consecutive days. Presence of a copulatory plug and/or sperm in the vaginal smear in the morning was considered evidence of mating and the day was designated GD 0.
Deviation from study protocol affecting interpretation of results:	Yes, at 45 mg/kg/day, dosing was discontinued on days 16 (females) & 22 (males) due to poor clinical condition

Observations and Results

Parameters	Major findings
Mortality	HD: dosing was discontinued on days 16 (females) & 22 (males) due to clinical signs of loose and/or discolored feces, decreased feces (F) abnormal posture, piloerection, alopecia, rough hair coat, salivation, focal lesions [abrasions and ulcerations] primarily located on the nose, cough/sneeze (F), red pigment in urine (F), red pigment around eye(s) (F) and positive skin tent.
Clinical Signs	Unremarkable for LD and MD
Body Weights	HD: -23% at day 22 (M); -13% at day 15 (F) MD: -9% in bodyweights at day 43 (M); -20% in bodyweight gain at week 39 (M); -12% body weight gain GD0 – 11 (F); -8% gravid uterine weight (F)
Food consumption	HD: -35% for days 15-21 (M); -33% for days 1-14 (F) MD: -8% for GD 0 – 7
Necropsy findings	Mating/Fertility Index: unremarkable Estrous Cycles: MD: 7/10 female rats were reported to be not cycling Ovarian and Uterine Contents:

Findings	Control	5 mg/kg/day	15 mg/kg/day	45 mg/kg/day
No of rats	**10**	**10**	**10**	**10**
Viable embryos	unremarkable			
Dead embryos	0	0	**0.5±1.27**	NA
Resorptions	1.2±1.03	1.88±1.96	**3.90±3.28**	NA
Total implantations	unremarkable			
Preimplantation loss (%)[a]	unremarkable			
Postimplantation loss (%)[b]	7.5	10.6	**26.5**	NA

LD: low dose; MD: mid dose; HD: high dose; F: females; M: males

Study title/number: Study of Fertility and Early Embryonic Development to Implantation of PB272 (Neratinib Maleate) Administered by Oral Gavage in Rats (20070057)

Key Study Findings

- The NOAEL for maternal and paternal toxicity was 12 mg/kg/day
- NOAEL for fertility in male or female rats was 12 mg/kg/day
- The NOAEL for embryonic toxicity was 12 mg/kg/day

Conducting laboratory and location: (b) (4)

GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	3, 6, 12 mg/kg/day; Males were dosed with neratinib or vehicle once daily beginning 28 days before cohabitation, during cohabitation, and continuing through the day before euthanasia. Females were dosed with neratinib or vehicle once daily beginning 15 days before cohabitation, during cohabitation and continuing to GD 7. The high dose was selected based on the results of the range-finding study and findings at 15 and 45 mg/kg.
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF, and 0.5% methylcellulose (4000 cps) in R.O. deionized water
Species/Strain:	Crl:CD(SD) Sprague Dawley rats
Number/Sex/Group:	22/sex/group
Satellite groups:	None
Study design:	Untreated female rats were used for assessing fertility in the treated male rats. Untreated male rats were used only as breeders. Male and Female Rats (males used only for breeding). Females (treated or untreated) with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ* were at GD 0 and assigned to individual housing. Females (treated or untreated) not mated after completion of the 14-day cohabitation period were considered to be at GD 0 on the last day of cohabitation, assigned to individual housing and were euthanized 7 days following the completion of the cohabitation period
Deviation from study protocol	No

affecting interpretation of results:

Observations and Results

Parameters	Major findings
Mortality	1 HD female was euthanized on GD 1 with signs of trauma to right eye (dry, dark in color, smaller than right eye, partially closed, ulceration, corneal opacity). Reports suggest possible injury during cohabitation.
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Food consumption	Unremarkable
Necropsy findings	Mating/Fertility Index: unremarkable Estrous Cycles: unremarkable Ovarian and Uterine Contents: unremarkable

EmbryoFetal Development

Study title/ number: HKI-272: Oral (Gavage) Developmental Toxicity Dose Ranging Study in Rats (RPT-67315)

Key Study Findings

- NOAEL for maternal toxicity and embryo-fetal toxicity was 5 mg/kg/day.
- At 45 mg/kg/day, maternal toxicity (decreased bodyweight, body weight gain, gravid uterine weight, & food consumption) was observed.
- At ≥ 15 mg/kg/day fetal death (post-implantation loss) and at 45 mg/kg/day decreased fetal weights were observed.

Conducting laboratory and location: Wyeth Research; Chazy, NY
GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	5, 15, & 45 mg/kg/day; Administered once daily for 12 days on gestation days (GDs) 6 through 17
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF, and 0.5% methylcellulose (4000 cps) in purified water
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	10/sex/group
Satellite groups:	None
Study design:	Males and females were cohabited for up to 14 consecutive days. Presence of a copulatory plug and/or sperm in the vaginal smear in the morning was considered evidence of mating and the day was designated GD 0.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>None</td></tr>
<tr><td>Clinical Signs</td><td>HD: loose and discolored feces, alopecia, red pigmentation around genitals, nose, and mouth, focal lesions, and feces on fur</td></tr>
<tr><td>Body Weights</td><td>HD: -13% at GD 21 (F)</td></tr>
<tr><td>Body weight gain</td><td>HD: -40% between GDs 6-20
HD: -36% between GDs 6-20 (adjusted for gravid uterine weight)</td></tr>
<tr><td>Gravid uterine weight</td><td>HD: -40%</td></tr>
<tr><td>Food consumption</td><td>HD: -19% at GD 6 – 17 (F)</td></tr>
<tr><td>Necropsy findings
Cesarean Section Data</td><td>
<table>
<tr><th>Findings</th><th>Control</th><th>5 mg/kg/day</th><th>15 mg/kg/day</th><th>45 mg/kg/day</th></tr>
<tr><td>No of rats</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>Viable fetuses/dam</td><td>13.2±1.69</td><td>13±1.94</td><td>12.2±1.93</td><td>8.0±4.16</td></tr>
<tr><td>Dead fetuses/dam</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Early resorptions</td><td>0.5±0.53</td><td>0.73±0.90</td><td>0.90±0.88</td><td>5.60±4.6</td></tr>
<tr><td>Late resorptions</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Total implantations</td><td colspan="4">Unremarkable</td></tr>
<tr><td>No. of corpora lutea</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Preimplantation loss (%)[a]</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Postimplantation loss (%)[b]</td><td>3.6</td><td>4.1</td><td>6.9</td><td>41.2</td></tr>
</table>
</td></tr>
<tr><td>Necropsy findings
Offspring</td><td>Fetal body weight: -6% at HD
Sex distribution: unremarkable
Morphology: unremarkable</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose; F: females

Study title/ number: An Embryo-Fetal Development Study of PB272 (Neratinib Maleate) by Oral Gavage in Rats (20065668)

Key Study Findings

- NOAEL for maternal toxicity was 10 mg/kg/day.
- Maternal toxicity was evident at 15 mg/kg/day by decreased body weights gain and food consumption.
- NOAEL for embryo-fetal toxicity was 15 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	5, 10, & 15 mg/kg/day; Once daily from Gestation Day (GD) 7 to 17 (Day 0 = Plug date)
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF, and 0.5% methylcellulose (4000 cps) in R.O. water
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	22/sex/group
Satellite groups:	TK: n = 3 (controls) or 6 (treatment)
Study design:	Females were mated with males (males used only for breeding). Presence of a copulatory

	plug and/or sperm in the vaginal smear in the morning was considered evidence of mating and the day was designated GD 0.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	1 MD female was euthanized on GD 7 with a lesion in the ventral thoracic area. Necropsy shows red gelatinous material in the axillary region (subcutaneous) and an enlarged mandibular lymph node. COD possibly related to blood collection procedure to the jugular vein.
Clinical Signs	Unremarkable
Body Weight Gain	LD: -20% at GD 10-12 MD: -11% at GD 7-10; -14% at GD 10-12 HD: -11% at GD 7-11; -33% at GD 10-12
Food consumption	Unremarkable
Necropsy findings Cesarean Section Data	(see nested table below)

Findings	Control	5 mg/kg/day	10 mg/kg/day	15 mg/kg/day
	22	**22**	**22**	**22**
Pregnant	22	22	22	22
Number of implantations	12.6±2.2	12.9±1.8	13.7±1.9	12.9±1.4
Corpora lutea	13.±1.6	13.5±1.9	14.0±2.0	13.2±1.6
Live fetuses	11.9±2.6	12.1±2.0	13.2±1.9	12.3±1.3
Dead fetuses	0	0	0	0
Pre-implantation loss (%)	4.17±10.2	4.35±8.5	1.5±4.2	1.85±4.3
Placenta (normal)	21	22	22	22
Resorptions				
Resorptions	0.7±0.8	0.8±0.9	0.5±0.8	0.6±0.7
Early resorptions	0.7±0.9	0.8±0.9	0.5±0.8	0.5±0.6
Late resorptions	0.0	0.0	0.0	0.1±0.3
Total fetal death (%) (Post implantation loss)	6.6±9.05	6.45±7.2	**3.91±5.48**	**4.74±5.55**

***Bold** = test article-related findings (N) = number of dams per group*p<0.05, **p<0.01, significantly different from control*

Necropsy findings Offspring	Fetal body weight: unremarkable Malformations (external, fetal, and skeletal): unremarkable
Toxicokinetics	see ADME section for TK results

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: An Embryo-Fetal Development Study of PB272 (Neratinib Maleate) by Oral Gavage (Stomach Tube) in Rabbits (20065669)

Key Study Findings

- Maternal toxicity was evident at 6 mg/kg/day by decreased body weight gain, food consumption, and abortions. The number of resorptions and post-implantation loss were increased at 9 mg/kg/day compared to controls.
- Embryo-fetal death, skeletal and visceral malformations were observed at all doses.
- Embryo-fetal malformations included domed head, minimal or severe dilation of the lateral ventricles of the brain (9 mg/kg/day), persistent truncus arteriosus of the great vessels (≥ 3 mg/kg/day), ventricular septum defect of the heart (≥ 3 mg/kg/day), misshapen anterior fontanelle of the skull (9 mg/kg/day) and moderate enlargement of the fontanelles of the skull (≥ 3 mg/kg/day).

Conducting laboratory and location: (b) (4)
GLP compliance: **Yes**

Methods

Dose and frequency of dosing:	3, 6, & 9 mg/kg/day; Once daily from Gestation Day (GD) 7 to 19 (Day 0 = Plug date)
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF, and 0.5% methylcellulose (4000 cps) in R.O. water
Species/Strain:	Crl:KBL(NZW) rabbits
Number/Sex/Group:	22/sex/group
Satellite groups:	TK: n = 3
Study design:	Females were mated with males (males used only for breeding). Presence of a copulatory plug and/or sperm in the vaginal smear in the morning was considered evidence of mating.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality (neratinib-related)</td><td>
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day of Death</th><th>Sex (animal #)</th><th>Prior to Death and Necropsy Findings</th></tr>
<tr><td>6</td><td>GD 23</td><td>F, 6746</td><td>Euthanized due to abortion. dehydration, thin, fur loss, decreased feces, red aborted tissue, decreased body weight, decreased food consumption</td></tr>
<tr><td>9</td><td>GD 19</td><td>F, 6764</td><td>Euthanized due to abortion, red fur staining, decreased feces, red aborted tissue, red liquid material, decreased body weight, decreased food consumption</td></tr>
<tr><td>9</td><td>GD 26</td><td>F, 6766</td><td>Euthanized due to abortion, thin, decreased feces, red aborted tissue, decreased body weight, decreased food consumption</td></tr>
<tr><td>9</td><td>GD 27</td><td>F, 6773</td><td>Euthanized due to abortion, thin, fur loss, red fur staining, liquid/absent/decreased feces, red aborted tissue, decreased body weight, decreased food consumption</td></tr>
</table>
</td></tr>
<tr><td>Clinical Signs</td><td>LD: decreased feces output; red liquid material
MD: thin, dehydration, absent feces, decreased feces output, red liquid material
HD: thin, dehydration, red fur staining, absent feces, decreased feces output, red liquid material</td></tr>
<tr><td>Body Weight Gain</td><td>Unremarkable
MD: -13% at GD 7-29; HD: -54% at GD 7-29</td></tr>
<tr><td>Food consumption</td><td>MD: -15% at GD 7-29; HD: -39% at GD 7-29</td></tr>
<tr><td>Necropsy findings
Cesarean Section Data</td><td>
<table>
<tr><th>Findings</th><th>Control</th><th>3 mg/kg/day</th><th>6 mg/kg/day</th><th>9 mg/kg/day</th></tr>
<tr><td></td><td>20</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>Pregnant</td><td>19</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>Abortions</td><td>-</td><td>-</td><td>1</td><td>3</td></tr>
<tr><td>No. of implantations</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Corpora lutea</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Live fetuses</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Dead fetuses</td><td colspan="4">Unremarkable</td></tr>
<tr><td>Pre-implantation loss (%)</td><td>5.7±19.6</td><td>0.63±2.8</td><td>7.4±16.7</td><td>3.7±9.9</td></tr>
<tr><td>Placenta (normal)</td><td colspan="4">Unremarkable</td></tr>
<tr><td colspan="5">Resorptions</td></tr>
<tr><td>Resorptions</td><td>0.4±1.0</td><td>0.5±1.1</td><td>0.7±1.5</td><td>1.4±2.7</td></tr>
<tr><td>Early resorptions</td><td>0.4±1.0</td><td>0.5±1.1</td><td>0.2±0.4</td><td>0.9±2.7</td></tr>
<tr><td>Late resorptions</td><td>0.2±0.2</td><td>0.1±0.2</td><td>0.6±1.6</td><td>0.5±0.9</td></tr>
<tr><td>Post-implantation loss (%)</td><td>9.4±24.9</td><td>5.0±10.9</td><td>9.5±23.1</td><td>12.4±23.8</td></tr>
</table>
</td></tr>
</table>

Necropsy findings
Offspring

Fetal body weight: unremarkable
Ossification site averages: unremarkable
Malformations (external, fetal, and skeletal):

Findings		Control	3 mg/kg/day	6 mg/kg/day	9 mg/kg/day
No. of fetus evaluated		**182**	**212**	**182**	**172**
No. of litters evaluated		**17**	**20**	**18**	**16**
External					
Head/neck	Head, domed				1(1)
Paw	Forepaw, hyperextension				1 (1)
Visceral (Soft tissue)					
Brain	Ventricles, dilated; minimal				1(1)
	Ventricles, dilated; severe				1(1)
Great vessels	Truncus arteriosus, persistent		1(1)	1(1)	2(2)
Heart	Ventricular septum, defect			1(1)	2(2)
Skeletal					
Skull	Fontanelle, large, moderate		1(1)	1(1)	7(4*)
	Fontanelle, misshapen				2(1)

Toxicokinetics: see ADME section for TK results

LD: low dose; MD: mid dose; HD: high dose; (): # of litters;

Prenatal and Postnatal Development

Study title/ number: A Developmental and Perinatal/Postnatal Reproduction Study of PB272 (Neratinib Maleate) Administered by Oral Gavage in Rats, including a Postnatal Behavioral/Functional Evaluation (20065672)

Key Study Findings

- The NOAEL for maternal toxicity was 5 mg/kg/day and for developmental toxicity was 15 mg/kg/day
- Maternal toxicity was evident ≥ 10 mg/kg/day by body weight gains, and food consumption.
- A statistically significant decrease in long term memory was observed after maternal treatment at ≥ 5 mg/kg/day to male rats in 1 out of two trials.

Conducting laboratory and location: (b) (4)
GLP compliance:

Methods

Dose and frequency of dosing: 5, 10, 15 mg/kg/day; F0 - Once daily from GD 7 to lactation day (LD) 20; F1 – in utero exposure

	or via maternal milk during lactation
Route of administration:	Oral (gavage)
Formulation/Vehicle:	.5% polysorbate 80, NF, and 0.5% methylcellulose [4000 cps] in R.O. water
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	22/sex/group
Satellite groups:	Not done
Study design:	Females were bred with males (used only for breeding) at the supplier. The day mating occurred was designated GD 0.
Deviation from study protocol affecting interpretation of results:	Yes

Observations and Results

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td>Mortality: none
Clinical Signs: unremarkable
Body weight: unremarkable
Body weight gains: -7% (MD) & -8% (HD) at GDs 0-20; +13% (MD) & +25% (HD) at LDs 1-21
Food consumption: -5% (MD) & -6% (HD) at GDs 7-18
Natural Delivery: unremarkable</td></tr>
<tr><td>F1 Generation</td><td>Mortality & clinical signs: unremarkable
Sexual maturation: unremarkable
Behavioral observations: decreased latency to trial (long term memory) was observed after maternal treatment at ≥ 5 mg/kg/day to male rats in 1 out of two trials.
<table>
<tr><th>Findings</th><th>Control</th><th>5 mg/kg/day</th><th>10 mg/kg/day</th><th>15 mg/kg/day</th></tr>
<tr><th></th><th>22</th><th>22</th><th>22</th><th>22</th></tr>
<tr><td>Latency Trial-Males
-session 1
-session 2</td><td>
12.5±7.8
19.3±13.8</td><td>
12.1±5.6
12.7±7.8*</td><td>
12.8±7.1
11.5±8.0*</td><td>
14.8±8.0
12.8±8.3*</td></tr>
<tr><td>Latency Trial-Females
-session 1
-session 2</td><td>
14.7±12.9
14.7±9.5</td><td>
14.0±8.4
12.7±10.3</td><td>
12.1±7.8
12.1±6.0</td><td>
13.9±6.2
11.2±8.3</td></tr>
</table>
Mating & fertility: unremarkable
Necropsy: unremarkable
Organ weights: unremarkable
Ovarian & Uterine Examination: unremarkable</td></tr>
</table>

5.5.5. Other Toxicology Studies

Study title/ number: WYE-121529 (HKI-272, M3) Metabolite: Fourteen-Day Intravenous (bolus) Toxicity Study in Rats (RPT-75529)

Key Study Findings

- The NOAEL was 2 mg/kg/day (HD).
- Metabolite M3 is qualified up to 2.56%

Conducting laboratory and location: Wyeth European DSM Research Center; Catania, Italy

GLP compliance: Yes

Methods

Dose and frequency of dosing:	WYE-121529 (M3): 0, 0.3, and 2 mg/kg/day; Daily for 14 consecutive days
Route of administration:	Oral (gavage)
Formulation/Vehicle:	5% dextrose
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	10/sex/group
Age:	6 – 7weeks
Satellite groups/ unique design:	TK; 3/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology Adequate battery: **Yes** Signed Pathology Report: **Yes** Peer Reviewed: **Yes**	Unremarkable
Toxicokinetics	**Table 4: Rat – M3 Metabolite TK Parameters** *(Excerpted from Applicant's submission)*

Dosage (mg/kg/day)	Sex	C_{5min} (ng/mL)	AUC_{0-24} (ng•hr/mL)	AUC_{0-24}/Dose
0.3	M	114 ± 10	73.9 ± 4.2	246 ± 14
	F	109 ± 5	55.4 ± 5.2	185 ± 17
2.0	M	1836 ± 138	983 ± 49	491 ± 25
	F	996 ± 81	614 ± 33	307 ± 16

Study title/ number: (b) (4)

Key Study Findings

- Toxicities were similar between the toxicology batch and the impurity spiked batches.
- Impurities (b) (4) are qualified at (b) (4)%, respectively.

Conducting laboratory and location: Wyeth Research; Drug Safety; Chazy, NY
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Tox batch; MB3307 (impurity spiked batch), 90.25%: 0, and 45 mg/kg/day; Daily for 14 consecutive days
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF; 0.5% methylcellulose (4000 cps), (final concentrations) and purified (Type I) water
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	10/sex/group
Age:	6 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Tox batch: -10% at day 14 (M); Spiked batch MB3307: unremarkable
Food consumption	Tox batch: -5% at day 14 (M); Spiked batch MB3307: unremarkable
Hematology	Tox batch: +14% WBC (M), +70%/+1.4fold% NEU (M/F), +30%/+40% MON, (M/F), +1.1fold%/+67% EOS (M/F), +22%/+32% BAS (M/F) Spiked batch MB3307: +20%/+15% WBC (M/F), +72%/+1.5fold% NEU (M/F), +26%/+46% MON, (M/F), +68%/+89% EOS (M/F), +44% BAS (M)
Clinical Chemistry	Tox batch: -22% TBIL (M), -11% CHOL (M), -26% TRIG (M), +27% ALT (F) Spiked batch MB3307: -25%/-12% TBIL (M/F), -5% CHOL (M), -34% TRIG (M), +29% ALT (F); +26% ALP (F)
Gross Pathology	Unremarkable
Organ Weights	Unremarkable

Histopathology
Adequate battery: **Yes**
Signed Pathology Report: **Yes**
Peer Reviewed: **Yes**

Sex	Males			Females		
Dose (mg/kg/day)	0	Tox 45	Spiked 45	0	Tox 45	Spiked 45
Bone/Joint						
Physeal hypertrophy, slight	-	3	3	-	-	-
Ileum						
Villus atrophy						
-slight	-	5	5	-	4	4
-mild	-	-	1	-	-	-
Lymphangiectasis, slight	-	2	2	-	2	5
LN, mandibular						
Lymphoid hyperplasia						
-slight	-	-	2	-	-	-
-mild	-	-	-	-	-	-
Mammary gland						
Atrophy						
-slight	1	3	1	-	-	-
-mild	-	2	5	-	-	-
Prostate						
Atrophy				NA	NA	NA
-slight	1	3	3			
-mild	-	1	-			
Seminal vesicle						
Atrophy				NA	NA	NA
-slight	-	2	2			
-mild	-	2	2			

Study title/ number: Neratinib: Single Dose Oral (Gavage) Phototoxicity Study in Pigmented (Long Evans) Rats (RPT-77001)

Key Study Findings

- Neratinib was not phototoxic under the conditions tested.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10 or 200 mg/kg 24 hr before ultraviolet radiation (UVR) exposure; single dose
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% polysorbate 80, NF; 0.5% methylcellulose (4000 cps)
Species/Strain:	Long Evans rats
Number/Sex/Group:	5/sex/group
Age:	10 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One male rat (Animal No. 6492) dosed at 200 mg/kg neratinib was found dead on day 2 after removal from UV exposure. There were no clinical signs leading to death. Tissues appear normal.
Clinical Signs and skin reactions	Unremarkable; The positive control (8-methoxypsoralen, 8-MOP) produced skin reactions (erythemas and edema).
Opthalmoloscopy	Unremarkable; The positive control (8-MOP) produced expected phototoxicity (diffused corneal edema).

Reference List:

[1]Davis MI, Hunt JP, Herrgard S, et al. Comprehensive analysis of kinase inhibitor selectivity. Nature Biotechnology; 2011; 29(11) 1046 – 1052

{See appended electronic signature page}

Kimberly Ringgold, PhD
Primary Reviewer

Todd Palmby, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The proposed neratinib dosage regimen is 240 mg (40 mg × 6 tablets) given orally once daily (QD) with food, continuously for one year. Diarrhea was the main dose-limiting toxicity (DLT). The prophylactic use of loperamide is recommended along with the first dose of neratinib and maintained regularly during the first 1-2 months. The efficacy and safety of neratinib for the application was based on an international, randomized, double-blind, Phase 3 trial of neratinib versus placebo in women with early-stage ERBB2-positive breast cancer following standard locoregional treatment, chemotherapy, and adjuvant treatment with trastuzumab for 12 months (Study 3144A2-3004-WW).

The key review questions focus on appropriateness of the proposed neratinib dose with prophylactic use of loperamide to mitigate the diarrhea, recommendations for neratinib dose in patients with hepatic or renal impairment, and dose adjustments for neratinib due to drug-drug interaction (DDI).

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 208051. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness comes from a single Phase 3 study (Study 3144A2-3004-WW). Supportive evidence includes the exposure-response (E-R) analyses in patients with advance/metastatic breast cancer, which suggest a positive correlation between the objective response rate and steady state neratinib exposure. However, the E-R relationship for efficacy was not characterized due to the absent of pharmacokinetics data in the pivotal trial conducted in patient population with early-stage ERBB 2-positive breast cancer.
General dosing instructions	The recommended dose of 240 mg QD with food is safe. To reduce the incidence of diarrhea, which was the main DLT, we recommended prophylactic use of loperamide with neratinib during the first 1-2 months of treatment.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Due to changes in neratinib exposure the following are recommended: • Reduction of the starting dose to 80 mg for patients with severe hepatic impairment.

	• Avoiding co-administration of neratinib with strong / moderate CYP3A inhibitors, or strong / moderate CYP3A inducers. • Avoiding co-administration of neratinib with proton pump inhibitors or H_2 receptor antagonists. Separate dosing of neratinib by 3 hours after antacids Due to neratinib's potential to inhibit P-glycoprotein (P-gp) transport, patients on P-gp substrates that are narrow therapeutic agents should be monitored for adverse reactions.

Post-Marketing Requirements and Commitments

Post Marketing Requirements (PMR):

1. Conduct a physiologically-based pharmacokinetic modeling /simulation or a clinical pharmacokinetics trial to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to (b) (4)

Post Marketing Commitments (PMC):

1. Conduct a physiologically-based pharmacokinetic modeling /simulation or a clinical pharmacokinetics trial (b) (4) repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.
2. Conduct (b) (4) a clinical pharmacokinetics trial to evaluate whether separating the dosing of H_2-receptorantagonists and neratinib can minimize the drug-drug interaction potential.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Neratinib is an orally bioavailable small molecule inhibitor that irreversibly binds at the intracellular tyrosine kinase domain of the ERBB1, ERBB2, and ERBB4 receptors. The following is a summary of the clinical pharmacokinetics of neratinib:

Absorption: Neratinib exposure increases less than dose proportionally across the dose range from 40 to 400 mg. The median neratinib T_{max} ranged from 2-8 hours. Absolute bioavailability has not been determined. An oral solution formulation indicated bioequivalence to the capsule formulation in healthy subjects. A 2.2-fold increase in exposure was observed with a FDA high-fat meal and less than 20% increase in exposure with standard breakfast.

Distribution: The estimated volume of distribution is 6433 L. High plasma protein binding was observed (99 %). Neratinib is an inhibitor of P-gp with IC50 of 1 µM for the P-gp mediated transport of digoxin.

Metabolism: Neratinib is metabolized primarily by CYP3A and to a lesser extent by Flavin-dependent monooxygenases (FMO). CYP3A4 is responsible for the metabolism of neratinib to the active metabolites M3, M6, and to a small degree, M7. M7 is mainly formed by FMO.

Elimination: The mean (CV %) elimination half-life was 14.6 (38%) hours. With once daily dosing, the mean accumulation ratio of 1.2-1.5 was observed at steady-state. In an oral mass balance trial, radioactivity recoveries in feces and urine were 97% and 1%, respectively.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant proposes an oral dosing regimen of 240 mg once daily with food, continuously for one year. The phase 3 study 3144A2-3004-WW evaluated neratinib at the proposed dose in patients with early-stage HER2-positive breast cancer after prior trastuzumab adjuvant treatment. Since diarrhea was the main DLT, prophylactic use of loperamide is recommended along with the first dose of neratinib and maintained regularly during the first 1-2 months. The proposed dose is effective and appears to have acceptable safety profile.

Therapeutic Individualization

Specific Populations

Patients with Hepatic Impairment: A dedicated hepatic impairment trial in healthy subjects with normal hepatic function and non-cancer patients with mild, moderate, and severe hepatic impairment was conducted. The applicant reported that non-oncology patients with severe hepatic impairment (Child-Pugh C; N=6) had neratinib C_{max} and AUC increased by 2.7- and 2.8 – fold respectively. A dose reduction to 80 mg is recommended in patients with severe hepatic impairment.

Drug-Drug Interactions

Strong or moderate CYP3A Inhibitors: In a dedicated drug-interaction trial in healthy subjects (N=24), concomitant ketoconazole (a strong CYP3A4 inhibitor) increased neratinib C_{max} and AUC by 3.2- and 4.8-fold respectively. The main active metabolites were not measured. It is recommended that concomitant use be avoided for strong or moderate CYP3A4 inhibitors.

Strong or moderate CYP3A Inducers: Based on a dedicated drug-interaction trial in healthy subjects (N=24), concomitant rifampin (a strong CYP3A4 inducer) decreased the C_{max} and AUC of neratinib by 76% and 87%, respectively, when compared to neratinib given alone. The concomitant use of strong or moderate CYP3A4 inducers should be avoided.

Proton Pump Inhibitors (PPI): In a dedicated drug-interaction trial in healthy subjects (N=15), lansoprazole (a PPI) decreased neratinib's C_{max} by 71% and AUC by 65% when compared to neratinib given alone. The main active metabolites were not measured. It is recommended that concomitant use with treatments that alter gastrointestinal pH such as PPIs and H_2-receptor antagonists should be avoided. Neratinib can be administered with antacids if administered at least 3 hours after antacid.

P-gp Substrates: In a dedicated drug-interaction trial in healthy subjects, digoxin (a P-gp substrate) C_{max} and AUC were increased by 54% and 32%, respectively, when compared to digoxin dosed alone. The inhibition of P-gp by neratinib might be clinically relevant for digoxin and other P-gp substrates with a narrow therapeutic window dosed orally. Thus safety should be monitored for when used concomitantly used with P-gp substrates with a narrow therapeutic window.

Outstanding Issues

We have issued one PMR and two PMCs as discussed in the Post-Marketing Requirements and Commitments. There are no other outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Inhibitor of ERBB2 (HER2) kinase (IC_{50} ~59 nM) and EGFR kinase (IC_{50} ~92 nM). In a phosphorylation assay using polymeric amino acids as substrates, neratinib was active against ERBB2 (IC_{50}~39 nM), EGFR (IC_{50}~12 nM) and ERBB4 (IC_{50}~19 nM).
Active Moieties	Neratinib as the parent compound. There are 4 major active human metabolites detected in human: Pyridine N-oxide (M3), N-Desmethyl (M6), Dimethylamine N-oxide (M7), and Bis-N-oxide (M11). M3, M6, M7, and M11 are EGFR, HER2 and HER4 kinase inhibitors. The inhibitory activity of M3, M6, M7, and M11 are similar to that of neratinib for EGFR; M3, M7, and M11 have similar IC_{50} with HER4. M3, M6 and neratinib have similar IC_{50} values for HER2, but M7 and M11 have less potency HER2 as IC_{50} values of ~19 and ~33 fold higher respectively when compared to neratinib At steady-state after a 240 mg QD in healthy subjects, neratinib provides the majority of pharmacological activity for HER 2 inhibition (73%), with 20% provided by exposure to M6, 6% provided by M3, and negligible contribution (<1%) from M7 and M11, based on the potency normalized molar AUC for HER2
QT Prolongation	No QTc prolongation to any clinically relevant extent.
General Information	
Bioanalysis	Neratinib and its major metabolites (M3, M6, and M7) were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix.
Healthy Volunteers vs.	No apparent difference.

Patients	
Drug exposure at steady state following the therapeutic dosing regimen	The AUC_{0-24} and C_{max} (geometric mean (CV%)) based on intensive PK sampling in study 3144A1-102 in patients administered 320 mg daily dose (N=31) on Cycle 1 day 21 were 1123 (58%) ng *h/mL and 75.6 (52 %) ng/mL, respectively
Minimal effective dose or exposure	Not available.
Maximal tolerated dose or exposure	240 mg PO QD (based on the main DLT of diarrhea).
Dose Proportionality	Exposure increased less than dose proportionally across the dose range from 40 to 400 mg
Accumulation	The mean (CV %) accumulation ratio was 1.18-1.52 (36-47 %) at steady-state (day 21) for 240-320 mg QD dosing with food.
Variability	In patients with cancer at steady state (day 21), CV% for Cmax was 52 % and for AUC_{0-24} was 58 %;
Absorption	
Oral Bioavailability	Absolute oral bioavailability has not been determined. An oral solution formulation indicated bioequivalent to the capsule oral formulation in healthy subjects.
Bioequivalent (BE) between tablets and capsules formulation tablets/capsules GMR (90% CI)	BE between 40 mg tablets and 80 mg capsules at single dose of 240 mg: C_{max}: 1.02 (0.94, 1.12) AUC_{last}: 1.01 (0.93, 1.1) AUC_{inf}: 1.01 (0.93, 1.1)
Tmax (hours): Median (range)	Neratinib: 4 (2-8); M3: 4 (2-6); M6: 6 (4-8); M7: 4 (2-8)
Food effect (FDA high-fat meal*) for Capsule formulation fed/fasted GMR (90% CI)	C_{max}: 1.7 (1.1, 2.7) AUC_{inf}: 2.17 (1.4, 3.5)
Food effect (standard breakfast[&]) for tablets fed/fasted GMR (90% CI)	C_{max}: 1.17 (0.97, 1.42) AUC_{inf}: 1.13 (1.02, 1.24)
Distribution	
Volume of Distribution	Following multiple doses of neratinib in patients, the apparent volume of distribution at steady-state (Vss/F) was 6433 L (CV = 19%)
Plasma Protein Binding	99% for neratinib in in vitro protein binding assay, which was independent of concentrations.
Substrate transporter systems	Substrate of P-gp. Inhibitor of P-gp with IC50 of 1 µM for the P-gp mediated transport of digoxin
Elimination	
Half-life	Following 7 days of once-daily 240 mg oral doses of neratinib in healthy subjects, the mean (CV%) plasma half-life of neratinib, M3, M6, and M7 was 14.6 (38%), 21.6 (77%), 13.8 (50%) and 10.4 (33%) hours, respectively.
Clearance	In cancer patients, following multiple doses of neratinib once daily 240 mg, the mean (%CV) CL/F were 216 (34%) and 281 (40%) L/hour on day 1 and day 21, respectively. CL/F was 190 L/hour by population PK analysis with pooled data from healthy subjects and patients.
Metabolism	

Primary metabolic pathway(s)	CYP3A4 is responsible for the HLM metabolism of neratinib to M3 and M6 and to a small degree M7. M7 is mainly formed by Flavin-dependent monooxygenases (FMO).
Inhibitor/Inducer	Neratinib is not a mechanism-based inhibitor of CYP2C9, 2C19, 2D6, or 3A4 at concentrations up to 100 µM. Neratinib is not likely an inducer for CYP1A2, 2B6, 2C9 or 3A4 at concentrations up to 1 µM, which is > 10-fold of the total Cmax at steady state following the therapeutic dosing regimen.
Excretion	
Primary excretion pathways (% dose) ±SD	In an oral mass balance trial, radioactivity recoveries in feces and urine were 97.1% ± 8 5% and 1. 13 % ± 0.26%, respectively.

**FDA High-fat breakfast: (approximately 900 calories) with nutritional composition of approximately 55% fat, 31% carbohydrate, and 14% protein. [&] Standard breakfast: nutritional composition was to be approximately 50% carbohydrate, 35% fat, and 15% protein, with the daily caloric intake not to exceed approximately 3200 kcal*

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The clinical pharmacology program provided supportive evidence of effectiveness. As there were no PK data collected from the pivotal trial in the proposed populations with HER2-positive early-stage breast cancers, exploratory E-R analyses for efficacy were conducted with the evaluable PK data collected in neratinib-treated patients with advanced or metastatic breast cancers in the early stage supportive clinical trials, which suggest a positive correlation between the objective response rate and steady state neratinib exposure. The pivotal evidence of effectiveness comes from the efficacy results in Study 3144A2-3004-WW.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose 240mg QD is effective and appears to have acceptable safety profiles. The toxicities are generally reversible. Since diarrhea was the main DLT, the recommendation of prophylactic use of loperamide during the first 1-2 months appears appropriate. The appropriateness of the proposed dosing regimen in the general patient population is based on the following justification:

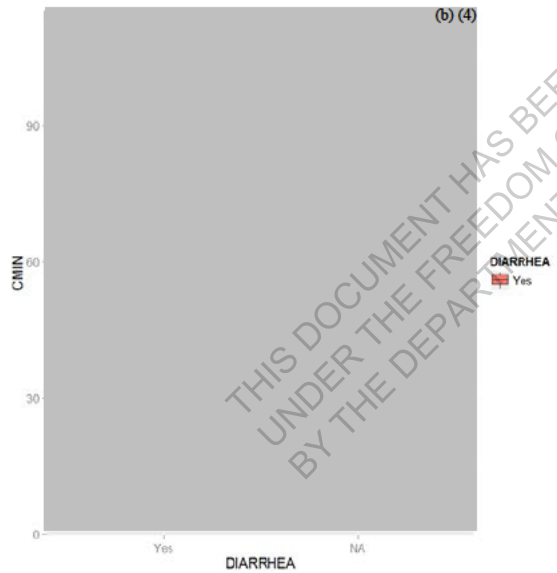
- 240 mg QD was determined as maximum tolerated dose (MTD) in patients with advanced or metastatic solid tumors including breast cancers and evaluated for the pivotal trial 3144A2-3004-WW in the patients with early-stage ERBB 2-positive breast cancers.
- Diarrhea was the primary DLT and was reversible via dose holding, dose-reduction, and non-mandatory anti-diarrhea medications including loperamide in early stage and pivotal clinical trials.
- Additional population pharmacokinetics (PPK)) analysis indicated that occurrence of diarrhea event (any grade) reduces neratinib bioavailability by less than 10%, and prophylactic use of anti-diarrhea medication is considered to have no apparent effect on neratinib PK and thus no clinically meaningful effect on the systemic toxicity.

- Supportive E-R relationship for efficacy and safety in advance/metastatic breast cancer patients also supports the proposed dose.

No apparent effect of diarrhea on the exposure at steady state:

In an early stage clinical trial in patients (Study 3144A1-200WW), ninety two (92) subjects with PK collected had evaluable C_{min} at steady state (day 1 month 2) after 240 mg daily administration of neratinib. The diarrhea was reversible and managed with non-mandatory co-medications including loperamide during the study. On day 1 month 2 among the 92 patients, 30 patients were still with or during episode of any grade diarrhea and 62 patients had no symptom of diarrhea or had been recovered from prior diarrhea. The exposure (C_{min}) comparison between patients with or without diarrhea at day 1 month 2 indicated no apparent difference of C_{min} for neratinib at steady state (**Figure 4**). This analysis could not rule out the confounding effects of anti-diarrhea co-medications and/or dehydrations from diarrhea on PK of neratinib. However, since most patients experienced diarrhea had taken anti-diarrheal medications during the trial, the effect of prophylactic use of loperamide is considered to be similar and expected to have no clinically meaningful effect on the neratinib exposure.

Figure 4. Effect of Any Grade Diarrhea on C_{min} of Neratinib at Month 2 after 240 Mg QD in Patients



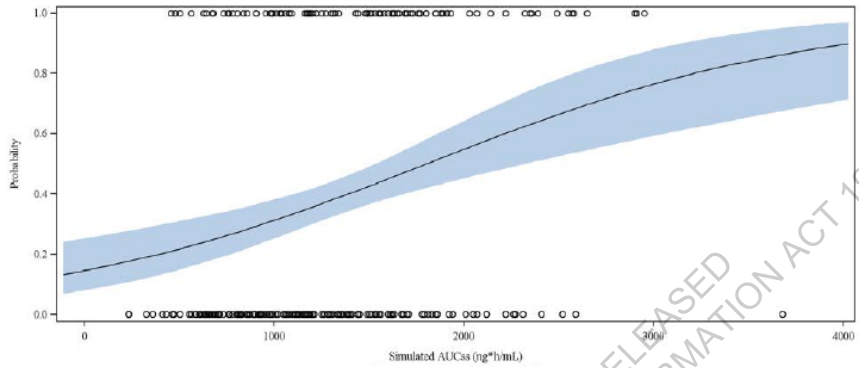
Source: Reviewer's analysis based on raw data from Clinical Pharmacology Information Requests for CSR 3144A1-200-WW

In addition, the PPK analysis using data from patients with advance/metastatic cancers and with diarrhea as a time dependent covariate indicated that: diarrhea (any grade) is associated with a 6% decrease (4 - 7% CI) in bioavailability and a 14% increase (9 - 19% CI) in apparent central volume (Refer to the PPK analysis). Given diarrhea event is reduced with prophylactic use of loperamide, increase of neratinib exposure is expected to be less than 10%, which is not considered clinically meaningful.

E–R relationship for Efficacy:

The E-R relationship for efficacy is not characterized in the proposed target patient population with early-stage ERBB 2-positive breast cancer as PK data was not collected in the pivotal trial. Supportive E-R analyses from other studies in patients with advance/metastatic breast cancer (n=284) suggest a positive correlation between the objective response rate (ORR) and steady state neratinib exposure (AUC_{ss}) (Figure 5).

Figure 5. Relationship of ORR and AUC_{ss} of Neratinib in Patients with Advanced Breast Cancers



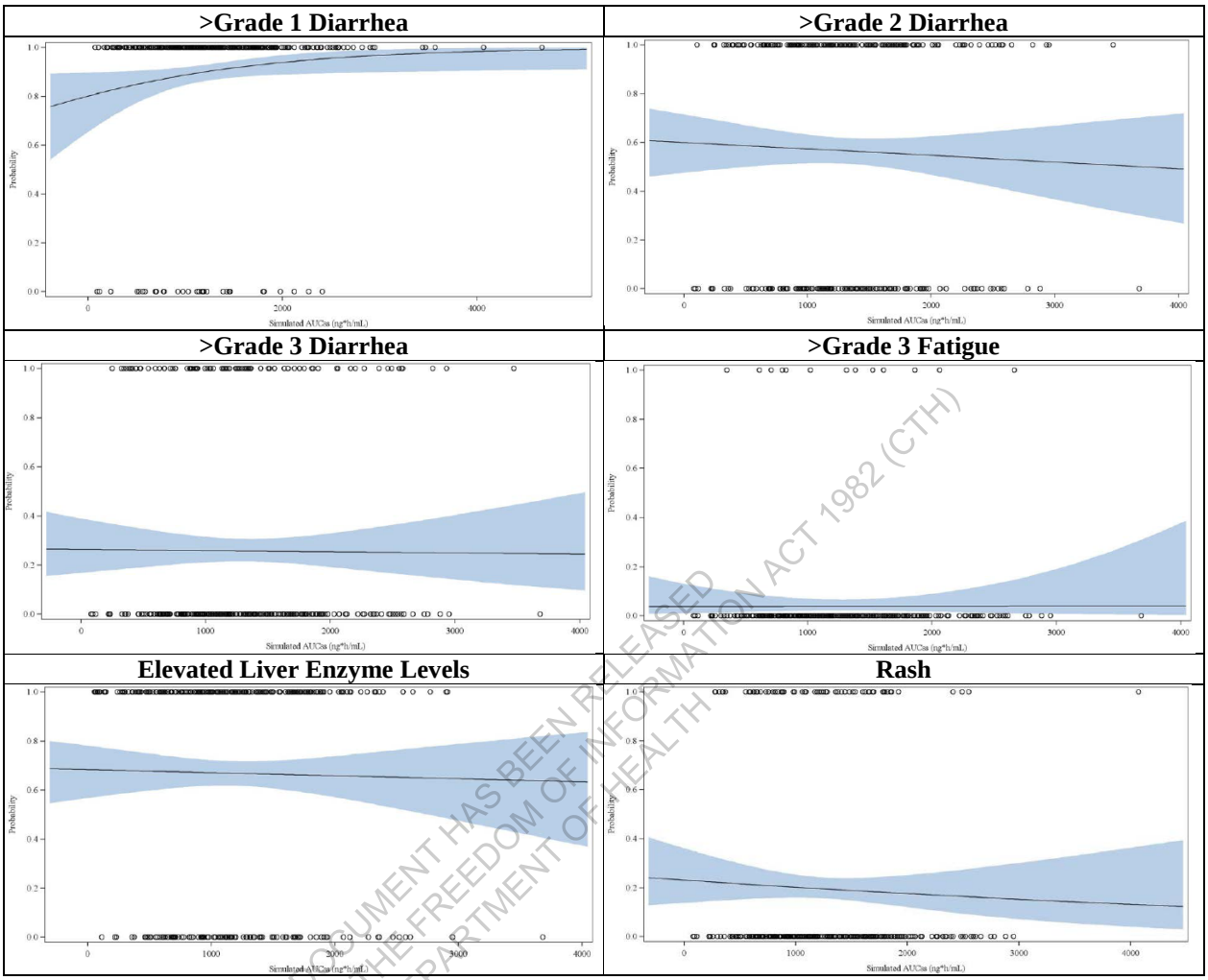
Source: Response to Population Pharmacokinetic Information Request, Figure 1

E-R relationship for Safety:

The E-R relationship for safety in the proposed target patient population with early-stage ERBB 2-positive breast cancer is not characterized as PK data was not collected in the pivotal trial. Supportive E-R analyses for safety in patients with advance/metastatic breast cancer (n=345) suggested no apparent relationship between systemic neratinib exposure and the safety endpoints of any Grade diarrhea (≥ Grade 1), ≥ Grade 2 diarrhea, ≥ Grade 3 diarrhea, ≥ Grade 3 fatigue, elevated liver enzyme levels, and ≥Grade 1 rash (Figure 6).

Neratinib was not associated with prolongation of the corrected QT interval (QTc) in healthy subjects at doses of 240 mg daily with food.

Figure 6. Relationship of Safety Endpoints and AUC_{ss} of Neratinib in Patients with Advanced Breast Cancers



Source: Response to Population Pharmacokinetic Information Request, Figure 10-15

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. In patients with severe hepatic impairment the neratinib dose should be reduced to 80 mg. No dose adjustments are needed for mild to moderate hepatic impairment, or other intrinsic factors such as age, sex, race, or renal impairment.

Hepatic Impairment:

A dedicated phase 1 hepatic impairment study 3144A1-1111-EU was conducted in non-cancer patients with chronic hepatic impairment (n=6 each in Child-Pugh Class A, B, and C) and in healthy subjects (n=9) with normal hepatic functions. A single 120 mg oral dose of neratinib was administered with a standard breakfast. Plasma concentrations of neratinib and

metabolites M3, M6, and M7 were measured by a validated HPLC-MS/MS assay.

The summary of neratinib PK parameters and statistical comparison (pair-wise comparison of Child-Pugh A, B, and C to healthy subjects) are described in Table 5. Neratinib exposure levels in the Child-Pugh Class A (mild impaired) and B (moderate impaired) patients were similar to that in normal healthy volunteers. Exposure to neratinib (AUC) was increased by approximately 2.8-fold in patients with severe hepatic impairment (Child-Pugh Class C). Based on the relative contributions of the pharmacological activities to HER2 inhibition for parent compound and each active metabolites M3, M6, and M7, the combined exposure (molar concentration based active AUCs) for neratinib and active metabolites are estimated to be 2.4-fold higher in subjects with severe hepatic impairments when compared to normal hepatic functions. Given the high variability of the observed PK and pan-tyrosine kinases inhibition of neratinib, it is recommended to reduce the starting dose of neratinib to 80 mg for patients with severe hepatic impairment.

Table 5. Summary of PK Parameters and Geometric LSM Test for Neratinib and Metabolites in Hepatic Impairments Study

Hepatic impairment levels	Cmax (ng/mL)			AUC (ng•h/mL)			*AUC (hr. mM) for Parent+Metabolites
	Mean (CV %)	Ratio GeoMean	95% CI	Mean (CV %)	Ratio GeoMean	95% CI	Ratio to Normal
Healthy (Normal)	18.5 (64%)	-	-	296 (61%)	-	-	-
Child-Pugh A (Mild)	31.2 (66%)	1.79	0.98-3.3	394 (83%)	1.27	0.66-2.43	1.21
Child-Pugh B (Moderate)	17.1 (58%)	1.02	0.56-1.88	286 (78%)	0.97	0.51-1.87	0.94
Child-Pugh C (Severe)	47.0 (59%)	2.73	1.49-5.02	767 (46%)	2.81	1.43-5.39	2.43

Notes: *Combined AUCs based on molar concentrations and normalized with relative potency to HER2 for parent and each metabolite M3, M6, and M7.
Source: Reviewer's analysis based on data from CSR of Study 3144A1-111-EU.

Renal Impairment: Dedicated studies in patients with renal impairment have not been performed, as ~1.1% of neratinib is excreted through the kidneys in a radio labeled mass balance study in healthy subjects. PPK analysis indicated that mild renal impairment (based on creatinine clearance) is not a covariate for PK of neratinib. No dose adjustment is needed for renal impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. Neratinib should be administered with food, because (1) high-fat food can increase the exposure of neratinib and (2) safety profile of neratinib administered with food was acceptable in the pivotal efficacy study 3144A2-3004-WW. Co-administration of neratinib with strong/moderate CYP3A inhibitors or strong/moderate CYP3A inducers should be avoided as co-administration with such medications can lead to an increase or decrease in neratinib exposure, respectively. The concomitant use of neratinib with agents that alter gastrointestinal pH such as PPIs and H_2-receptor antagonists should be avoided, and dosing of neratinib should be separated at least 3 hours after antacids due to the potential of such medications to lower neratinib exposure. Due to neratinib's potential to inhibit P-gp transport, patients on P-gp substrates that are narrow therapeutic agents should be monitored for adverse reactions.

Food effect:

The preliminary food effects were assess with standard FDA high fat meal using the capsule formulation in healthy subjects after oral single administration of 240-mg (crossover). High fat meal increased the exposure (AUC) by 2.2-fold as compared to the fasted conditions (Table 6).

In a dedicated food effect study in healthy subjects, neratinib tablets (commercial 40-mg tablet) were given after 8 hours fast (fasted) or with a standard breakfast (nutritional composition was to be approximately 50% carbohydrate, 35% fat, and 15% protein, with the daily caloric intake not to exceed approximately 3200 kcal). Standard breakfast increased AUC_{inf} and C_{max} by 13% and 17% respectively when compared to fasted condition (Table 6).

Table 6. Food Effect under High Fat and Standard Breakfast

	Fed Conditions (Test)			Fasted Conditions (Reference)			LSGM Test/Reference	
Parameters	**n**	**Geo Mean**	**CV %**	**n**	**Geo Mean**	**CV %**	**Ratio**	**90% CI**
Capsule; High fat meal								
Cmax (ng/mL)	5	72	28	6	42	34	1.7	1.1-2.7
AUCinf (ng*h/mL)	5	1314	28	6	605	40	2.17	1.4-3.5
40-mg Tablets; Standard breakfast								
Cmax (ng/mL)	27	45.6	52	25	39	50	1.17	0.97-1.42
AUCinf (ng*h/mL)	24	868.4	34	22	770.8	41	1.13	1.02-1.24

Source: Reviewer's analysis based on adapted data from CSR 3144A1-1127-US & CSR 3144A1-107-US;

Strong CYP3A Inhibitor:

A dedicated randomized, 2-period, 2-sequence crossover drug-drug interaction study (n=24) was conducted to assess the PK of a single 240 mg oral dose of neratinib administered with or without multiple (5 days) 400 mg daily oral doses of ketoconazole. Based on geometric mean ratios for parent compound neratinib, a 3.2-fold increase in C_{max} and a 4.8-fold increase in AUC

were observed when neratinib was co-administered with ketoconazole (Strong CYP3A inhibitor) as compared with neratinib administered alone (Table 7). The active metabolite concentrations were not measured in the dedicated study. The concomitant use with strong or moderate CYP3A inhibitors should be avoided.

Table 7. PK and Geometric LSM Test for Neratinib in Subjects when Neratinib Concomitantly Dosed with Ketoconazole

	Treatment		LSGM Test: Combo /alone	
Mean ± SD (CV %)	240 mg	240 mg+ Keto	Ratios	90% CI
Cmax (ng/mL)	55.32 ± 19.71 (36)	201 ± 116 (58)	3.21	2.41-4.28
AUC (ng*hr./mL)	903 ± 411 (45)	4660 ± 2490 (53)	4.81	3.59-6.45

LSGM: least squares geometric mean
Source: CSR for study 3144A1-106-US; Table 7-1 & 7-2;

Strong CYP3A Inducer:

A dedicated, nonrandomized, crossover, sequential dose study was conducted to assess the effects of multiple doses of rifampin on the PK of a single 240 mg oral dose of neratinib (n=24). Neratinib was given on Day 1 and Day 14 with a standard breakfast, and rifampin (600 mg) was administered under fasted conditions on Days 8-15. On Day 14 neratinib 240 mg was administered with a meal one hour after rifampin. Plasma concentrations of neratinib and active metabolites M3, M6, and M7 were measured by a validated HPLC-MS/MS assay.

When 240 mg of neratinib was given with the CYP3A4 inducer rifampin, neratinib C_{max} and AUC were significantly decreased to 24% and 13% respectively of those values when neratinib administrated alone. The ratios of active metabolites M6 and M7 were also reduced to 50-63% based on the AUC values. By converting to molar concentration based AUCs and combining relative activities of HER2 inhibition for neratinib and each active metabolites, there is ~74% reduction of the combined activity exposures when given with the CYP3A4 inducer rifampin (Table 8 below). Thus, the concomitant use of neratinib with strong or moderate CYP3A inducers should be avoided.

Table 8. Summary of PK and Geometric LSM Test when Neratinib Concomitantly Used with Rifampin

Analytes	Cmax (ng/mL) Mean (CV %)				AUC (ng•h/mL) Mean (CV %)				*AUC (hr. mM) combined
	Ref.	Test	GeoMean Test		Ref.	Test	GeoMean Test		Ratio
			Ratio	95%CI			Ratio	95% CI	(Test/ Ref.)
P	47.6 (52%)	10.7 (39%)	0.24	0.20--0.30	928 (47%)	113 (38%)	0.13	0.10-0.16	0.26
M3	5.7 (54%)	13.2 (46%)	2.35	1.97-2.79	76 (39%)	73 (30%)	1.04	0.85-1.28	
M6	12.2 (57%)	17.4 (47%)	1.53	1.16-2.01	189 (36%)	97(43%)	0.51	0.41-0.63	
M7	8.4 (46%)	11.9 (46%)	1.43	1.23-1.67	147 (64%)	83(40%)	0.63	0.48-0.83	

Notes: P: Neratinib, Ref.: neratinib 240 mg alone; Test: neratinib 240 mg+ rifampin
*Combined AUCs were based on molar concentrations and normalized with relative potency to HER2 for parent and each metabolite M3, M6 and M7.
Source: Reviewer's analysis based on data adapted from CSR of Study 3144A1-1110-US.

Proton Pump Inhibitors (PPIs):

The solubility of neratinib is pH dependent. Treatments that alter gastrointestinal pH such as PPIs, H_2-receptor antagonists, and antacids may lower the solubility of neratinib, thus decreasing exposure.

An open label, 2-period, fixed sequence study was conducted to assess the effects of multiple doses of lansoprazole (30 mg) on the PK of a single 240 mg oral dose of neratinib (n=15). Neratinib was given on Day 1 with a standard meal, and PK samples were collected extensively from 0 to 72 h post-dose. After a 14-day washout, lansoprazole (30 mg) was administered following an overnight fast on Days 1-7 and together with neratinib on Day 5.

The PK parameters and statistical test are summarized in Table 9. Neratinib C_{max} and AUC) were reduced by approximately 70% when neratinib concomitantly used with lansoprazole. Thus, the concomitant use with agents that alter gastrointestinal pH such as PPIs and H_2-receptor antagonists should be avoid, and dosing neratinib should be separated at least 3 hours after antacids dosing.

Table 9. PK and Geometric LSM Test when Neratinib Concomitantly Used with Lansoprazole

Pharmacokinetic Parameter	Geometric LSM Treatment B (Period 2): Neratinib + Lansoprazole (test, N=15[a])	Geometric LSM Treatment A (Period 1): Neratinib Alone (reference, N=15)	Geometric Mean Ratio (%)	90% Confidence Intervals	Intra-Subject %CV
C_{max} (ng/mL)	24.486	84.502	28.977	22.17 – 37.87	43.5
AUC_{0-t} (ng*hr/mL)	426.15	1478.0	28.833	22.68 – 36.65	38.6
AUC_{0-inf} (ng*hr/mL)	541.57	1557.2	34.778	28.68 – 42.18	30.0

[a] N = 14 for AUC_{0-inf} for Treatment B

Source: Summary of clinical pharmacology, Table 33, page 79

P-glycoprotein substrates:

A phase 1, open label, nonrandomized, crossover study was conducted to assess the effects of multiple once daily 240 mg oral doses of neratinib on the PK of a single 0.5 mg oral dose of digoxin in the fed state. Pharmacokinetics was available from 27 subjects given digoxin alone and 18 subjects receiving digoxin and neratinib.

Digoxin C_{max} and AUC were increased by approximately 54% and 32%, respectively, when concomitantly used with neratinib (Table 10). The inhibition of P-gp by neratinib might be clinically relevant for digoxin and other substrates with a narrow therapeutic window dosed orally. Thus, safety should be monitored.

Table 10. PK and Geometric LSM Test for Digoxin when Neratinib Concomitantly Used with Digoxin

Factor	C_{max} (ng/mL)	AUC_T (ng•hr/mL)	AUC (ng•hr/mL)
Analyte	Digoxin	Digoxin	Digoxin
Treatment[a]	<0.05	<0.05	<0.05
Intrasubject CV%	31.0	21.5	20.6
	Pairwise Comparison: Digoxin+Neratinib 240 mg (Test) vs. Digoxin (Reference)		
Ratio of Least Square Geometric Means (%)	154	135	132
90% Confidence Interval around Ratio	132-180	121-150	119-147

Note: Treatments: [Reference group=digoxin alone; Test group = digoxin+neratinib 240 mg].
P-values from log-transformed analysis of variance.

Source: Summary of clinical pharmacology, Table 35, page 81

{See appended electronic signature page}

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7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The single trial supporting the efficacy review of this NDA is the Phase 3 randomized double-blind, placebo-controlled trial ExteNET, or study 3004. As discussed later in the section detailing safety analyses, additional data were reviewed as part of this application. The supportive trials are listed in Table 25.

7.1.2. Review Strategy

The FDA clinical NDA review was conducted by two primary clinical reviewers. Dr. Harpreet Singh conducted the efficacy review and Dr. Amanda Walker conducted the safety and PRO reviews. Statistical review of efficacy and PRO was conducted by Dr. Joyce Cheng.

The review included the following:

1. Review of the current literature on breast carcinoma epidemiology, and treatment, including other targeted therapies.
2. Review of Applicant submitted Trial 3144A2-3004-WW including CSR, case report forms protocols, protocol amendments and selected datasets.
3. Review and assessment of Applicant analysis of neratinib efficacy and safety, for evaluation of Applicant's claims.
4. Review of datasets and SAS programming algorithm submitted by the Applicant.
5. Review of patient narratives of serious adverse events, deaths, and events of special interest.
6. Review of meeting minutes conducted during drug development.
7. Assessment of the Module 2 summaries including the Summary of Clinical Safety.
8. Evaluation of reviews conducted by other FDA disciplines including Biostatistics.
9. Review of consultation reports from the Office of Scientific Investigations.
10. Requests for additional information from the Applicant and review of Applicant responses.
11. Formulation of the benefit-risk analysis and recommendations.
12. Review and evaluation of proposed labeling.

Data and Analysis Quality

The Applicant attested that it had complied with the laws and regulatory requirements of all countries that had sites participating in this study. The Applicant used a medical monitor throughout Study 3004. Further comments are provided throughout Section 7.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study 3004/ExteNET

Trial Design and Endpoints

This application is primarily supported by a single study, 3004, which was a multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in women with early stage HER2 overexpressed/amplified breast cancer after adjuvant treatment with trastuzumab.

After discontinuing study treatment, patients were followed for disease recurrence for another year. Randomization was stratified by the following:

1. ER and/or PgR positive vs. ER and PgR negative.
2. Nodal status (negative, 1-3 positive nodes or ≥4 positive nodes).
3. Trastuzumab given sequentially vs. concurrently with chemotherapy.

The key eligibility criteria were as follows:

1. Women with locally confirmed invasive HER2-positive breast cancer stage 1 to 3c without evidence of recurrence (note that after Amendment 3 this was limited to stage 2 or 3).
2. HER2 positivity determined locally by immunohistochemistry (IHC) 3+ or in situ hybridization and archived tumor tissue was required to be submitted for central review (the archived tumor tissue requirement was removed in Amendment 9).
3. Prior adjuvant therapy with anthracycline and/or taxane or CMF type regimen plus trastuzumab and where trastuzumab was completed no less than 2 weeks and not more than 2 years (changed to 1 year in Protocol Amendment 3) of randomization; patients with at less than 1 year of adjuvant trastuzumab were eligible provided they had received at least 8 weekly or 3 q3 weekly doses and were either ineligible to receive further trastuzumab or unable to receive trastuzumab due to toxicity.
4. No evidence of recurrence based on imaging studies (mammogram, chest X-ray, bone scan if elevated alkaline phosphatase, CT/MRI of chest and abdomen if transaminases or alkaline phosphatase is elevated).
5. Known ER/PR status and normal organ and left ventricular ejection fraction.
6. ECOG performance score 0-1.

Concurrent adjuvant endocrine therapy for HR positive disease was recommended.

Patients were excluded if they received prior neoadjuvant therapy that resulted in pCR or DCIS and axillary pCR, received prior HER2 directed therapy other than trastuzumab, NYHA Class II-IV heart failure, underlying GI disorders with diarrhea, or other medical conditions that would preclude them from participation.

Reviewer's Comment: ***Patients were stratified by concurrent vs sequential trastuzumab therapy. It is important to note that most patients in the United States are currently treated with concurrent trastuzumab therapy in the adjuvant setting. Exceptions may be if the HER2 status changes throughout the course of therapy, which may occur.***

The primary efficacy endpoint was invasive disease-free survival (iDFS) defined as the time from randomization to the first occurrence of invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause.

Reviewer's Comment: ***While invasive disease free survival is an accepted endpoint for approval in adjuvant breast cancer trials, there are varied definitions of DFS. The breast cancer community developed and published the STEEP criteria in 2007 by Hudis et al. The magnitude of benefit varies between trials with each application taking into account a benefit-risk assessment. The ExteNET trial used slightly different definition from the STEEP iDFS criteria, which are defined as the following:***

- ***Ipsilateral invasive breast tumor recurrence (IIBTR): invasive breast cancer involving the same breast parenchyma as the original primary.***
- ***Regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.***
- ***Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.***
- ***Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.***
- ***Contralateral invasive breast cancer or secondary primary nonbreast invasive cancer. At the time of the initial protocol review by FDA, it was not recommended that STEEP criteria be required for defining recurrence in adjuvant breast cancer, however the FDA's current thinking is to allow the use of any standardized criteria to define iDFS, including but not limited to STEEP criteria.***

Secondary endpoints included the following:

1. DFS including Ductal carcinoma in situ (DFS-DCIS), defined as the time from randomization to the first occurrence of DCIS or a DFS event as previously defined.
2. Distant disease-free survival (DDFS), defined as the time from randomization to the first occurrence of distant recurrence or death from any cause.
3. Time to distant recurrence (TTDR), defined as the time between randomization and the date of the first distant tumor recurrence or death from breast cancer.
4. Incidence of Central Nervous System (CNS) recurrence, where cumulative incidence of CNS recurrence as a site of first distant recurrence (either isolated CNS metastases or diagnosed concurrently with other sites of metastatic disease, i.e., within 28 days of first documented distant recurrence) is defined as time from randomization to CNS recurrence as first distant recurrence.
5. Overall Survival (OS), defined as the time from the date of randomization until the date of death, censored at the last date known alive.

Other exploratory endpoints included the following:

1. Biomarker analyses, including central confirmation of ERBB2 status, performed on tumor tissue samples from original diagnosis and (if available) at time of recurrence.
2. Patient-reported Quality of Life with the following health outcome assessments:
    a. Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B): a validated instrument used to measure disease-specific quality of life in breast cancer patients (Brady et al., 1997).
    b. Euroqol-5D (EQ-5D): a standardized instrument that provides a simple descriptive profile and index value for health status.

<u>Reviewer's Comment:</u> Per the Applicant, patient-reported outcome data and tumor samples for biomarker analysis were no longer collected after Amendment 9.

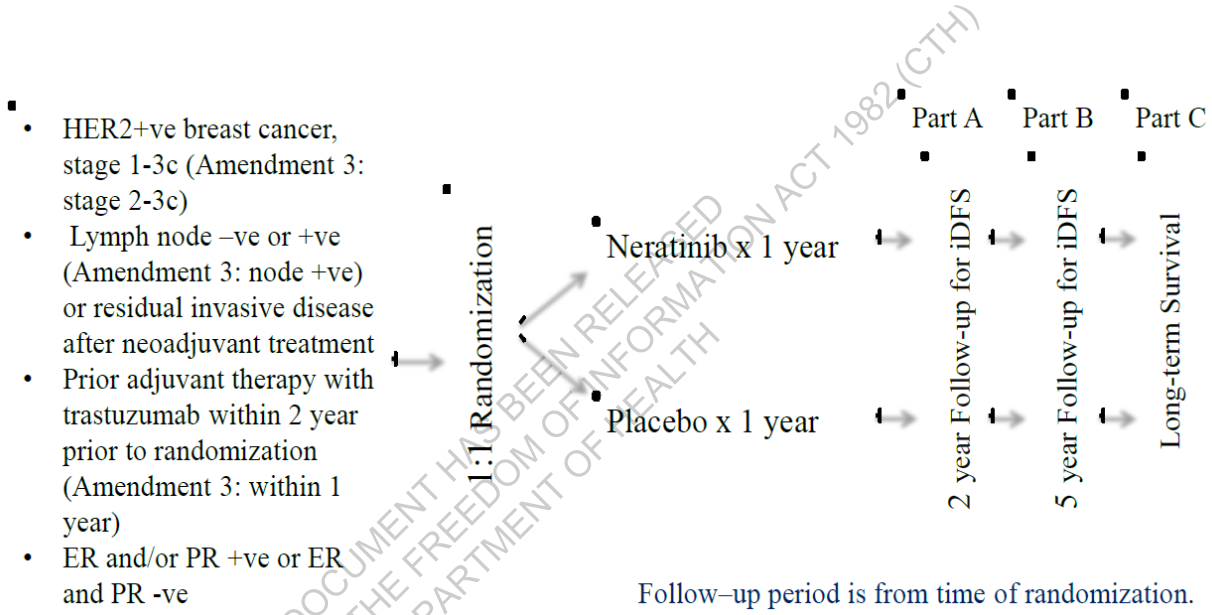


Figure 7: Applicant's Final Study Schematic

[Source: CSR Figure 1]

The study design underwent a number of protocol amendments and the most major ones are detailed in the next section. Under the final amendment (Amendment 13), the study was to consist of three parts (see Figure 7):

1. Part A: Follow-up period of 2 years post randomization. All data collected during this period formed the primary analysis for the study. iDFS was based upon the recurrent disease events and deaths that occurred during this 2-year period.
2. Part B: Expansion of the follow-up period from 2 years through 5 years post-randomization. Recurrent disease events and deaths will be ascertained from patients' medical records upon re-consent of the patients. The expanded follow-up period would

evaluate the durability of the treatment effect on iDFS and the impact on OS. The statistical evaluations for this part of the study will be considered sensitivity analyses.

3. Part C: Long-term follow-up of OS to remain blinded until the requisite 248 deaths are reported.

Statistical Analysis Plan & Protocol Amendments

Study 3004 was held by three different sponsors, leading to several major protocol amendments. Under Wyeth's original protocol (April 2009), the study was designed to enroll 3850 patients in order to observe the 337 DFS events necessary to detect a hazard ratio of 0.70 with 90% power and a one-sided significance level of 0.025. There were two planned interim analyses at approximately 135 (for futility only) and 236 (for futility and efficacy; efficacy boundary: p-value<0.0005) DFS events.

Subsequent major amendments are detailed in Table 11.

Table 11: Major Protocol Amendments and Changes to Statistical Analysis Plan

Amendment	Major Changes to Protocol	Sample Size Requirements
February 25, 2010 Amendment 3 Sponsor: Pfizer (who acquired Wyeth)	Study population was enriched to be more high-risk, excluding those with Stage 1 and/or node negative disease, and restricting to treatment within 1 year of Herceptin treatment instead of 2 years. This was to increase the likelihood of success of the trial based on data from adjuvant Herceptin trials, which showed a higher risk of recurrence closer to completion of Herceptin. Primary analysis was to be conducted on this enriched population, referred to as the amended intent-to-treat (aITT) population.	Sample size was reduced to 3300 to observe 375 events to detect a hazard ratio of 0.713 at 90% power and a one-sided 0.025 significance level. Interim analyses were to be conducted on the aITT population at 150 (for futility only) and 262 (for futility and efficacy; efficacy boundary: p-value<0.0005) DFS events.
October 14, 2011 Amendment 9 Sponsor: Pfizer	Due to changes in organizational strategy, recruitment stopped and follow up was shortened from 5-years to 2-years after randomization.[1] Interim analyses were also removed.	Enrollment stopped at 2840 patients. The time-driven analysis precluded a pre-specified number of events but total sample size of the aITT population was expected to be 1700 with a total of 165 events. Assuming a hazard ratio of 0.67

		and a one-sided significance level of 0.05, the power of the analysis was expected to be approximately 83%.
March 21, 2012 Amendment 11	Pfizer transferred sponsorship of the IND to Puma	
January 16, 2014 Amendment 13 Sponsor: Puma Biotechnology	Primary analysis population was reverted back to ITT (including lower risk patients). [2] Reconsent process was implemented for all randomized patients in an attempt to collect extended follow-up data for 5-years post-randomization.	ITT population consisted of 2840 patients. Again no pre-specified number of events in a time-driven analysis but it was expected that 241 DFS events would be observed to provide approximately 88% power to detect a hazard ratio of 0.667 at a one-sided significance level of 0.025.

[1]The MBC Study 3003 (neratinib vs lapatinib + capecitabine) was presented at SABCS 2011.
[2]The I-SPY 2 Study (neratinib HER2-negative arm graduation) was presented at ASCO 2014.

Database lock occurred on July 7, 2014. The major changes to the protocol appeared to be the result of outside factors (i.e. external information and changes in organizational strategy). The applicant's decision to attempt reconsent of all patients for extended follow-up data for 5-years post-randomization was driven by advice they received from outside statistical consultants.

Reviewer's Comment: ***The Applicant has stated that all changes made to the study were due to external information. Thus, we believe that these changes were unlikely to have an impact on the control of type-1 error rate.***

Under the final version of the SAP (dated April 6, 2016), the primary analysis of iDFS was performed on the ITT population. The primary analysis included iDFS events up to a cutoff date of 2 years + 28 days from randomization unless the events occurred after 2 or more missing physical exams. The following censoring rules were used:

1. Patients who did not have an iDFS event by cutoff had their iDFS time censored at the date of the last physical exam (including targeted PE), either scheduled or unscheduled, occurring within 2 years, 4 months, and 28 days from randomization.
2. Patients who had an iDFS event after 2 or more missing physical exams (8 month gap) had their iDFS times censored at the last available physical exam prior to the event.

A stratified log-rank test with type-1 error controlled at a one-sided significance level of 0.025 was conducted. The stratified Cox proportional hazards model was used to estimate the treatment hazard ratio and corresponding 95% confidence interval, and a Kaplan-Meier plot was created. Similar methods were used for the applicant's exploratory analyses of iDFS after

extended follow-up was collected following Amendment 13, but there was no adjustment of type-1 error for multiplicity for any of these analyses.

Also, there was no planned adjustment of type-1 error for multiplicity for any of the secondary endpoints, except for OS. Analyses of time-to-event related secondary endpoints were similar to that of the primary endpoint. For CNS recurrences, nonparametric maximum likelihood estimations of the stratified cumulative incidence were generated, with comparison of treatment groups using a stratified one-sided Gray's test with a 0.025 level of significance.

OS will be tested with type-1 error controlled at a one-sided significance level of 0.025, given the primary analysis of iDFS was significant. The final analysis for OS is planned for when 248 OS events are observed to detect a hazard ratio of 0.7 with 80% power. Interim analyses of OS may be performed by IDMC after the primary analysis of iDFS. There is one planned interim analysis for OS at 50% information. The applicant plans to use a Lan-DeMets alpha spending function approximating the O'Brien Fleming boundary for interim analyses of OS.

For quality-of-life parameters, changes from baseline were compared between treatments using analysis of covariance (ANCOVA), with baseline score as a covariate. A repeated measures mixed model approach was used as a sensitivity analysis.

Reviewer's Comments:

1. ***Changes to the SAP made post-database lock mainly had to do with changes to censoring rules and the addition of an interim analysis for OS (with an O'Brien-Fleming efficacy boundary for alpha adjustment), both per FDA request.***

2. ***Randomization was initially stratified by 3 categories of nodal status (negative, 1-3, ≥4). After Amendment 3, patients with node negative disease were excluded and randomization stratification was revised to 2 categories of nodal status (1-3 and ≥4). Amendment 5 clarified eligibility criteria so that patients who were node negative or had unknown nodal status in the axilla after neoadjuvant therapy but have residual invasive disease in the breast were eligible and stratified in the 1-3 group. Amendment 13 changed the analysis population back to ITT, which included node negative patients.***

   The primary analysis was stratified by nodal status dichotomized into two categories (≤3 or ≥4), as well as by prior trastuzumab (concurrent or sequential) and ER/PgR status (positive or negative).

3. ***The Applicant notes that an unstratified analysis was stated in the protocol but was revised to a stratified analysis in the SAP prior to unblinding.***

4. ***For the primary analysis, protocol specified physical exams were to occur every 3 months during the first year and every 4 months during the second year.***

Note that there were no protocol specified assessments for patients reconsented for extended follow-up. According to the Applicant, the assessment schedule for these patients were likely to follow standard of care which includes physical examinations performed every 3 to 6 months for the first 4 years, every 6 to 12 months for years 4 and 5, and annually afterwards.

5. ***Per the Applicant, patient-reported outcome data and tumor samples for biomarker analysis were no longer collected after Amendment 9.***

7.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that this study was conducted in accordance with GCP by qualified investigators using a single protocol. Written informed consent was obtained from each participant in the study. The study protocol and the amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB). Please see below for a discussion of the protocol deviations.

Table 12: Summary of Patient Disposition

	Neratinib N= 1420 n (%)	Placebo N=1420 n (%)
Patients Randomized	1420 (100)	1420 (100)
Patients Who Received at least 1 dose of study drug	1408 (99)	1408 (99)
Discontinued treatment due to AEs	372 (26)	72 (5)
Discontinued treatment due to Patient Request	121 (9)	69 (5)
Patients who completed study	1095 (77)	1183 (83)
Patients who did not complete study*	300 (21)	237(17)

*Reasons for not completing the study include patient request, investigator decision, discontinuation of study by sponsor, lost to follow-up, other, and screen failure.

<u>Reviewer's comment:</u> Of note there were 26% of patients in the neratinib arm who discontinued treatment due to adverse events, versus 5% in the placebo arm. This is likely secondary to the side effect profile of neratinib, which includes diarrhea and GI toxicities.

Protocol Violations/Deviations

Relevant protocol deviations were defined as the following:

1) Patients who entered the study even though they did not strictly meet inclusion/exclusion criteria,
2) Patients who met withdrawal criteria but were not withdrawn,
3) Patients who received the wrong treatment or incorrect dose and patients who received an excluded concomitant treatment.

A summary of important protocol deviations is shown in Table 13.

In all, there were 152 (5.4%) of patients with at least one important protocol deviation, 67 (4.7%) in the neratinib arm and 85 (6.0%) in the placebo arm. The most frequent category of important protocol deviations was eligibility criteria with a total of 137 patients (4.8%); 60 (4.2%) in the neratinib arm and 77 (5.4%) in the placebo arm.

Table 13: Summary of Important Protocol Deviations, ITT Population

	Neratinib (N=1420) n (%)	**Placebo (N=1420) n (%)**	**Total (N=2840) n (%)**
Any Important Protocol Deviation	67 (4.7)	85 (6.0)	152 (5.4)
Prohibited Medications	1 (0.1)	0 (0.0)	1 (0.0)
Eligibility Criteria	60 (4.2)	77 (5.4)	137 (4.8)
Study Drug	6 (0.4)	8 (0.6)	14 (0.5)

<u>Reviewer's comment:</u> These protocol deviations are not expected to have an effect on the analyses or conclusions of the overall study. The eligibility criteria deviations that were of most concern were those which enrolled patients with node negative disease or tumors less than 1 cm. Of the total deviations due to eligibility criteria, there were 13 that met these criteria. More common eligibility criteria deviations were ECG criteria, which again were unlikely to affect the outcome of the overall study.

Table 14: Demographic Characteristics

	Neratinib (n=1420)	Placebo (n=1420)	Total (n=2840)
Region, n (%)			
North America	519 (36.5)	477 (33.6)	996 (35.1)
Western Europe, Australia, and South Africa	487 (34.3)	532 (37.5)	1019 (35.9)
Asia Pacific, East Europe, and South America	414 (29.2)	411 (28.9)	825 (29.0)
Race, n (%)			
Asian	188 (13.2)	197 (13.9)	385 (13.6)
Black or African American	27 (1.9)	47 (3.3)	74 (2.6)
White	1165 (82.0)	1135 (79.9)	2300 (81.0)
Other	40 (2.8)	41 (2.9)	81 (2.9)
Age (year)			
N	1420	1420	2840
Mean (SD)	52.31 (10.08)	52.27 (10.28)	52.29 (10.18)
Median	52.00	52.00	52.00
Min, Max	25.0, 83.0	23.0, 82.0	23.0, 83.0
Age Group, n (%)			
< 35 years	46 (3.2)	55 (3.9)	101 (3.6)
35-49 years	523 (36.8)	515 (36.3)	1038 (36.5)
50-59 years	497 (35.0)	488 (34.4)	985 (34.7)
≥ 60 years	354 (24.9)	362 (25.5)	716 (25.2)
Sex, n (%)			
Female	1420 (100.0)	1420 (100.0)	2840 (100.0)
Male	0	0	0
Height (cm)			
n	1379	1367	2746
Mean (SD)	162.50 (6.89)	162.61 (7.08)	162.56 (6.98)
Median	162.60	162.60	162.60
Min, Max	134.6, 184.0	125.7, 186.1	125.7, 186.1
Weight (kg)			
n	1384	1371	2755
Mean (SD)	72.51 (16.29)	72.64 (16.41)	72.57 (16.35)
Median	70.00	70.50	70.10
Min, Max	39.5, 139.4	34.0, 151.5	34.0, 151.5
BMI (kg/m2)			
n	1376	1361	2737
Mean (SD)	27.43 (5.83)	27.45 (5.80)	27.44 (5.82)
Median	26.29	26.57	26.42
Min, Max	16.8, 56.2	16.2, 65.2	16.2, 65.2

[Source: CSR Table 12, FDA Confirmed]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 15: Baseline Characteristics

	Neratinib (n=1420)	Placebo (n=1420)	Total (n=2840)
ECOG Performance Status, n (%)			
0	1317 (92.7)	1303 (91.8)	2620 (92.3)
1	98 (6.9)	114 (8.0)	212 (7.5)
Nodal Status, n (%)			
Negative	335 (23.6)	336 (23.7)	671 (23.6)
1-3 Positive Nodes	664 (46.8)	664 (46.8)	1328 (46.8)
>=4 Positive Nodes	421 (29.6)	420 (29.6)	841 (29.6)
Hormone Receptor Status, n (%)			
Positive	816 (57.5)	815 (57.4)	1631 (57.4)
Negative	604 (42.5)	605 (42.6)	1209 (42.6)
Prior Trastuzumab, n (%)			
Concurrent	884 (62.3)	886 (62.4)	1770 (62.3)
Sequential	536 (37.7)	534 (37.6)	1070 (37.7)
Menopausal Status at Diagnosis, n (%)			
Premenopausal	663 (46.7)	664 (46.8)	1327 (46.7)
Postmenopausal	757 (53.3)	756 (53.2)	1513 (53.3)
Stage, n (%)			
I	139 (9.8)	152 (10.7)	291 (10.2)
IIA	328 (23.1)	306 (21.5)	634 (22.3)
IIB	268 (18.9)	258 (18.2)	526 (18.5)
IIIA	273 (19.2)	260 (18.3)	533 (18.8)
IIIB	27 (1.9)	24 (1.7)	51 (1.8)
IIIC	144 (10.1)	146 (10.3)	290 (10.2)
Unknown	241 (17.0)	274 (19.3)	515 (18.1)
T-stage, n (%)			
T1	440 (31.0)	459 (32.3)	899 (31.7)
T2	585 (41.2)	555 (39.1)	1140 (40.1)
T3 and above	144 (10.1)	117 (8.2)	261 (9.2)
Unknown	251 (17.7)	289 (20.4)	540 (19.0)
N-stage, n (%)			
0	383 (27.0)	389 (27.4)	772 (27.2)
1	598 (42.1)	580 (40.8)	1178 (41.5)
2	270 (19.0)	274 (19.3)	544 (19.2)
3	144 (10.1)	146 (10.3)	290 (10.2)
Unknown	25 (1.8)	31 (2.2)	56 (2.0)
Histology Grade, n (%)			

Undifferentiated	7 (0.5)	18 (1.3)	25 (0.9)
Poorly Differentiated	663 (46.7)	680 (47.9)	1343 (47.3)
Moderately Differentiated	461 (32.5)	416 (29.3)	877 (30.9)
Well Differentiated	76 (5.4)	65 (4.6)	141 (5.0)
Unknown	213 (15.0)	241 (17.0)	454 (16.0)
Primary Cell Type, n (%)			
Ductal Carcinoma	1328 (93.5)	1343 (94.6)	2671 (94.0)
Lobular Carcinoma	58 (4.1)	41 (2.9)	99 (3.5)
Tubular/Cribriform	8 (0.6)	15 (1.1)	23 (0.8)
Mucinous	6 (0.4)	7 (0.5)	13 (0.5)
Medullary	6 (0.4)	6 (0.4)	12 (0.4)
Metaplastic	3 (0.2)	1 (0.1)	4 (0.1)
Adenoid Cystic	1 (0.1)	0	1 (0.0)
Missing	10 (0.7)	7 (0.5)	17 (0.6)
Time from Diagnosis to Randomization (months)			
n	1419	1420	2839
Mean (SD)	23.90 (7.90)	23.97 (8.00)	23.94 (7.95)
Median	21.82	22.29	22.05
Min, Max	7.7, 73.7	7.8, 103.0	7.7, 103.0
Time from Last Trastuzumab to Randomization (months)			
n	1420	1420	2840
Mean (SD)	6.86 (6.49)	6.93 (6.45)	6.90 (6.47)
Median	4.40	4.65	4.50
Min, Max	0.2, 30.9	0.3, 40.6	0.2, 40.6
Time from Last Trastuzumab to Randomization (groups)			
<= 1 year	1152 (81.1)	1145 (80.6)	2297 (80.9)
1-2 years	262 (18.5)	270 (19.0)	532 (18.7)
> 2 years	6 (0.4)	5 (0.4)	11 (0.4)

[Source: CSR Table 13, FDA Confirmed]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

IP compliance was monitored by study site personnel by collecting patient-completed diaries and documenting verbal information from the patient on source documents, the drug inventory record, and eCRFs. To be considered compliant, patients were expected to have taken the prescribed investigational product dose 75% of the days in the treatment period. If a dose adjustment was required, site personnel followed the dose adjustments and adverse event management sections described in the protocol.

Site personnel reviewed the diaries at every visit and documented the observations on drug accountability forms provided to the sites. Dose administration was recorded on Applicant's accountability forms.

Concomitant Medications

The following treatments were permitted during the study; all medications were recorded in the eCRF:

- Standard therapies for preexisting medical conditions and for medical and/or surgical complications.
- Adjuvant endocrine therapy for HR-positive disease.
- Bisphosphonates, regardless of the indication.

Raloxifene or other selective ER modulators were not prohibited for use in approved indications, although little data are available for such agents in patients with a history of breast cancer. Bone mineral density was documented in the source documents confirming osteoporosis/osteopenia. Raloxifene is not approved for the treatment of adjuvant breast cancer and was not to be used for this purpose during a patient's participation in the trial.

<u>Reviewer's comment:</u> Hormone receptor status was a stratification factor in the study, thus attempting to account for any differences.

Efficacy Results – Primary Endpoint

Results from the applicant's primary analysis of iDFS with 2 years and 28 days of follow-up are shown in Table 16. A total of 173 iDFS events were observed, consisting of 67 (4.7%) events on the neratinib arm and 106 (7.5%) events on the placebo arm. A statistically significant difference favoring neratinib was observed with a stratified hazard ratio of 0.66 (95% CI: 0.49, 0.90) and two-sided stratified log-rank test (p-value = 0.008). The estimated absolute difference in iDFS rates at 2-years was 2.3% (94.2% on the neratinib arm compared to 91.9% on the placebo arm).

The Kaplan-Meier curves are shown in Figure 8. From the start of the study to 3 months in this analysis, a larger decrease in number at risk on the neratinib arm compared to the placebo arm was observed. This was due to a large amount of censoring on the neratinib arm prior to 3 months and an imbalance between the two arms in the number of patients who stopped treatment early.

Table 16: Primary Analysis of Disease-free Survival, ITT Population

	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	67 (4.7)	106 (7.5)
Local/Regional Invasive Recurrence	8 (0.6)	25 (1.8)
Invasive Ipsilateral Breast Tumor Recurrence	4 (0.3)	4 (0.3)
Invasive Contralateral Breast Cancer	2 (0.1)	5 (0.4)
Distant Recurrence	51 (3.6)	71 (5.0)
Death From Any Cause	2 (0.1)	1 (0.1)
Patients Censored	1353 (95.3)	1314 (92.5)
On date of 2 years + 28 days	353 (26.1)	338 (25.7)
On date of last physical exam	963 (71.2)	947 (72.1)
On date of last physical exam 8 months prior to determination of DFS event (2 missed assessments)	3 (0.2)	3 (0.2)
On date of last physical exam prior to death	1 (0.1)	1 (0.1)
On date of latest physical exam which is more than 2 weeks before DFS event	2 (0.1)	4 (0.3)
On randomization date*	31 (2.3)	21 (1.6)
Kaplan-Meier Estimate		
At 12 months	97.9 (97.0, 98.6)	95.6 (94.3, 96.5)
At 24 months	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)
Stratified log-rank p-value (two-sided)	0.008	
Unstratified log-rank p-value (two-sided)	0.009	
Stratified Hazard Ratio	0.66 (0.49, 0.90)	
Unstratified Hazard Ratio	0.67 (0.49, 0.90)	

* Reasons for study withdrawal at randomization were: 1 screen failure, 2 lost to follow-up, 29 by subject request, and 20 for other reasons
[Source: CSR Table 17, FDA Confirmed]

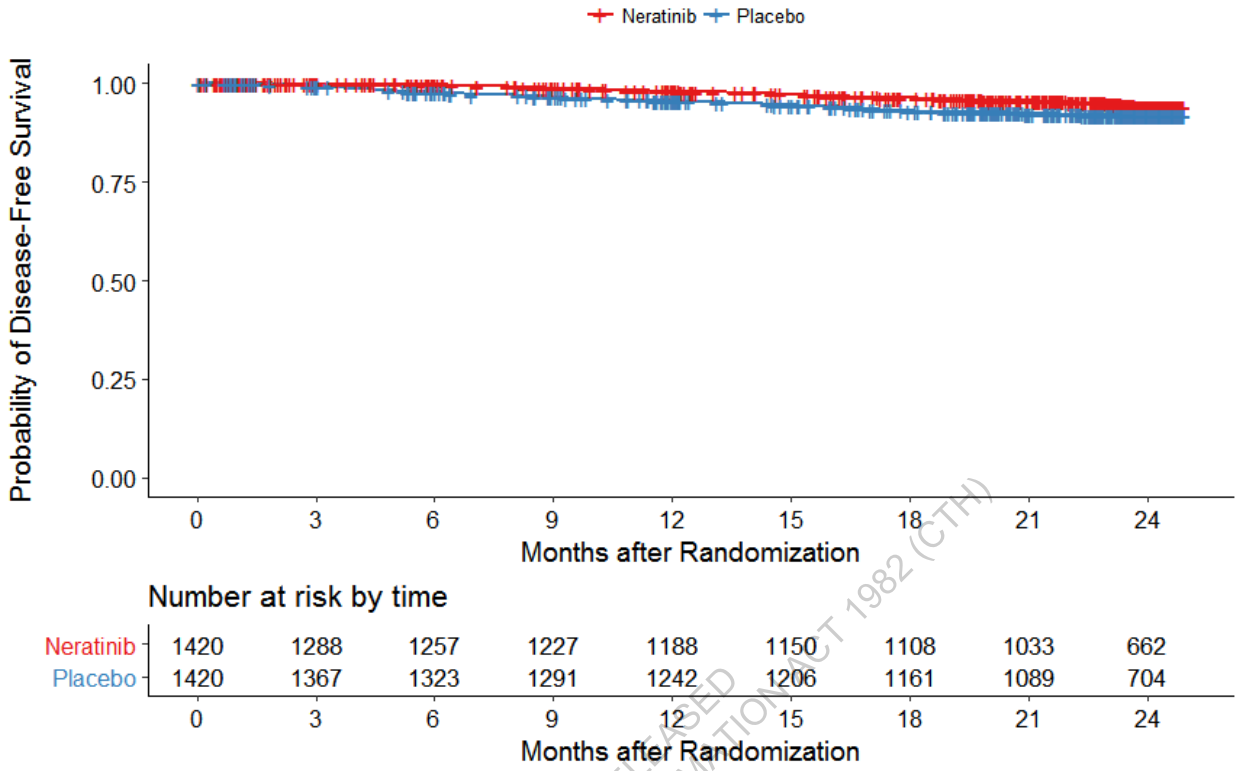


Figure 8: Kaplan-Meier Plot of Disease-free Survival, ITT Population

[Source: FDA Analysis]

Reviewer's comments:

1. ***The Applicant's decision to truncate follow-up at 2-years and 28 days post-randomization in Amendment 9 modified the primary analysis from being event-driven to time-driven. Time-driven analyses are generally not preferred because they do not allow for a pre-specified number of events and analyses run the risk of being under or over powered depending on the number of events that happen to be observed at the cutoff time. The truncation was a business decision, and thus this particular truncation cutoff does not appear to have been based on information from the blinded trial.***

2. ***The Kaplan-Meier plot for the primary analysis (Figure 8) indicated an imbalance between arms in the number of patients who dropped out at less than 3 months. There were 130 such patients on the neratinib arm compared to only 44 on the placebo arm. The most common reasons for neratinib dropouts were adverse events (58%) and subject request (31%). There is concern that the censoring of these observations in the time-to-event analysis could be informative as patients dropped out due to treatment related toxicity. This issue will be further discussed in the FDA Sensitivity Analyses section.***

Applicant's Exploratory Analyses of iDFS with Extended Follow-up

The applicant implemented a reconsent process to acquire extended follow-up data from 2-years through 5-years post-randomization. Per the applicant, recurrent disease and deaths were ascertained from subjects' medical records upon reconsent. The final update submitted April 2017 showed that 2117 (74.5%) of the 2840 primary analysis patients had been reconsented, consisting of 1028 patients on the neratinib arm and 1089 patients on the placebo arm. There appear to be no differences in baseline characteristics between the reconsented population and the full ITT population or between arms among the reconsented patients.

Reviewer's Comment: ***At the time of the final update of reconsent, all patients were past 5 years post-randomization as the last patient was randomized on October 24, 2011.***

Two additional exploratory analyses were conducted with the extended follow-up data collected. The updated 2-year analysis was intended to address the imbalance in early dropouts seen in the primary analysis. The 5-year analysis was intended to explore whether the effect shown at 2-years is sustainable to 5-years.

Results from the updated 2-year analysis with reconsent data from 74.5% of the ITT patients are shown in Table 17 and Kaplan-Meier curves are shown in Figure 9. A total of 190 events were observed with 76 (5.4%) events on the neratinib arm and 114 (8.0%) events on the placebo arm. The stratified hazard ratio was 0.68 (95% CI: 0.51, 0.91) and the estimated iDFS rate at 2-years was 94.3% on the neratinib arm and 91.7% on the placebo arm for an absolute difference of 2.6%.

Reviewer's Comment: ***The updated 2-year analysis included an additional 17 events across both arms. There was also an overall decrease in early dropouts from a total of 174 (130 on the neratinib arm and 44 on the placebo arm) to 105 (80 on the neratinib arm and 25 on the placebo arm).***

Results from the Applicant's 5-year analysis with reconsent data from 74.5% of the ITT patients are shown in Table 17 and Kaplan-Meier curves are shown in Figure 10. A total of 279 events were observed with 116 (8.2%) events on the neratinib arm and 163 (11.5%) events on the placebo arm. The stratified hazard ratio was 0.73 (95% CI: 0.57, 0.92) and the estimated iDFS rate at 5-years was 90.2% on the neratinib arm and 87.7% on the placebo arm for an absolute difference of 2.5%.

Reviewer's Comment: ***The 5-year analysis of iDFS shows that the initial 2-year difference seen in the primary analysis appears to be sustained for up to 5-years.***

Table 17: Exploratory Analyses of iDFS with Extended Follow-up

	Updated 2-year iDFS		5-year iDFS	
	Neratinib (N=1420)	**Placebo (N=1420)**	**Neratinib (N=1420)**	**Placebo (N=1420)**
iDFS Events	76 (5.4)	114 (8.0)	116 (8.2)	163 (11.5)
Patients Censored	1344 (94.6)	1306 (92.0)	1304 (91.8)	1257 (88.5)
Kaplan-Meier Estimate				
At 24 months	94.3 (92.9, 95.4)	91.7 (90.1, 93.1)	94.3 (92.9, 95.4)	91.7 (90.1, 93.1)
At 60 months	N/A		90.2 (88.3, 91.8)	87.7 (85.7, 89.4)
Stratified log-rank p-value (two-sided)	0.009*		0.008*	
Stratified Hazard Ratio	0.68 (0.51, 0.91)		0.73 (0.57, 0.92)	

* Nominal p-value without adjustment for multiple comparisons
[Source: Applicant's April 7, 2017 Submission Tables 1 and 2, FDA Confirmed]

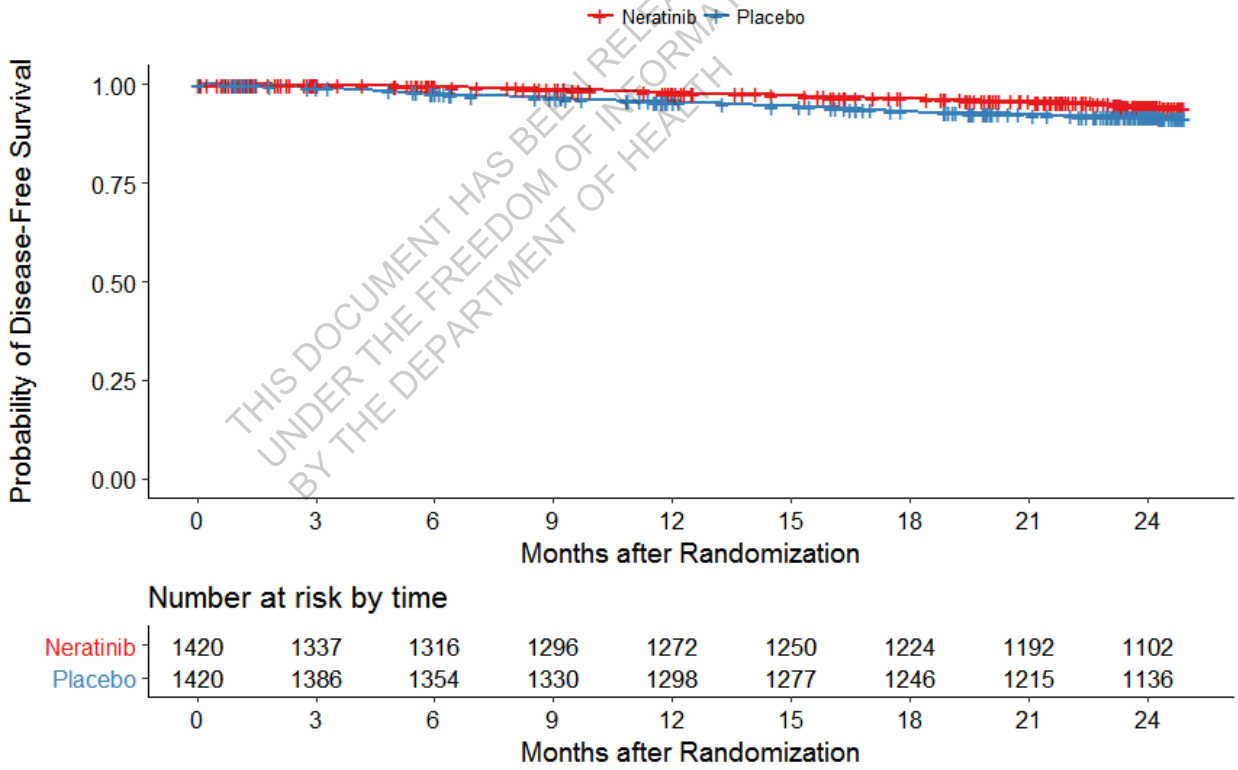


Figure 9: Kaplan-Meier Plot of Disease-free Survival; 2-years of follow-up (updated) with 74.5% of patients reconsented

[Source: FDA Analysis]

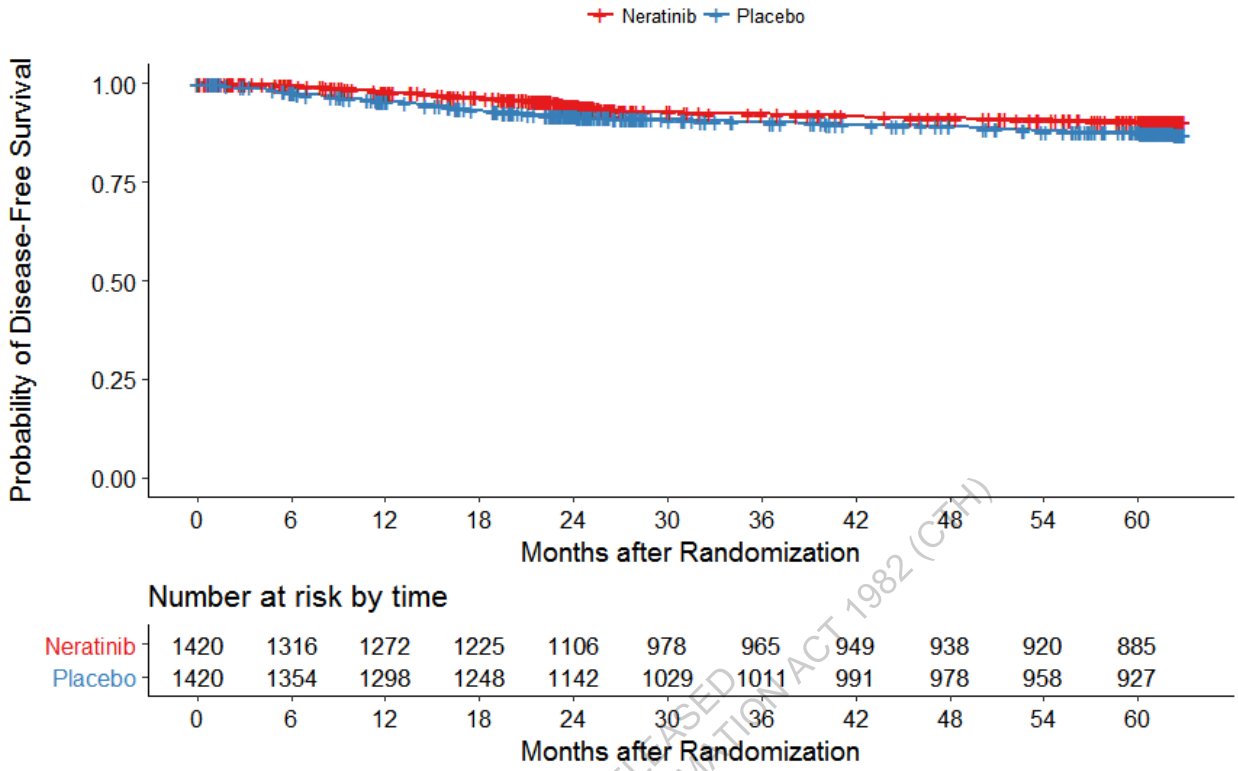


Figure 10: Kaplan-Meier Plot of Disease-free Survival; 5-years of follow-up with 74.5% of patients reconsented

[Source: FDA Analysis]

FDA Sensitivity Analyses

Early Dropouts in the Primary Analysis

In the ExteNET study, 23% of patients on the neratinib arm and 17% of patients on the placebo arm did not complete the study. This was relatively higher than prior adjuvant trials whose withdrawals per arm ranged from 4-16% even when patients were followed for longer than 2 years.

We noted earlier that overall there was an imbalance in patients who dropped out early in the primary analysis. There were a larger number of patients censored prior to 3 months on the neratinib arm (n=130) compared to the placebo arm (n=44). After the applicant's updated 2-year analysis, this number decreased with 80 early dropouts remaining on the neratinib arm compared to 25 on the placebo arm. In general, relevant demographic and baseline characteristics were similar between patients who dropped out early and those who did not (see Table 18).

Table 18: Relevant Demographic and Baseline Characteristics for Patients Who Dropped Out Early versus Followed for Longer

	Initial Submission		After Update	
	Dropped out early[a] (n=174)	**Followed for longer[b] (n=2655)**	**Dropped out early[a] (n=105)**	**Followed for longer[b] (n=2723)**
Hormone Receptor Status, n (%)				
Positive	107 (61.5)	1519 (57.2)	63 (60.0)	1563 (57.4)
Negative	67 (38.5)	1136 (42.8)	42 (40.0)	1160 (42.6)
Nodal Status, n (%)				
0-3 Positive Nodes	126 (72.4)	1865 (70.2)	76 (72.4)	1914 (70.3)
>=4 Positive Nodes	48 (27.6)	790 (29.8)	29 (27.6)	809 (29.7)
Prior Trastuzumab				
Concurrent	97 (55.7)	1667 (62.8)	61 (58.1)	1703 (62.5)
Sequential	77 (44.3)	988 (37.2)	44 (41.9)	1020 (37.5)
Stage[c]				
I	24 (13.8)	267 (10.1)	16 (15.2)	275 (10.1)
II	75 (43.1)	1081 (40.7)	41 (39.0)	1114 (40.9)
III	49 (28.2)	820 (30.9)	28 (26.7)	841 (30.9)
Tumor Size				
T1	66 (37.9)	832 (31.3)	40 (38.1)	858 (31.5)
T2	67 (38.5)	1067 (40.2)	36 (34.3)	1097 (40.3)
T3 and above	13 (7.5)	246 (9.3)	9 (8.6)	250 (9.2)

[a] Defined as patients censored within 3 months

[b] Does not include patients with DFS events in the first 3 months

[c] Stage II includes Stage IIA and IIB patients; Stage III includes Stage IIIA, IIIB, and IIIC patients

Before the updated data from reconsent was available, the Applicant initially addressed the early dropouts with a simulation study assuming the neratinib early dropouts behaved as if they were on placebo. Neratinib early dropout patients were assigned "updated" iDFS times via resampling from the placebo arm. Balance in the stratification factors was maintained by matching patients in each group by these factors prior to resampling. After the updated data from reconsent became available, FDA conducted a similar simulation as a sensitivity analysis. In the FDA's simulation, the remaining 80 neratinib early dropout patients were assigned "updated" iDFS times via resampling from the 50 neratinib patients with real updated iDFS times. Results from both simulations are summarized in Table 19.

Table 19: Results Across Simulated Trials

	Number of Additional Events, mean (range)	Hazard Ratio, mean (range)	Absolute difference in 2-year iDFS rates, mean (range)
Applicant Simulation (Primary Analysis)	9 (1-23)	0.69 (0.61-0.82)	2.1% (1.1%-2.8%)
FDA Simulation (After Update)	5 (0-13)	0.69 (0.64-0.76)	2.5% (2.0%-2.9%)

[Source: Applicant's Response to FDA's November 17, 2016 Information Request Table 1 and FDA Analysis]

Missing Data in 5-year Follow up

The applicant's exploratory analyses of iDFS with extended follow-up appeared to show that the benefit seen in the primary analysis was upheld to 5-years post-randomization but incomplete follow-up lends these results to uncertainty. The follow-up data collected was incomplete in two ways:

1. Of the 723 (25.5%) patients not reconsented, 101 patients had already had an iDFS event, leaving 622 patients (351 neratinib, 271 placebo) with censored iDFS times.
2. Of the 2117 (74.5%) patients reconsented, 132 patients (68 neratinib, 64 placebo) had their iDFS times censored prior to 5-years, even though all patients were past 5 years after start of treatment.

Thus, a total of 622+132=754 patients (419 neratinib, 335 placebo) had their iDFS times censored prior to 5-years.

To address concerns regarding the missing data, the FDA conducted a tipping point analysis to determine how many of these 754 patients would need to have an event (recurrence) at their next assessment to "tip" the results against the neratinib arm. Assumptions made in the analysis were as follows:

1. A select number of patients with censored observations on both arms were randomly chosen to have events at their next assessment. This assessment was assumed to occur in 4 months.
2. All patients whose iDFS times remained censored were assumed to have been followed for the full 5-years.

Based on what was seen in patients reconsented and followed from 2-years through 5-years, we determined that the rate of new events in these reconsented patients was approximately 5.1% on the neratinib arm and 5.8% on the placebo arm.

Given that the placebo patients whose iDFS times were censored before 5-years had events at the same rate, we assumed that 19 additional placebo patients would have events (approximately 5.8% of the 335 with missing data). With this many additional events on the placebo arm, we increased the number of events on the neratinib arm among the 419 missing observations until two tipping points were reached:

1. Tipping Point #1: The p-value exceeds 0.05 (two-sided)
2. Tipping Point #2: The hazard ratio equals or exceeds 0.9

Results for the tipping points are shown in Table 20. In both cases, the results did not tip unless the rate of new neratinib events was higher than the expected 5.1%. These simulation results are limited to the assumptions made.

Table 20: Results of Tipping Point Analyses

	New Neratinib Events	New Placebo Events	Stratified HR	Stratified log-rank p-value[a] (two-sided)
Tipping Point #1	35/419 (8.4%)	19/335 (5.7%)	0.81 (0.65, 1.01)	0.056
Tipping Point #2	51/419 (12.2%)	19/335 (5.7%)	0.90 (0.73, 1.11)	0.339

[a] Nominal p-value for descriptive purposes only
[Source: FDA Analysis]

<u>Reviewer's Comment:</u> Results from these FDA Sensitivity Analyses (simulation to address early dropouts and tipping point analysis) should be considered exploratory only.

Efficacy Results – Secondary and other relevant endpoints

Results from analyses of the secondary endpoints are summarized in Table 21 and appear to be generally in favor of the neratinib arm. However, no multiplicity adjustment was pre-specified, so these results should be considered exploratory.

Overall survival data are not yet mature with 53 deaths observed so far.

Table 21: Summary of Results from Secondary Endpoint Analyses

Endpoint	iDFS Rate at 24 months[a] (%, 95% CI)		Stratified HR (95% CI)	Stratified log-rank test p-value[b] (two-sided)
	Neratinib	Placebo		
DFS-DCIS	94.2 (92.6, 95.4)	91.3 (89.6, 92.7)	0.61 (0.45, 0.83)	0.001
DDFS	95.3 (93.9, 96.4)	94.0 (92.6, 95.2)	0.74 (0.52, 1.05)	0.094
TTDR	95.5 (94.1, 96.6)	94.2 (92.8, 95.3)	0.73 (0.51, 1.04)	0.087
CNS Recurrence Cumulative Incidence Estimate	0.92 (0.49, 1.59)	1.16 (0.68, 1.87)	NA	0.548[c]

[a] Kaplan-Meier estimate unless otherwise noted
[b] Nominal p-value without adjustment for multiple comparisons
[c] By stratified Gray's test
[Source: CSR Table 20, FDA Confirmed]

Patient-Reported Outcome Results

Patient-reported outcome (PRO) data were collected as part of Study 3004. The Applicant chose to use the Breast Cancer Specific Quality of Life – Functional Assessment of Cancer Therapy (FACT)-B (version 4), a 37-item questionnaire and the EuroQol five dimension questionnaire (EQ-5D), an instrument used to assess generic health status and outcomes. The PRO analysis was considered exploratory with the stated study objective of better understanding the perspective of the patient experience during neratinib therapy in the extended adjuvant setting. PRO data were collected up to Amendment 9.

Instruments Used:

The FACT-B questionnaire has 37 items with 5 subscales, including 4 subscales within the general questionnaire on cancer (FACT-G) which are physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB), as well as an additional breast cancer-specific subscale (BCS). Each item/statement has equal weighting and is scored on a 5-point scale: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. The overall total score is calculated as the sum of the 5 subscale scores, each based on a different formula; a greater score means a better quality of life for the breast cancer patient.

The EQ-5D questionnaire is a standardized instrument for health status consisting of 5 items including 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a health state score measured with a vertical visual analog scale. For each dimension, subjects are asked to select from the following 3 levels: 1, no problem; 2, some problem; and 3, extreme problem. The scoring system represents full health with a score of 1 and fractional subtractions are made from this according to the scoring algorithm. Lower scores correspond to poorer self-reported quality of life.

Reviewer's Comments:

1. ***PRO measurements can be quite valuable in assessing how side effects of treatment are perceived by a patient and how they impact one's quality of life; however, none of the questionnaires asked specifically about diarrhea, the most common adverse reaction of neratinib.***

2. ***The overall FACT-B score is problematic from a regulatory perspective because it combines assessments of disease symptoms and treatment side effects with more global impacts such as quality of life and anxiety/depression which may be unrelated to therapy. Elements more distal to treatment related symptoms, such as anxiety and depression as well as global quality of life, are influenced by multiple factors. Including these global elements in the overall score may decrease responsiveness with limited changes in the composite and makes the analysis of the composite score difficult to interpret. Furthermore, clear guidance is not provided to the patient on how to discriminate between levels of severity. What is "a little bit" to one person may be very different to another person. Additionally, the item "I have pain," is broad and not specific (for example, could represent chest wall pain secondary to reconstruction that is not related to neratinib treatment).***

These quality of life measures were assessed at baseline, months 1, 3, 6, 9, and 12 (end of treatment). The Applicant planned to present descriptive statistics for each treatment arm for each of the FACT-B subscales and total scores (FACT-G, FACT-B, TOI-PFB, and TOI-ESB) and EQ-5D health index and health state score at each visit. These variables were also summarized by plotting mean score versus assessment visit, and change from baseline for each of these variables were compared between treatment arms at each visit using ANCOVA with baseline score as a covariate. Subjects with missing baseline assessments of FACT-B and EQ-5D were excluded from their respective analyses and missing values were not imputed.

The Applicant also planned for a sensitivity analysis using a repeated measures mixed model approach with change from baseline as the response variable and treatment arm, visit, interaction of treatment arm and visit, and baseline assessment as the model fixed effects. Repeated measurements at different visits would be modeled via an unstructured covariance matrix and missing assessments post-baseline would be assumed missing at random.

After an FDA information request dated May 2017, the Applicant provided two completion rate tables for the FACT-B and EQ-5D questionnaires: Table 22 shows completion rates taking into account the fact that assessments were no longer expected after Amendment 9 while Table 23 shows completion rates ignoring that fact. In both tables, the applicant notes that the number of expected patients and patients with questionnaire data are limited to patients still on treatment at each visit.

Table 22: Completion Rates Taking into Account Protocol Amendment 9 Changes

	# of Expected Patients		# of patients with FACT-B data (%)		# of patients with EQ-5D data (%)	
	Neratinib	Placebo	Neratinib	Placebo	Neratinib	Placebo
Baseline	1420	1420	1264 (89.0)	1273 (89.6)	1275 (89.8)	1277 (89.9)
Month 1	1408	1408	1200 (85.2)	1274 (90.5)	1211 (86.0)	1285 (91.3)
Month 3	1011	1279	913 (90.3)	1177 (92.0)	919 (90.9)	1183 (92.5)
Month 6	831	1112	759 (91.3)	1025 (92.2)	760 (91.5)	1029 (92.5)
Month 9	692	941	622 (89.9)	859 (91.3)	629 (90.9)	865 (91.9)
Month 12	575	811	516 (89.7)	729 (89.9)	519 (90.3)	732 (90.3)

[Source: Applicant's Response to FDA's May 4, 2017 Information Request Table 1]

Table 23: Completion Rates Ignoring Protocol Amendment 9 Changes

	# of Expected Patients		# of patients with FACT-B data (%)		# of patients with EQ-5D data (%)	
	Neratinib	Placebo	Neratinib	Placebo	Neratinib	Placebo
Baseline	1420	1420	1264 (89.0)	1273 (89.6)	1275 (89.8)	1277 (89.9)
Month 1	1408	1408	1200 (85.2)	1274 (90.5)	1211 (86.0)	1285 (91.3)
Month 3	1074	1356	955 (88.9)	1230 (90.7)	961 (89.5)	1237 (91.2)
Month 6	973	1292	830 (85.3)	1121 (86.8)	832 (85.5)	1126 (87.2)
Month 9	913	1228	708 (77.6)	973 (79.2)	716 (78.4)	982 (80.0)
Month 12	863	1165	598 (69.3)	841 (72.2)	601 (69.6)	844 (72.4)

[Source: Applicant's Response to FDA's May 4, 2017 Information Request Table 2]

***Reviewer's Comment:* Completion rates are above 69% even when ignoring the impact of Amendment 9.**

The Applicant's descriptive results across various FACT-B measures (subscale and total scores) and EQ-5D measures (health state and index) mostly showed a marked decrease in average scores on the neratinib arm (favoring placebo) compared to the placebo arm in the first month before leveling out to smaller differences between arms from month 3 on. This can possibly be attributed to treatment toxicity and the imbalance in early dropouts that was previously noted.

The Applicant noted that analysis of covariance and mixed model results were consistent with the descriptive results. None of the differences between arms were thought to be clinically meaningful.

The FDA analysis of the PRO data focused on the physical well-being (PWB) subscale of the FACT-B questionnaire, noting that this appears to be the most relevant measure as none of the instruments specifically captured diarrhea, which was the most common reason for early dropout.

Figure 11 plots the mean change from baseline in FACT-B PWB score over the various assessments. Again, as was observed by the applicant in their analysis, there is a larger mean difference between arms of approximately 2.5 points at month 1 against neratinib, but this shrinks down to approximately 1 point starting at month 3.

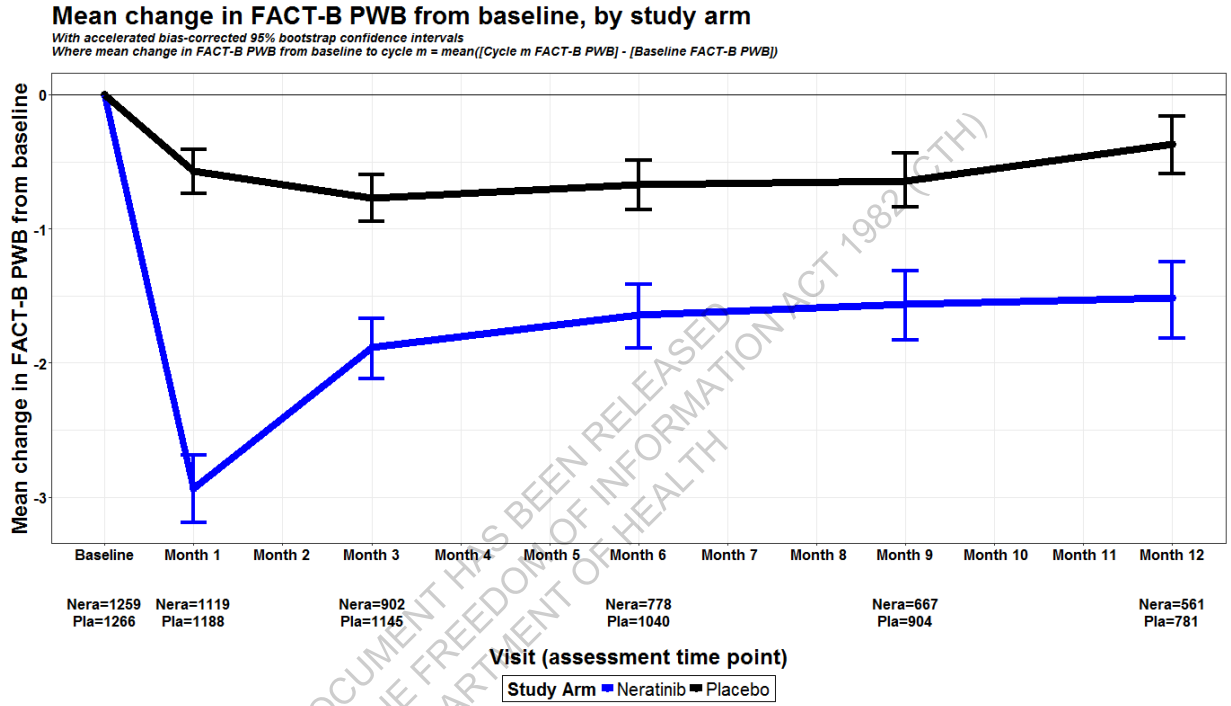


Figure 11: Mean Change in FACT-B PWB from Baseline Over Time

[Source: FDA Analysis]

Reviewer's Comment:

1. ***It is difficult to interpret the clinical meaningfulness of a 1-2 point drop in the physical well-being subscale given that the patients treated with neratinib have a higher likelihood to be event-free, the intent of extended adjuvant therapy is to reduce disease recurrence, and the toxicities of treatment are reversible upon discontinuation.***

2. ***The number of patients who provided PRO data at each time point on each arm as shown in the x-axis in Figure 11 differ from what is seen in the completion rate tables (Table 22 and Table 23).The FDA analysis used the safety population (n=4816), excluded patients with no baseline assessment, and excluded 106 assessments that occurred more than 30 days after the patients' date of last exposure to treatment.***

Exploratory Subgroup Results

Notable results in select exploratory subgroups, including the stratification factors, are shown in Table 24.

Table 24: Study 3004/ExteNET Exploratory Subgroup Analyses

Population	Number of Events/ Total N (%)		KM Estimate for iDFS at 24 months (%, 95% CI)		Unstratified HR (95% CI)
	Neratinib	Placebo	Neratinib	Placebo	
Age Group					
<35 years	5/46 (10.9)	12/55 (21.8)	86.9 (71.1, 94.4)	73.3 (57.7, 83.9)	0.43 (0.14, 1.17)
35-49 years	28/523 (5.4)	40/515 (7.8)	93.4 (90.5, 95.4)	91.4 (88.5, 93.6)	0.71 (0.44, 1.15)
50-59 years	17/497 (3.4)	33/488 (6.8)	95.8 (93.3, 97.4)	92.7 (89.9, 94.8)	0.53 (0.29, 0.94)
≥ 60 years	17/354 (4.8)	21/362 (5.8)	93.8 (90.3, 96.1)	93.7 (90.5, 95.9)	0.93 (0.48, 1.76)
Region					
North America	23/519 (4.4)	28/477 (5.9)	94.6 (91.9, 96.4)	93.7 (91.0, 95.6)	0.81 (0.46, 1.40)
Western Europe, Australia, and South Africa	24/487 (4.9)	38/532 (7.1)	93.9 (91.0, 95.9)	92.2 (89.4, 94.2)	0.74 (0.44, 1.22)
Asia Pacific, East Europe, and South America	20/414 (4.8)	40/411 (9.7)	94.0 (90.9, 96.1)	89.4 (85.9, 92.1)	0.50 (0.29, 0.85)
Race					
Asian	12/188 (6.4)	16/197 (8.1)	92.2 (86.7, 95.5)	91.1 (85.8, 94.5)	0.78 (0.36, 1.64)
Black or African American and Other	2/67 (3.0)	5/88 (5.7)	96.4 (86.5, 99.1)	93.7 (85.5, 97.3)	0.57 (0.08, 2.62)
White	53/1165 (4.5)	85/1135 (7.5)	94.4 (92.8, 95.7)	91.9 (90.0, 93.4)	0.65 (0.46, 0.91)
Hormone Receptor Status					
Positive	29/816 (3.6)	63/815 (7.7)	95.6 (93.8, 96.9)	91.5 (89.2, 93.3)	0.49 (0.31, 0.75)
Negative	38/604 (6.3)	43/605 (7.1)	92.2 (89.4, 94.3)	92.4 (89.8, 94.3)	0.93 (0.60, 1.43)
Nodal Status					
Negative	7/335 (2.1)	11/336 (3.3)	97.2 (94.1, 98.7)	96.5 (93.7, 98.0)	0.72 (0.26, 1.83)
1-3 Positive Nodes	31/664 (4.7)	47/664 (7.1)	94.4 (92.2, 96.1)	92.4 (90.0, 94.2)	0.68 (0.43, 1.07)
≥ 4 Positive Nodes	29/421 (6.9)	48/420 (11.4)	91.4 (87.9, 94.0)	87.3 (83.4, 90.2)	0.62 (0.39, 0.97)
Prior Trastuzumab					
Concurrent	49/884 (5.5)	66/886 (7.4)	93.2 (91.0, 94.8)	92.0 (89.9, 93.7)	0.80 (0.55, 1.16)

Sequential	18/536 (3.4)	40/534 (7.5)	95.8 (93.4, 97.3)	91.6 (88.7, 93.8)	0.46 (0.26, 0.78)
Completion of Prior Trastuzumab					
≤ 1 year	58/1152 (5.0)	95/1145 (8.3)	93.8 (92.0, 95.2)	90.9 (89.0, 92.5)	0.63 (0.45, 0.88)
1-2 years	9/262 (3.4)	11/270 (4.1)	95.8 (92.0, 97.8)	95.7 (92.3, 97.6)	0.92 (0.37, 2.22)
Tumor Size					
T1	10/440 (2.3)	15/459 (3.3)	97.2 (94.8, 98.5)	96.4 (94.1, 97.8)	0.75 (0.33, 1.66)
T2	24/585 (4.1)	41/555 (7.4)	94.9 (92.5, 96.6)	91.9 (89.2, 94.0)	0.58 (0.34, 0.95)
T3 and above	11/144 (7.6)	12/117 (10.3)	91.2 (84.6, 95.0)	89.0 (81.4, 93.6)	0.77 (0.33, 1.76)
Clinical Stage[a]					
I	1/139 (0.7)	3/152 (2.0)	99.1 (93.9, 99.9)	97.8 (93.5, 99.3)	0.41 (0.02, 3.21)
II	15/596 (2.5)	27/564 (4.8)	97.0 (95.0, 98.2)	94.8 (92.6, 96.4)	0.55 (0.29, 1.03)
III	30/444 (6.8)	40/430 (9.3)	91.9 (88.5, 94.3)	89.7 (86.2, 92.4)	0.46 (0.46, 1.19)

[a] Stage II includes Stage IIA and IIB patients; Stage III includes Stage IIIA, IIIB, and IIIC patients
[Source: CSR Figure 6 and FDA Analysis]

Reviewer's Comments: ***There may be a difference in the magnitude of benefit based on hormone receptor status. However, all subgroup analyses presented are considered exploratory or hypothesis generating and no formal inference can be drawn.***

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Not applicable as the primary efficacy evaluation for neratinib was based on one trial as described in sections 7.1 and 7.2.

7.3.2. Integrated Assessment of Effectiveness

Not applicable as the primary efficacy evaluation for neratinib was based on one trial as described in sections 7.1 and 7.2.

7.4. Review of Safety

7.4.1. Safety Review Approach

In this NDA, the Applicant submitted safety data from Study 3004, a Phase 3 trial of neratinib vs. placebo, with the original submission. The entire safety analysis set supporting the approval of neratinib is comprised of 31 studies in 3,252 people, including 12 studies in healthy volunteers (n=357); 8 studies of neratinib monotherapy (4 in breast cancer and 4 in other solid tumors; n = 2,079), 3 studies of neratinib in combination therapy in breast cancer and 8 studies of neratinib combination therapy in other solid tumors (n = 816). There were no clinical holds for safety during the development of neratinib.

Table 25 outlines the relevant safety studies using neratinib monotherapy in breast cancer that were submitted with this NDA.

Table 25: Studies with Neratinib Monotherapy in Patients with Breast Cancer

Study	Phase	Population	Total Subjects	Data cut off
3144A1-201-WW	2	Advanced, HER2+, neratinib monotherapy	136	July 23, 2012
3144A2-3003-WW	2	Advanced, HER2+, neratinib vs. lapatinib + capecitabine	116	July 26th, 2013
3144A2-3004-WW	3	Early stage, HER2+, extended adjuvant	2840	July 7th, 2014
PUMA-NER-6201*	3	Early stage, HER2+, extended adjuvant, with loperamide prophylaxis	227	March 22nd, 2017

*open to enrollment

The integrated summary of safety provided by the Applicant also contained studies of neratinib in other settings in which antidiarrheal prophylaxis was mandated. These studies are summarized below.

Table 26: Studies with Neratinib and Antidiarrheal Prophylaxis

Study	Phase	Population	Total Subjects	Data cutoff
PUMA-NER-5201	2	Solid tumors with EGFR mutations or amplifications, neratinib monotherapy	92	March 31, 2015
PUMA-NER-4201	2	Neratinib vs. neratinib + temserolimus in NSCLC	60	March 31, 2015
10-005	1 / 2	Neratinib + temserolimus in HER2+ advanced breast cancer*	60	April 10, 2015

Reviewer's comments:

1. ***This review primarily focused on the safety data from Study 3004 (3144A2-3004-WW) because this is the patient population for which the indication is sought.***

2. ***Our review also included safety data from studies that required loperamide prophylaxis, including Study 6201, a single arm, phase 2 study designed to characterize the incidence and severity of diarrhea in patients treated with neratinib when administered with intensive antidiarrheal prophylaxis.***

3. ***A focused pooled safety analysis was also conducted to explore evidence of neratinib-induced hepatotoxicity and is described further in Section 7.4.5.***

7.4.2. Review of the Safety Database

Overall Exposure

In Study 3004, a total of 1,408 patients received neratinib (1,420 patients randomized). The duration of exposure to neratinib is summarized in Table 27 below. The median duration of treatment was 11.6 months (range 0.03-13.3 months) in the neratinib arm and 11.3 months (range 0.01 – 13.2) in the placebo arm. Dose reductions were allowed during treatment with neratinib.

Table 27: Summary of Patient Exposure to Neratinib in Study 3004

	Neratinib (n=1408)	Placebo (n=1408)
Duration of treatment (months)		
Median	11.60	11.83
Q1, Q3	2.48, 11.93	11.50, 11.99
Range	0.03 – 13.34	0.13 – 13.17
Number of dose interruptions (%)		
No dose interruptions	39.7	55.8
1 dose interruption	21.0	15.5
2 dose interruptions	12.2	8.4
≥ 3 dose interruptions	27.1	20.4
Number of dose reductions (%)		
No dose reduction	63.1	92.0
Reduce to 200 mg/day	18.3	4.3
Reduce to 160 mg/day	10.5	0.9
Reduce to <160 mg/day	8.0	2.7
Mean cumulative dose in mg (SD)	54,193 (34,205)	76,749 (20,842)
Median cumulative dose in mg (range)	70,200 (240-92,400)	85,200 (960-95,040)
Mean relative dose intensity (SD)[1]	87.6 (17.9)	98.1 (4.9)
Median relative dose intensity (range)	98.1 (8.1-100.3)	100.0 (45.5-100.6)

[1] Relative dose intensity = (actual dose intensity/intended dose intensity)*100
Source: CSR, modified Table 26 and 27; Exposure dataset (adex.xpt)

Relevant characteristics of the safety population:

Demographic information for the 2,816 patients in Study 3004 is included in Section 7.2.2. In summary, the two treatment arms were well balanced in terms of baseline characteristics and prior therapies. All patients in this study were women whose median age was 52 (25-83) years in the neratinib arm and 52 (23-82) years in the placebo arm. Most patients in either treatment arm were white (82.0% in the neratinib arm and 79.9% in the placebo arm). More than half of the patients in either treatment arm had hormone receptor positive disease (57.5% in the neratinib arm and 57.4% in the placebo arm), a minority of patients had stage I disease (9.8% in the neratinib arm and 10.7% in the placebo arm), and most patients had node positive disease (71.2% in the neratinib arm and 70.4% in the placebo arm). Approximately one fourth of patients in each arm had received prior neoadjuvant chemotherapy (24.1% in the neratinib arm and 26.7% in the placebo arm), and the majority of patients in both arms had also received prior adjuvant radiation therapy (79.6% in the neratinib arm and 81.0% in the placebo arm).

Adequacy of the safety database:

The safety database included with this application is considered adequate to determine the risk benefit profile of neratinib in the extended adjuvant setting. The age and sex of the patients is as expected for patients with breast cancer. Of note, there were no males included in Study 3004 and minorities are also underrepresented in this trial. Clinical studies with antidiarrheal prophylaxis are ongoing (b) (4)

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, data quality for this study was acceptable. Case report forms (CRFs) were reviewed and compared to the datasets and patient narratives and few inconsistencies were uncovered.

Categorization of Adverse Events

In Wyeth's original protocol, an adverse event was defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person administered an investigational product or in a clinical study. The event does not need to be causally related to the investigational product or clinical study. An AE includes, but is not limited to, the following:

1. Any clinically significant worsening of a preexisting condition.
2. An AE occurring from overdose of an investigational product, whether accidental or intentional.
3. An AE that has been associated with the discontinuation of the use of an investigational product.

A Significant Adverse Event (SAE) was defined as an AE that:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity.
5. Results in cancer.
6. Results in a congenital anomaly or birth defect.
7. Results in an important medical event. Important medical events are AEs that may not result in death, be life-threatening, or require hospitalization, but when based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

<u>Reviewer comment</u>: Although a number of protocol amendments included changes to the definition of AE and SAE, all modifications were minor and would not have led to substantial underreporting of toxicity.

Routine Clinical Tests

In Study 3004, adverse events were assessed during the treatment period and for at least 28 days after the last dose of study drug. Laboratories were collected at screening and then at least at months 0, 1, 3, 6, 9, and 12 (or the final visit) per the initial protocol (4/29/09). Hematology labs included white blood cell count plus differential, hemoglobin, and platelet count. Blood chemistries included sodium, potassium, chloride, calcium, magnesium, blood urea nitrogen or urea serum creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, phosphorus, total bilirubin, and alkaline phosphatase (ALP). Of note, after amendment #3 (2/25/10), the frequency of safety monitoring for hepatotoxicity was increased. LFTs (total bilirubin, ALT, AST, and ALP) were tested at screening, day 0, day 7, month 1, month 2, month 3, and every 6 weeks thereafter, and as clinically indicated. A MUGA or echocardiogram and EKG were performed at baseline and every 3 months thereafter during treatment visits. An additional EKG was performed on day 7.

7.4.4. Safety Results

Deaths

Deaths in Study 3004: As of (b) (6) two patients in the neratinib arm and one patient in the placebo arm had AEs with fatal outcome. There were no deaths within 28 days after the last dose of neratinib/placebo. The Applicant collected information concerning the cause of death in both a CRF as well as detailed safety narrative summaries. The two patient deaths in the neratinib arm are described in detail below.

Subject 004252 was a 52-year-old Caucasian woman who received neratinib from 1/26/11 to 7/9/2011. Brain MRI on 6/30/11 revealed leptomeningeal carcinomatosis affecting bilateral cerebellar hemispheres. The leptomeningeal disease was presumably secondary to breast cancer, although it is unclear if pathologic confirmation was obtained. The patient was treated with a number of therapies over the following months including whole brain irradiation and she died on (b) (6) The investigator assessed the cause of death as unrelated to study drug.

Subject 006591 was a 56-year-old Caucasian woman who received neratinib from 12/17/09 to 9/15/10. She was initially diagnosed with TXN1M0 invasive lobular carcinoma in February 2008. She received neoadjuvant TCH (docetaxel, carboplatin, trastuzumab) initiated in March 2008 to an unspecified date. This was followed by mastectomy and radiation therapy. On 9/15/10 she experienced Grade 4 neutropenia that led to study drug discontinuation. Bone marrow biopsy on 10/7/10 revealed acute myeloid leukemia. Per the investigator, the cause of AML was unknown, but possibly related to study drug. According to the CIOMS report (AER #2010US000813), the Sponsor assessed the adverse event of AML to be unrelated to study drug and study procedure. The prior therapy with an alkylating agent had been assessed to have played a contributory role because of a plausible temporal relationship, and the time to onset of AML with reference to the start of neratinib therapy did not suggest a causative relationship.

In the placebo arm, one patient (subject 011416) died due to gastric cancer 1104 days after the

last dose of study drug.

Reviewer comment: ***An increased incidence of AML is seen after therapy with alkylating agents, such as carboplatin, with a time to onset ranging between 2-7 years (Green et al, N Engl J Med. 1982). While we agree with the Sponsor that the time to onset of AML with reference to the start of neratinib therapy does not suggest a causal relationship, we cannot rule out the possibility that neratinib may have contributed to the etiology of what we presume is a treatment-related secondary malignancy. It is reassuring, however, that TKIs as a class are not associated with an increased incidence of AML and this was the only case of AML or MDS identified in the dataset. It will important for the Agency to review the overall survival data as it matures as the impact of any late toxicities associated with neratinib therapy is unknown at this time.***

Serious Adverse Events

Information within the CSR, Applicant's narrative summaries, and the CRFs were used to analyze Serious Adverse Events. SAEs of any grade up to 28-days after the last dose of study drug occurred in 7.3% of patients receiving neratinib and 6.0% of patients receiving placebo. No SAE occurred in ≥ 2% of patients. The most frequent treatment-related SAE was diarrhea with 22 patients on the neratinib arm and 1 patient on the placebo arm. All SAEs in the neratinib arm were reversible after discontinuation of study drug except one patient with herpes zoster opthalmicus and one patient with left sided paresis in the setting of glioblastoma. Diarrhea and hepatotoxicity will be discussed further below.

Reviewer Comment: ***It is reassuring that the only irreversible SAEs in the neratinib arm were likely unrelated to study drug.***

Table 28. Incidence of Serious Treatment-Emergent Adverse Events in Descending Order of Incidence in Neratinib Arm

	Neratinib (N=1408)	Placebo (N=1408)
Any Serious TEAE – n (%)	103 (7.3)	85 (6.0)
Diarrhea	22 (1.6)	1 (0.1)
Vomiting	12 (0.9)	1 (0.1)
Dehydration	9 (0.6)	1 (0.1)
Cellulitis	6 (0.4)	4 (0.3)
Renal failure[1]	6 (0.4)	0
Erysipelas	5 (0.4)	0
ALT increased	4 (0.3)	0
AST increased	4 (0.3)	0
Nausea	4 (0.3)	1 (0.1)
Abdominal pain[2]	3 (0.2)	0
Fatigue	3 (0.2)	0
Non-cardiac chest pain	3 (0.2)	0
Pulmonary Embolism	3 (0.2)	3 (0.2)
Syncope	3 (0.2)	2 (0.1)
Basal cell carcinoma	2 (0.1)	2 (0.1)
Bronchitis	2 (0.1)	1 (0.1)
Cholelithiasis	2 (0.1)	0
Dyspnea	2 (0.1)	1 (0.1)
Mental status changes	2 (0.1)	0
Pancreatitis	2 (0.1)	1 (0.1)
Pyrexia	2 (0.1)	1 (0.1)

[1] includes renal failure, acute renal failure, blood creatinine increased
[2] includes abdominal pain and upper abdominal pain
Source: AE dataset (ADAE.xpt); CSR, modified Table 35; patient narratives

Dropouts and/or Discontinuations Due to Adverse Effects

Patients were allowed to be withdrawn from the active treatment phase in the case of disease recurrence, adverse event, subject request, protocol violation, being lost to follow-up (defined as 3 attempts by phone followed by 1 attempt of sending a certified letter), death, or other.

A total of 388 (27.6%) patients in the neratinib arm and 76 (5.4%) patients in the placebo arm experienced TEAEs that led to discontinuation. The most frequently reported AEs causing discontinuation of study drug were related to GI disorders: 282 (20%) patients in the neratinib arm and 12 (0.9%) patients in the placebo arm.

Table 29. Summary of TEAEs Leading to Permanent Discontinuation from Treatment Occurring in >1% of Patients in the Neratinib Arm

	Neratinib (N=1408)	Placebo (N=1408)
Any TEAE – n (%)	388 (27.6)	76 (5.4)
Diarrhea	237 (16.8)	3 (0.2)
Vomiting	54 (3.8)	2 (0.1)
Nausea	39 (2.8)	4 (0.3)
Fatigue	25 (1.8)	9 (0.6)
Abdominal Pain	21 (1.5)	2 (0.1)
ALT increased	17 (1.2)	1 (0.1)

Source: AE dataset (ADAE.xpt); CSR Modified Table 36

Adverse Events Leading to Dose Reduction

A total 31.3% of patients in the neratinib arm had their neratinib dose reduced; 18.3% had their dose reduced from 240mg to 200mg, 10.5% had their dose reduced to 160mg, and 8% had their dose reduced to <160mg. Per protocol, the lowest allowed dose level was 120mg daily. In the placebo arm a total of 8.0% of patients had their dose reduced.

The most common AEs leading to dose reductions in the neratinib arm were diarrhea (26.4%), nausea (2.8%), abdominal pain (1.6%), vomiting (1.3%), and fatigue (1.2%). A summary of TEAEs associated with neratinib/placebo dose reduction is shown below.

Table 30. Summary of TEAEs Leading to Dose Reduction Occurring in >1% of Patients in the Neratinib Arm

	Neratinib (N=1408)	Placebo (N=1408)
Any TEAE – n (%)	440 (31.3)	35 (2.5)
Diarrhea	372 (26.4)	8 (0.6)
Nausea	39 (2.8)	1 (0.1)
Abdominal pain	22 (1.6)	1 (0.1)
Vomiting	19 (1.3)	1 (0.1)
Fatigue	17 (1.2)	3 (0.2)

Source: AE dataset (ADAE.xpt); CSR Modified Table 38

Significant Adverse Events

The most common Grade 3/4 TEAEs observed following treatment with neratinib were diarrhea, vomiting, and abdominal pain. The rate of diarrhea was 39.9% (39.8% grade 3 and 0.1% Grade 4) and the rate of vomiting was 3.3% in the neratinib arm (3.3% Grade 3 and 0% Grade 4). In the placebo arm, the rate of Grade 3 diarrhea and vomiting was 1.6% and 0.4%, respectively.

A total of 16 patients (1.1%) in the neratinib arm and 14 patients (1.0%) in the placebo arm experienced a Grade 4 TEAE. A list of Grade 4 events in the neratinib arm is shown below.

Table 31. Grade 4 TEAEs in the Neratinib Arm

	Neratinib (N=1408)
Any Grade 4 TEAE – n (%)	16 (1.1%)
ALT increased	3
AST increased	3
Blood creatinine increased	2
Anemia	1
Dehydration	1
Diarrhea	1
Glioma	1
Hypernatremia	1
Hyperuricosuria	1
Hypokalemia	1
Multiple injuries	1
Myocardial infarction	1
Neutropenia	1
Pulmonary embolism	1
Rectal cancer	1

Source: AE dataset (ADAE.xpt)

Reviewer Comment: ***All cases of hepatotoxicity and renal failure/blood creatinine increased were reversible upon treatment discontinuation.***

The three patients who experienced Grade 4 AST/ALT elevations (Subjects 001683, 001860, and 003919) are described in detail below.

Subject 001683 was a 54-year-old Caucasian woman who received her first dose of neratinib on 8/5/10. Fourteen days later, on (b) (6), she experienced more than 20 episodes of diarrhea associated with abdominal pain, diaphoresis, blurry vision, and a brief syncopal episode while at work. She was admitted to the hospital with hypotension (80/40). Labs were significant for Grade 4 transaminase elevations (ALT was 1376 and AST was 1757), which led to permanent discontinuation of neratinib. Bilirubin remained within normal limits. She was treated with IV hydration. The transaminase elevations were considered recovered/resolved on (b) (6).

Subject 001860 was a 55-year-old Caucasian woman who received her first dose of neratinib on 10/9/09. Seven days later, on 10/16/09, she experienced Grade 3 diarrhea and Grade 4 AST/ALT elevations. Bilirubin was also elevated at 27.36 (ULN = 17). Alkaline phosphatase was slightly elevated at 130 (ULN = 120). Abdominal ultrasound revealed fatty infiltration of the liver with mild enlargement of the common bile duct s/p cholecystectomy. She discontinued neratinib and 11 days later her laboratory values had normalized.

Subject 003919 was a 52-year-old Caucasian woman who received her first dose of neratinib on May 7th, 2010. Fifteen days later, on 5/22/10, she reported abdominal pain and nausea and labs revealed Grade 4 SAEs of elevated ALT and AST which led to discontinuation of neratinib. Abdominal ultrasound revealed Cholelithiasis. The transaminase elevations were considered recovered/resolved on 6/3/10.

Treatment Emergent Adverse Events and Adverse Reactions

A brief summary of TEAEs is shown in the table below. Overall, 98.5% of patients in the neratinib arm and 88.1% of patients in the placebo arm experienced at least 1 TEAE.

Table 32. Overall Summary of TEAEs in Study 3004

	Neratinib (N=1408) (%)	Placebo (N=1408) (%)
Any TEAE	98.5	88.1
Grade 3 or 4 TEAE	49.7	13.1
Serious TEAE	7.3	6.0
Treatment-related TEAE	96.1	57.2
Serious treatment-related TEAE	3.0	0.6
TEAE leading to discontinuation	27.6	5.4
TEAE leading to study withdrawal	2.3	0.5
TEAE leading to dose reduction	31.3	2.5
TEAE leading to hospitalization	6.6	5.3
TEAE leading to dose interruption	44.7	13.1

Source: AE dataset (ADAE.xpt); CSR Modified Table 31

The following table provides a summary of commonly reported adverse reactions experienced in ≥ 2% of patients treated with neratinib in Study 3004 sorted by MedDRA System Organ Class then relative frequency. The most frequently reported adverse reactions (i.e. ≥ 10% of patients) in the neratinib arm were diarrhea (95%), nausea (43%), abdominal pain (36%), fatigue (27%), vomiting (26%), rash (18%), stomatitis (14%), decreased appetite (12%), and muscle spasms (11%).

Table 33. Summary of Adverse Reactions occurring in ≥ 2% of patients treated with neratinib in Study 3004

System Organ Class Preferred Term	Neratinib (N=1408)			Placebo (N=1408)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhea	95.4	39.8	0.1	35.4	1.6	0
Nausea	43.0	1.8	0	21.5	0.1	0
Abdominal Pain[1]	35.6	2.5	0	15.4	0.4	0
Vomiting	26.2	3.3	0	8.0	0.4	0
Stomatitis[2]	13.9	0.6	0	6.4	0.1	0
Dyspepsia	9.9	0.4	0	4.2	0	0
Abdominal distention	5.2	0.3	0	3.5	0	0
Dry mouth	3.3	0.1	0	1.6	0	0
General Disorders and Administrative Site Conditions						
Fatigue	27.1	1.6	0	20.1	0.4	0
Hepatobiliary Disorders						
ALT increased	18.5	1.1	0.2	3.2	0.2	0
AST increased	7.4	0.5	0.2	3.3	0.3	0
Infections and Infestations						
Urinary Tract Infection	5.1	0.1	0	1.6	0	0
Investigations						
Weight decreased	4.8	0.1	0	0.5	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	12.1	0.2	0	2.8	0	0
Dehydration	3.6	0.9	0.1	0.4	0.1	0
Musculoskeletal and Connective Tissue Disorders						
Muscle Spasms	11.3	0.1	0	3.2	0.1	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	5.0	0	0	1.3	0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash[3]	18.4	0.6	0	8.5	0	0
Nail Disorder[4]	8.2	0.3	0	1.9	0	0
Dry Skin	6.0	0	0	2.3	0	0
Skin Fissures	2.0	0.1	0	0.1	0	0

[1] Abdominal Pain includes: Abdominal Pain, Abdominal Pain Upper, and Abdominal Pain Lower.

[2] Stomatitis includes: stomatitis, oropharyngeal pain, mucosal inflammation, mouth ulceration, oral pain, aphthous stomatitis, glossodynia, oral mucosal blistering, glossitis, and cheilitis.

[3] Rash includes: rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rush pustular, rash maculo-papular, rash popular, dermatitis, dermatitis acneiform, and toxic skin eruption.

[4] Nail disorder includes: nail disorder, paronychia, onychoclasis, and nail discoloration, nail toxicity, nail growth abnormality, and nail dystrophy.
Source: AE dataset (adae.xpt)

***Reviewer Comment**: There are a number of differences between the incidences of Adverse Reactions reported above compared to the Applicant's analysis as reported in Table 175 in the CSR. These differences are related to inappropriate splitting of Preferred Terms and are summarized below.*

- ***Abdominal Pain. The following preferred terms were added to the definition of Abdominal Pain: Abdominal Pain Upper and Abdominal Pain Lower.***
- ***Stomatitis. The following preferred terms were added to the definition of Stomatitis: oropharyngeal pain, mucosal inflammation, oral pain, glossodynia, glossitis, and cheilitis.***
- ***Rash. The following preferred terms were added to the definition of Rash: rash maculo-papular, rash popular, dermatitis, dermatitis acneiform, and toxic skin eruption.***
- ***Nail Disorder. The following preferred terms were added to the definition of Nail Disorder: nail toxicity, nail growth abnormality, and nail dystrophy.***

Laboratory Findings

Overall, hematological indices and blood electrolyte levels were comparable between treatment arms in Study 3004. In regards to liver function, there were notable differences in AST and ALT values. For ALT, the mean change from baseline to maximum post-baseline values was 9 U/L (range, -66 – 1339) in the neratinib arm and 5 U/L (range, -63 -1646) in the placebo arm. For AST, the mean change from baseline to maximum post-baseline values was 6 U/L (range, -39 – 1727) in the neratinib arm and 4 U/L (range, -62 – 1953) in the placebo arm. LFT abnormalities are discussed in greater detail in section 7.4.5. Other laboratory parameters related to liver function (bilirubin, albumin, ALP, and LDH) were comparable between arms.

Table 34. Summary of Abnormal Clinical Hematology Laboratory Findings by Maximum Severity Grade in Study 3004

	Neratinib (N=1408)			Placebo (N=1408)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
WBC decreased	57.9	0	0	61.4	0	0.1
Neutrophils decreased	40.5	0.1	0.1	45.8	0.5	0.4
Anemia	35.9	0.2	0.4	26.2	0	0.4
Platelets decreased	9.6	0	0.4	9.1	0.2	0.5

Source: Laboratory dataset (adlb.xpt); CSR Modified Table 14.3.5.3.2

Table 35. Summary of Abnormal Clinical Chemistry Laboratory Findings by Maximum Severity Grade in Study 3004

	Neratinib (N=1408)			Placebo (N=1408)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
ALT	37.8	1.5	0.2	24.8	0.4	0.1
AST	27.5	0.8	0.1	19.8	0.4	0.1
Bilirubin	11.1	0.1	0	11.4	0.4	0.1
Alkaline phosphatase	22.7	0	0	25.0	0.1	0
Creatinine	12.5	0.1	0.1	9.2	0	0
Hypercalcemia	3.6	0	0.1	5.1	0	0.3
Hyperkalemia	11.2	0.4	0.2	12.5	0.5	0.1
Hypermagnesemia	5.2	0.9	0.1	6.0	1.2	0
Hypernatremia	10.3	0.1	0.1	10.6	0.1	0
Hypoalbuminemia	8.4	0.1	0	6.5	0	0
Hypocalcemia	48.9	0.1	0.9	42.9	0.2	0.6
Hypokalemia	7.5	0.3	0.1	7.8	0.6	0
Hypomagnesemia	7.2	0.4	0.2	5.2	0.3	0.1
Hyponatremia	11.6	0.9	0	10.9	0.5	0.3

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.
Source: Laboratory dataset (adlb.xpt); CSR Modified Table 14.3.5.3.1

There were slightly more blood creatinine elevations in the neratinib arm compared to the placebo arm; however, the majority of abnormalities were Grade 1 as demonstrated in the table below.

Creatinine Elevation	Neratinib (N=1408) (%)	Placebo (N=1408) (%)
Grade 1	11.3	8.9
Grade 2	1.0	0.3
Grade 3	0.1	0
Grade 4	0.1	0

Source: Laboratory dataset (adlb.xpt)

***Reviewer comment:* Overall, the abnormal clinical laboratory findings are generally consistent with the corresponding abnormal clinical findings reported as TEAEs.**

Vital Signs

Overall, the mean and median temperature, heart rate, systolic blood pressure, and diastolic blood pressure were well balanced between the two treatment arms at baseline. The median values for each vital sign measurement in each treatment cycle were generally comparable

between treatment arms. No clinically relevant changes from baseline in any of the vital sign measurements were observed in either treatment arm.

QT

A Standardized MedDRA query for Torsade de pointes/QT prolongation was performed. The incidence of Torsades de pointes/QT prolongation was 4.7% in the neratinib arm and 7.3% in the placebo arm.

Table 36. Summary of SMQ for Torsade de Pointes/QT Prolongation in Study 3004

	Neratinib (N=1408) (%)	Placebo (N=1408) (%)
Torsade de pointes/QT prolongation	4.7	7.3
ECG QT interval abnormal	0	0.1
ECG QT prolonged	3.5	6.6
Loss of consciousness	0.1	0.1
Syncope	1.1	0.6
Ventricular arrhythmias	0.1	0
Torsade de pointes	0	0

Source: AE dataset (adae.xpt)

Reviewer comments:

1. ***The SMQ for Torsade de pointes/QT prolongation is reassuring.***

2. ***The overall frequency and severity of any cardiac toxicity in Study 3004 was low in spite of previous exposure to other cardiotoxic chemotherapy regimens including anthracyclines and trastuzumab. In general, there is no evidence to suggest that neratinib is associated with cardiac toxicity.***

Immunogenicity

Not applicable

7.4.5. Analysis of Submission-Specific Safety Issues

Diarrhea

The frequency of severe (≥Grade 3) diarrhea in Study 3004 was substantially higher in the neratinib arm (39.8%) compared to the placebo arm (1.6%). A summary of characteristics of treatment-emergent diarrhea in Study 3004 is shown in the Tables below.

Table 37. Summary of Characteristics of Treatment-emergent Diarrhea in Study 3004

	Neratinib (N=1408)	Placebo (N=1408)
Any Diarrhea	1343 (95.4)	499 (35.4)
Serious	22 (1.6)	1 (0.1)
Treatment Related	1330 (94.5)	411 (29.2)
Serious Treatment Related	22 (1.6)	1 (0.1)
Action Taken		
Discontinuation	237 (16.8)	3 (0.2)
Withdrawn from Study	23 (1.6)	0
Dose Reduction	372 (26.4)	8 (0.6)
Dose Hold	477 (33.9)	26 (1.8)
Hospitalization	20 (1.4)	1 (0.1)
Concomitant Medication	1232 (87.5)	196 (13.9)
Maximum Toxicity		
Grade 1	323 (22.9)	382 (27.1)
Grade 2	458 (32.5)	94 (6.7)
Grade 3	561 (39.8)	23 (1.6)
Grade 4	1 (0.1)	0
Outcome of Last Diarrhea Episode		
Persisted	67 (4.8)	16 (1.1)
Resolved	1276 (90.6)	483 (34.3)

Source: AE dataset (adae.xpt); CSR Modified Table 41

The median time to first onset of any Grade diarrhea was 2 days (range, 1-320) and the median time to first onset of Grade ≥ 3 diarrhea was 8 days (range, 1-350). The median cumulative duration of any Grade diarrhea was 59 days (range, 1-523) and the median cumulative duration of Grade ≥ 3 diarrhea was 5 days (range, 1-139).

Table 38. Summary of Time to First Onset, Cumulative Duration, and Number of Episodes of Treatment-emergent Diarrhea in Study 3004

	Neratinib (N=1408)	Placebo (N=1408)
Time to First Onset in Days (any Grade)		
Median	2	18
Q1,Q3	2, 4	4, 82
Range	1-320	1-376
Time to First Onset in Days (Grade ≥ 3)		
Median	8	124
Q1,Q3	4, 33	21, 257
Range	1-350	1-350
Cumulative Duration in Days (any Grade)		
Median	59	6
Q1,Q3	14, 164	2, 34
Range	1-523	1-570
Cumulative Duration in Days (Grade ≥ 3)		
Median	10	3
Q1,Q3	5, 27	2, 7
Range	1-450	1-340
Number of Episodes (any Grade)		
1-2	329 (23.4)	302 (21.4)
3-5	243 (17.3)	72 (5.1)
6-9	149 (10.6)	35 (2.5)
≥ 10	622 (44.2)	90 (6.4)
Number of Episodes (Grade ≥ 3)		
1	280 (19.9)	19 (1.3)
2	119 (8.5)	2 (0.1)
3-5	102 (7.2)	2 (0.1)
6-9	36 (2.6)	0
≥ 10	25 (1.8)	0

Source: AE dataset (adae.xpt); CSR Modified Table 41

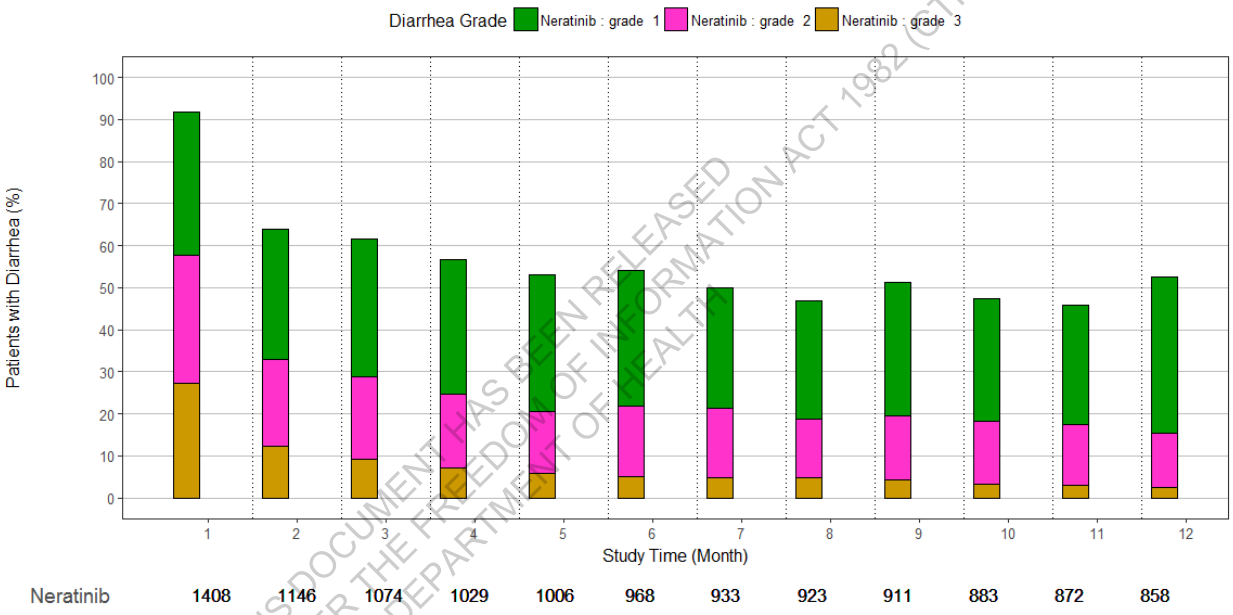
There was one episode of Grade 4 diarrhea in Study 3004. The details are summarized below.

Subject 05781 was a 65-year-old Caucasian woman who received her first dose of neratinib on 3/24/11. No prior medical history was reported and no concomitant medications were reported within 30 days of the onset of diarrhea. The patient had experienced multiple episodes of Grade 3 diarrhea during her course of treatment, and on 6/30/11, approximately 3 months after starting treatment with neratinib, she experienced an episode of non-serious Grade 4 diarrhea. This event was recorded as having resolved the same day. The Grade 4 diarrhea did not lead to hospitalization or temporary discontinuation of neratinib.

The majority of patients (93%) had diarrhea in the first month of treatment and the overall incidence of diarrhea decreased over time. Overall, the percentage of patients in the neratinib arm reporting Grade 1 diarrhea did not change appreciably over time with about 30% of patients reporting Grade 1 diarrhea from the first month through 12 months of treatment. The incidence of Grade 2 diarrhea declined from approximately 30% in the first month to 18-19% in months 2 and 3, and to about 12% in month 12. The incidence of Grade 3 diarrhea declined from about 29% in the first month of treatment to about 11% and 8% in months 2 and 3, respectively, and ultimately to approximately 3% in month 12.

A bar chart of the occurrence of Grade 1-3 treatment-emergent diarrhea by treatment month for patients who received neratinib is shown in the Figure below.

Figure 12. Treatment-emergent Diarrhea (Grades 1-3) by Treatment Month in Study 3004



Note: the number at risk at each time point is the number of patients who were still receiving neratinib (i.e. had not permanently discontinued treatment) on the first day of each month.
Source: Study 3004 AE dataset (adae.xpt)

The Original Study 3004 protocol instructed providers to treat diarrhea at the very first occurrence. Subjects were to have ready access to antidiarrheal agents (Loperamide preferred) at home starting on Day 1 of treatment and were to be encouraged to contact the site to report and discuss the severity of diarrhea and the appropriate course of treatment. If clinically indicated, stool cultures were recommended to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3 -4 neutropenia).

A summary of concomitant medications taken for diarrhea by patients in Study 3004 is shown below.

Table 39. Summary of Antidiarrheal Medications in Study 3004

	Neratinib (N=1408) (%)	Placebo (N=1408) (%)
Any Antidiarrheal Medication	91.6	43.5
Loperamide	85.1	14.7
Antibiotics	12.6	7.5
Diphenoxylate/Atropine	13.0	1.1
Probiotics	5.5	2.3
Acetorphan	0.9	0.1
Octreotide	0.4	0
Other	40.3	31.0
Time to 1st Antidiarrheal Medication (days)		
Median	3	9
Q1, Q3	1, 5	1, 85
Range	1-350	1-381

Source: AE dataset (adae.xpt); CSR Modified Table 45

Study 6201 - Antidiarrheal Prophylaxis

Given the high rates of diarrhea observed in Study 3004, in 2014 the Applicant opened Study PUMA-NER 6201 (Study 6201), an open-label study to characterize the incidence and severity of diarrhea in patients with early stage HER2+ breast cancer treated with neratinib and intensive loperamide prophylaxis. As described above, patients on Study 3004 were not required to receive antidiarrheal prophylaxis.

Loperamide is an over-the-counter (OTC) antidiarrheal sold under the brand name Imodium, among others. Loperamide is an opioid-receptor agonist and acts on the u-opioid receptors in the myenteric plexus in the large intestine. It is an opioid with no significant absorption from the gut and does not cross the blood brain barrier when used at normal doses.

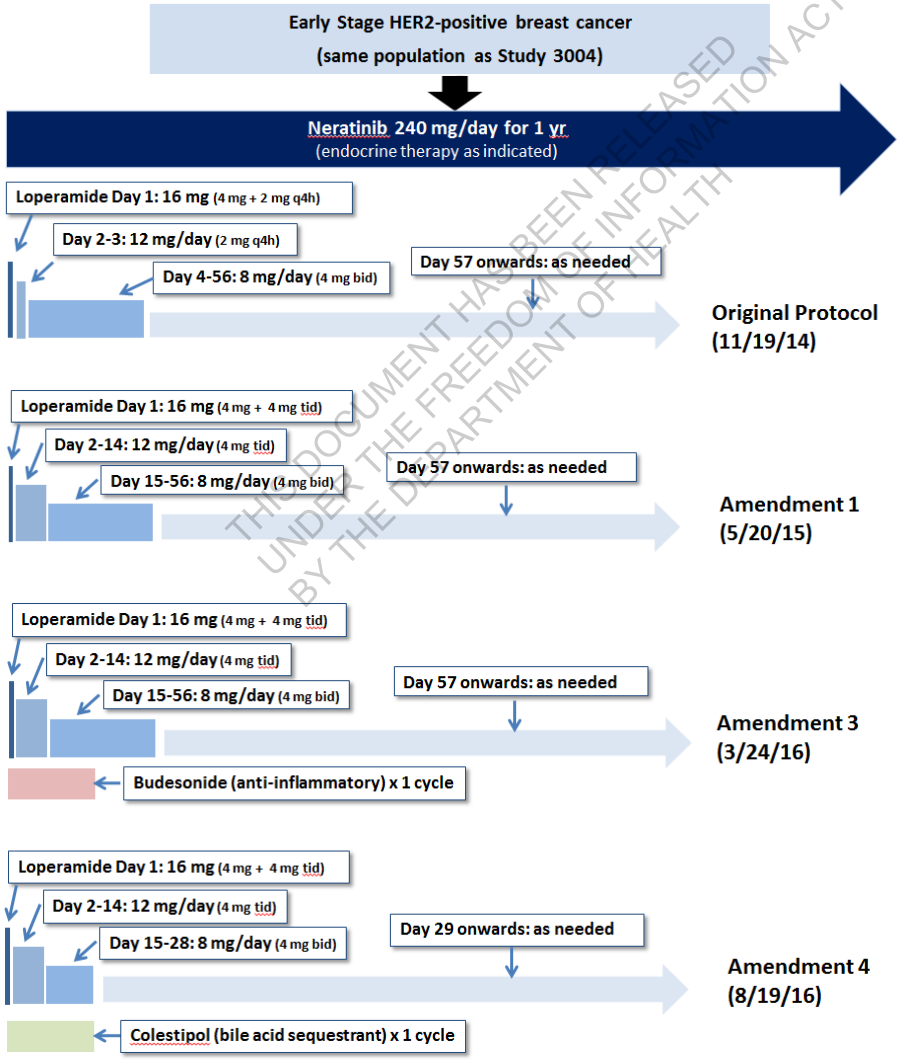
Reviewer comment: ***The Agency published a Drug Safety Communication on OTC loperamide in June 2016 regarding the risk of serious heart problems that can lead to death when patients take higher than recommended doses of loperamide. The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing Loperamide by taking extremely high doses in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria. The prophylactic doses of Loperamide in Study 6201 do not exceed the maximum recommended dose of 16mg/day and would not be expected to increase the risk of serious heart problems.***

The primary endpoint of ongoing Study 6201 is the incidence and severity of diarrhea. The original protocol dated 11/19/14 had an accrual goal of 70 patients. Patients were treated with neratinib 240 mg daily and also received loperamide at the following schedule: Initial dose of

4 mg (2 tablets/capsules) with the first dose of neratinib followed by 2 mg (1 tablet/capsule) every four hours for the first 3 days (Day 1 = 16mg/day; Days 2-3 = 12 mg/day). After the first 3 days, loperamide 2mg every 6-8 hours through the first 2 cycles of therapy (Days 4-56 = 6-8 mg/day) from start of neratinib.

With the first amendment of the protocol dated 5/20/15, the accrual goal was increased to 120 patients and the dosing regimen of loperamide was modified from q4h dosing to tid dosing to increase patient compliance. Patients received loperamide at the following schedule: Initial dose of 4 mg with first dose of neratinib followed by 4mg tid for the first 14 days (Day 1 = 16mg/day; Days 2-14 = 12 mg/day). After the first 14 days, loperamide 4mg bid through the first 2 cycles of therapy (Days 15-56) from start of neratinib. There have been two additional amendments. Amendment #3 on 3/24/16 in which the protocol added the anti-inflammatory, budesonide, to the regimen and Amendment #4 on 8/19/16 which added the bile-acid sequestrant, colestipol, to the regimen.

Figure 13. Study 6201 - Schema

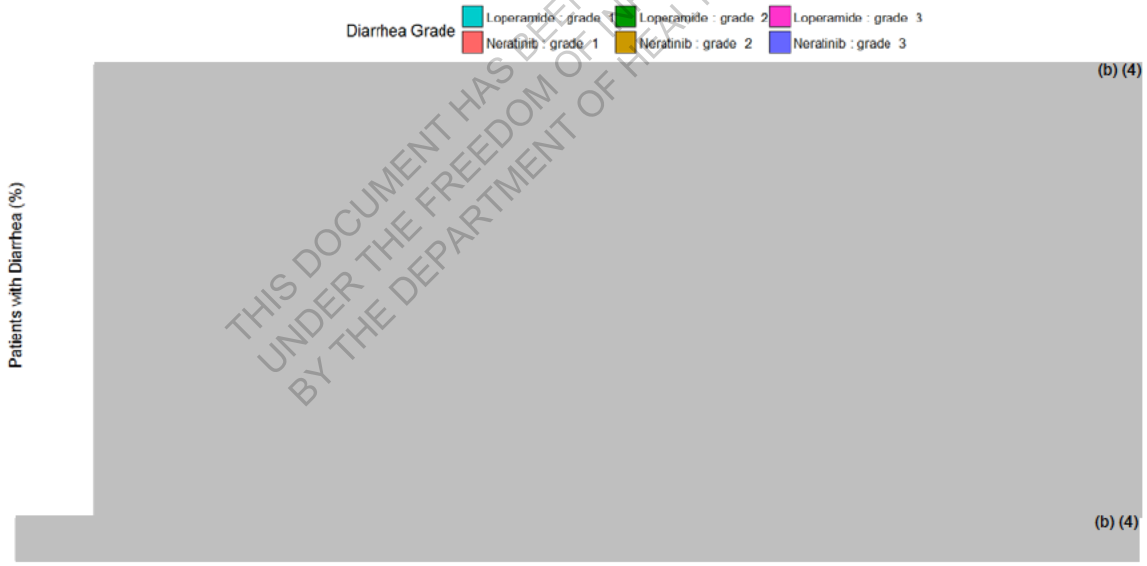


As of the March 22nd, 2017 safety cutoff date, 137 patients received prophylaxis with Loperamide alone (the Loperamide Cohort; representing patients enrolled on the Original Protocol through Amendment #2), 64 patients with Loperamide plus Budesonide (the Loperamide plus Budesonide Cohort), and 26 patients with Loperamide plus Colestipol (the Loperamide plus Colestipol Cohort). The median duration of treatment with neratinib was 10.6 months for the Loperamide Cohort, 5.1 months for the Loperamide plus Budesonide Cohort, and 1.7 months for the Loperamide plus Colestipol Cohort.

Reviewer comment: ***The Loperamide Cohort was used as a comparator during our review since this cohort has the longest follow-up (median duration of treatment with neratinib of 10.6 months as of Mar 22nd 2017 safety cutoff), and we are interested in the incidence of AEs and actions taken throughout the entire duration of the 12-month treatment period.***

The Figure below presents the occurrence and severity of diarrhea by Grade in the Loperamide Cohort of Study 6201 and the safety population in Study 3004 by treatment month. The number at risk at each time point is the number of patients who were still receiving neratinib (i.e. had not permanently discontinued treatment) on the first day of each month.

Figure 14. Treatment Emergent Grades 1-3 Diarrhea by Treatment Month in Study 3004 ("Neratinib") and the Loperamide Cohort of Study 6201 ("Loperamide")



Note: the number at risk at each time point is the number of patients who were still receiving neratinib (i.e. had not permanently discontinued treatment) on the first day of each month.
Source: Study 3004 and 6201 AE datasets (adae.xpt)

In general, the incidence of diarrhea is highest early in the course of treatment and then declines and stabilizes by month 4. The results of Study 6201 suggest that intensive Loperamide prophylaxis decreases the incidence and severity of diarrhea.

A comparison of common adverse reactions in the Neratinib Arm of Study 3004 and the Loperamide Cohort of Study 6201 is shown below.

Table 40. Common Adverse Reactions in Study 3004 and the Loperamide Cohort of Study 6201

	Study 3004 Neratinib Arm (N=1408)			Study 6201 Loperamide Cohort (N=137)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Diarrhea	95	40	<1	(b) (4)		
Constipation	8	0	0			
Nausea	43	2	0			
Abdominal pain	36	2	0			
Fatigue	27	2	0			
Vomiting	26	3	0			
Decreased appetite	12	<1	0			

Source: Study 3004 AE dataset (adae.xpt); Study 6201 Interim Safety Update Report (March 22 , 2017 data cutoff)

Reviewer comment: ***While these results suggest that antidiarrheal prophylaxis with loperamide decreases the incidence and severity of diarrhea, a higher incidence of constipation, fatigue, and nausea was reported in the loperamide cohort of Study 6201 compared to the neratinib arm of Study 3004.***

A comparison of dose modifications and discontinuations in the neratinib arm of Study 3004 and the Loperamide Cohort of Study 6201 is shown below. Again, the Loperamide Cohort is used as a comparator since this cohort has the longest follow-up.

Table 41. Incidence of Treatment-emergent Diarrhea Leading to Dose Hold, Dose Reduction, Treatment Discontinuation, or Hospitalization

	Study 3004 Neratinib Arm (N=1408)	Study 6201 Loperamide Cohort (N=137)
Dose hold	34%	(b) (4)
Dose reduction	26%	
Discontinuations		
Due to diarrhea	17%	
Due to any AE	28%	
Hospitalization	1.4%	

Source: Study 3004 AE dataset (adae.xpt); Study 6201 Interim Safety Update Report (March 22nd, 2017 data cutoff)

***Reviewer comment**: While there were fewer dose holds and dose reductions in the Loperamide Cohort of Study 6201 compared to patients in Study 3004, there remained a substantial rate of treatment discontinuations despite antidiarrheal prophylaxis with loperamide. The rates of hospitalization are similar between the cohorts.*

Enrollment in the Colestipol Cohort is ongoing. The final analysis of Study 6201 will be performed when all patients have completed 12 months of neratinib treatment.

***Reviewer comment**: We await the final results of Study 6201 including results from the Loperamide plus Budesonide and Loperamide plus Colestipol Cohorts.*

Hepatotoxicity

AST or ALT elevations occurred more frequently in the neratinib arm compared to the placebo arm of Study 3004. Elevations of AST or ALT > 10 x ULN and > 20 x ULN occurred in few patients overall, although numerically more in neratinib-treated than placebo-treated patients. There have been no cases of drug induced liver injury associated with neratinib.

Labs Greater than Upper Limit of Normal

The following analysis lists the count and percent of subjects and event count where the post-baseline lab results for ALT, AST, ALP, and TB were greater than or equal to 2 times, 3 times, 5 times, 10 times, and 20 times the upper limit of normal. This analysis used the lab test short name variable (LBTESTCD), the numeric results (LBSTRESN) in standard units, the reference range upper limit-Std Units (LBSTNRHI), the sponsor-derived baseline flag (LBBLFL) and study days (LBDY) from the laboratory test results (LB) dataset.

Table 42. Liver Labs Great than Upper Limit of Normal in Study 3004

Liver Lab Test	Neratinib (N=1408)			Placebo (N=1408)		
	Event count	Subject Count	% of Subjects	Event count	Subject Count	% of Subjects
ALT ≥ ULN						
2 x ULN	305	140	9.94	152	57	4.05
3 x ULN	135	69	4.90	53	18	1.28
5 x ULN	49	27	1.92	17	7	0.50
10 x ULN	16	11	0.78	9	2	0.14
20 x ULN	4	3	0.21	3	1	0.07
AST ≥ ULN						
2 x ULN	155	75	5.33	76	39	2.77
3 x ULN	62	40	2.84	22	9	0.64
5 x ULN	23	15	1.07	14	6	0.43
10 x ULN	6	5	0.36	4	1	0.07
20 x ULN	3	2	0.14	2	1	0.07
ALP ≥ ULN						
2 x ULN	368	89	6.32	636	122	8.66
3 x ULN	40	21	1.49	78	24	1.70
5 x ULN	1	1	0.07	8	2	0.14
10 x ULN	1	1	0.07	0	0	0.00
20 x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN						
1.5 x ULN	68	28	1.99	85	29	2.06
2 x ULN	12	8	0.57	39	11	0.78
3 x ULN	3	2	0.14	31	9	0.64

Source: Study 3004 Laboratory dataset (adlb.xpt)
Note: All scores are post-baseline; subject scores may be counted more than once in that they will be counted in all conditions (e.g. 2x, 3x, etc.) that apply.

Possible Hy's Law Cases

Hy's Law criteria were used to assess the incidence of severe hepatotoxicity. A patient was considered to be a Hy's Law case if laboratory measurements met the following criteria: peak ALT or AST > 3 x ULN and total bilirubin (TBL) ≥ 2 x ULN at any time post-baseline, with alkaline phosphatase (ALP) ≤ 2 x ULN, and lacking an underlying clinical condition. This analysis used the lab test short name variable (LBTESTCD), the numeric results (LBSTRESN), the reference range upper limit-std units (LBSTNRHI), the baseline flag (LBBLFL), visit number (VISITNUM) and study days (LBDY) from the laboratory test results (LB) dataset. Results are determined to be a baseline value if they have a "Y" in LBBLFL.

There were a total of six patients in the neratinib arm that met the laboratory criteria for potential Hy's Law Case, and only one patient did not have an obvious potential alternative explanation. The details of this case are described below.

Subject 018168 was a 29-year-old woman who received her first dose of neratinib on 3/11/11. Her baseline bilirubin was 22 (ULN = 17) with 75% conjugated, suggesting the possibility of underlying Gilbert's Syndrome. On 3/17/11, seven days after initiating treatment, her serum ALT was 139 (3.8 x ULN), serum AST was 94.2 (2.7 x ULN), and total bilirubin was 43 (2.5 x ULN). She permanently discontinued study drug on 3/24 due Grade 3 hepatotoxicity. By 4/7/11 all of her labs (including bilirubin) had normalized.

Reviewer comments:

1. ***This case is complicated by the presence of elevated serum bilirubin that is primarily unconjugated at baseline, which suggests underlying Gilbert's Syndrome. It is well known that Gilbert's Syndrome can become more evident with fasting; therefore, the rise in serum ALT and bilirubin may actually reflect two separate effects of treatment with the drug – 1) drug related elevations in serum ALT and 2) fasting due to drug-induced GI symptoms. In addition, the peak serum ALT measured in this patient was only 4 x ULN and it is very unlikely that larger values were missed since this was measured just 7 days on study drug. In a typical Hy's Law case, the peak serum ALT is generally > 10 x ULN.***

2. ***In addition, the Applicant obtained an external consultant on (b) (4) to review this case. (b) (4) reviewed the details of this case and concluded that this single case should not be viewed as a Hy's Law Case in terms of livery safety implications.***

When evaluating laboratory data from all Puma sponsored and Investigator initiated studies with neratinib, there were a total of five patients identified who were identified as potential Hy's Law cases. The patient narratives were requested from the Sponsor and reviewed carefully. In all five cases, alternative etiologies were identified and none of the lab abnormalities were likely related to neratinib drug induced liver injury.

Reviewer comment: ***In summary, although hepatotoxicity manifesting as elevated aminotransferases is not uncommon with neratinib treatment, the overall risk of neratinib causing drug induced liver injury is low. The product label will include clear instructions on how to monitor patients for signs of hepatotoxicity and management guidelines in terms of dose interruptions and dose reductions.***

7.4.6. Safety Analyses by Demographic Subgroups

Age

Safety data reported in Study 3004 were analyzed by age (<65 and ≥65 years old). Overall, the incidence of TEAEs in both age groups was similar. There was a higher frequency of SAEs reported in the ≥ 65 age group (9.9%) than in the <65 age group (7.0%); however, the relative

increase was similar for both neratinib and placebo arms. The serious adverse reactions most frequently reported in the ≥ 65 years-old group were vomiting (2.3%), diarrhea (1.7%), renal failure (1.2%), and dehydration (1.2%). There was a higher frequency of treatment discontinuations due to AEs in the ≥65 age group (44.8%) than <65 age group (25.5%). The rate of discontinuations for ≥65 and <65 groups were similar in the placebo arm (6.4% and 5.3%, respectively). The differences between the two age groups were largely due to the higher discontinuation rate due to diarrhea in the ≥65 group compared with <65 group (29.1% vs. 15.1%) in the neratinib arm. There was also a higher percentage of hospitalizations due to AEs in the ≥65 age group (8.4%) than in <65 age group (5.6%); however, this rate was balanced between the neratinib and placebo arms in each age group (8.7% and 8.1%, respectively, for ≥65 and 6.3% and 4.9%, respectively, for <65).

Sex
No analysis of neratinib safety data with regard to patients' sex was performed on the data from Study 3004 since all patients in the study were women.

Race
There were a total of 385 Asian patients in Study 3004. There was no notable difference in the incidence of Grade 3 or 4 TEAEs in the neratinib arm of the groups (about 50% each). The incidence of SAEs reported in the White population was 7.0% overall (neratinib 7.7%, placebo 6.3%) and in the Asian population SAEs were reported at 4.7% overall (neratinib 5.3%, placebo 4.1%). The percentage of TEAEs that led to dose reduction was higher in the White population (17.7% overall; neratinib 32.4%, placebo 2.5%) than the Asian population (12.2% overall; neratinib 23.4%, placebo 1.5%).

Geographic Region
There were no notable differences in the incidence of any category of TEAEs reported (TEAE, SAE, AE leading to discontinuation, etc.) between the 2 arms in the 3 different regions of the world [(1) North America; (2) Western Europe, Australia and South Africa; and (3) Asia Pacific, Eastern Europe, and South America]).

Concurrent CYP3A4 inhibitors
Neratinib is predominantly metabolized by the CYP3A4 isoenzyme. Although the protocol recommended that strong CYP3A4 inducers or inhibitors should be avoided during the treatment period, 298 patients received drugs that were CYP3A4 inhibitors. Overall, there were no notable differences in the incidence of TEAEs reported in these patients compared with those who did not receive any CYP3A4 inhibitors. There were higher percentages of Grade 3 or 4 TEAEs, SAEs, and TEAEs leading to hospitalization or TEAEs leading to dose holds in patients who received concomitant CYP3A4 inhibitors (42.3%, 12.4%, 11.7%, and 39.3%, respectively) compared with patients who did not receive CYP3A4 inhibitors (30.1%, 6.0%, 5.3%, and 27.8%); however, the number of patients are small in the CYP3A4 inhibitor group making comparisons difficult. The respective higher incidences were reflected fairly consistently both in the neratinib arm and in the placebo arm in each case.

7.4.7. Specific Safety Studies/Clinical Trials

Ongoing Study 6201 is an open-label study to characterize the incidence and severity of diarrhea in patients with early stage HER2+ breast cancer treated with neratinib and intensive loperamide prophylaxis. This study is described in detail in Section 7.4.5.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No accidental overdoses were reported in Study 3004 and there are no data available on the potential for abuse or dependence. A formal study has not been conducted by the applicant to investigate withdrawal and/or rebound.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Not applicable.

7.4.10. Integrated Assessment of Safety

No additional safety concerns have been identified based on the cumulative safety data submitted in this NDA.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

The major statistical review issues identified in Study 3004 were unplanned adaptations due to multiple amendments, imbalance in early dropouts, and incomplete extended follow-up resulting in missing data.

The study underwent major protocol amendments throughout its development program due in part to sponsor changes-the population was enriched to high risk then changed back to all-comers, follow-up was truncated at 2-years changing the primary analysis from event-driven to time-driven, and patients were reconsented for extended follow-up for 5-years post-randomization. However, these changes appear to be due to outside factors (i.e. external information and organizational changes) rather than premature trial unblinding.

The remaining two issues were addressed by FDA sensitivity analyses. An FDA simulation conducted to address the impact of early dropouts on the primary analysis showed that results after imputation were indeed similar. An FDA tipping point analysis conducted under the assumptions stated previously to address the impact of missing data in the extended follow-up collected showed that study results only tip against neratinib if the number of events occurring among neratinib patients with missing data was larger than expected. Thus, both of these FDA analyses favored a positive treatment effect with neratinib.

There remains some uncertainty regarding the true magnitude of the treatment effect since the primary analysis (truncated at 2-years follow-up) observed a hazard ratio of 0.66 (95% CI: 0.49, 0.90) which changed to 0.68 (95% CI: 0.51, 0.91) with the exploratory updated 2-year analysis, and the exploratory 5-year analysis observed a hazard ratio of 0.73 (95% CI: 0.57, 0.92).

7.6. Conclusions and Recommendations

Breast cancer is the most frequently diagnosed malignancy in women and is the leading cause of cancer mortality in women worldwide. HER2 (ERBB2)-positive breast cancer comprises approximately 20 to 25% of the entire breast cancer population. ERBB2 protein overexpression or ERBB2 gene amplification in breast cancer tumors is associated with more aggressive clinical disease and poorer prognosis. Current standard of care for patients with HER2-positive early breast cancer is chemotherapy and one year of adjuvant trastuzumab, however approximately 20% of patients with HER2-positive early breast cancer will recur within 5 years after adjuvant therapy.

The clinical benefit for neratinib for patients with early stage HER2-positive breast cancer following one year of adjuvant trastuzumab is based on the results of Study 3004 or ExteNET (Extended Adjuvant Treatment of Breast Cancer with Neratinib), a randomized, double-blind, placebo-controlled trial of neratinib after trastuzumab in women with early-stage HER2/neu overexpressed/amplified breast cancer. The primary endpoint was to compare invasive disease-free survival (iDFS) of women with early-stage ERBB2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting, receiving neratinib compared with that of women receiving placebo. There were several major amendments to the study design throughout the development program, which created uncertainty around the magnitude of effect. However FDA review team and Applicant conducted various simulations and exploratory analysis which were described in detail in this review, which demonstrated a consistent trend in favor of neratinib.

The reported number of patients with an iDFS event that occurred within 2 years after randomization was 173; of these, 67 (4.7%) were in the neratinib arm and 106 (7.5%) were in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than in the placebo arm, 94.2% and 91.9%, respectively. Results from the Applicant's 5-year exploratory analysis with reconsent data from 74.5% of the ITT patients show that the initial 2-year difference seen in the primary analysis appears to be sustained for up to 5-years. Certain subgroup analyses demonstrate the potential for a difference in magnitude of benefit; however, no subgroups demonstrated a potential detriment, and these analyses were exploratory.

There appears to be no evidence of long-term sequelae after treatment with neratinib and the toxicities are generally manageable with dose interruptions, dose reductions, and/or standard medical care. Diarrhea was the most common adverse event in ExteNET study with a 39.9% incidence of Grade 3-4 diarrhea and represents the most common AE leading to treatment discontinuation (16.8% of patients in Study 3004). Other frequent adverse events (≥10% incidence) in ExteNET study were nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, and muscle spasms. Other than diarrhea, neratinib is associated with a low incidence of severe AEs. Diarrhea leading to severe dehydration, renal insufficiency, and electrolyte abnormalities is uncommon and reversible with treatment interruption and/or discontinuation. Results from ongoing Phase 2 Study 6201 suggest that antidiarrheal prophylaxis with loperamide decreases the incidence and severity of diarrhea; however, there may be a trade-off in terms of toxicities with more constipation and nausea in the setting of loperamide prophylaxis, and approximately one-fourth to one-third of patients still discontinued treatment due to toxicity.

In summary, the benefit: risk assessment for the use of neratinib in the extended adjuvant setting must be carefully considered for each patient.

The key issues concerning this application were:

- Risk-benefit profile of neratinib for extended adjuvant therapy in an early and often curative disease setting.
- Is there uncertainty in the magnitude of treatment effect due to unplanned adaptations to multiple amendments and incomplete follow up data?
- The totality of evidence of neratinib's efficacy data in the context of other approvals in the adjuvant setting.

Given these uncertainties, the Division convened an Oncologic Drug Advisory Committee (ODAC) meeting on May 24, 2017, to advise and offer insight on the overall benefit-risk of neratinib in the proposed population. The committee voted 12-4 that the efficacy and safety results of ExteNET supports a positive benefit-risk assessment of neratinib for the proposed population.

The reviewers recommend regular approval for neratinib 240 mg daily for one year following adjuvant trastuzumab in patients with early stage HER2+ breast cancer.
As suggested by the ODAC, a detailed description of exploratory subgroup analyses is provided

in labeling. The safety profile is acceptable in the intended population. Appropriate labeling for dose modification and inclusion of diarrhea and hepatotoxicity in Warnings and Precautions identifies these concerns to prescribers and assists with appropriate management. The Applicant will additionally evaluate OS as this data matures.

{See appended electronic signature page}

Joyce Cheng, PhD
Primary Statistical Reviewer

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Amanda Walker, MD
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8 Advisory Committee Meeting and Other External Consultations

Given the uncertainty surrounding the benefit-risk profile of neratinib in the extended adjuvant setting, the multiple amendments which led to uncertainty in the magnitude of treatment effect, and the totality of neratinib's efficacy data in the context of other approvals in the adjuvant setting, an Oncology Drug Advisory Committee was convened on May 24, 2017 to discuss and provide advice on this NDA.

ODAC members were asked to discuss the following issues:

1. Is the benefit-risk profile of neratinib sufficient to support treatment in the proposed population?

The committee voted in favor of the benefit-risk profile for the neratinib for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed breast cancer who have received prior adjuvant trastuzumab-based therapy. The vote was 12-4. Committee members commented that the proposed indication may be too broad, with different subsets of patients more responsive to neratinib therapy than others. Many committee members commented that a full description of the study population and subgroups should be provided in labeling so providers and patients could make an informed decision about treatment. Committee members also commented that the data presented by the sponsor and the FDA were consistent and demonstrated efficacy. There was concern about the adverse event of diarrhea, but committee members noted that this adverse event was short-lived and manageable.

9 Pediatrics

Neratinib has not been studied in a pediatric population and the Applicant has received a waiver for this indication since breast cancer is rare in children.

Specifically, HER2 is not overexpressed in pediatric cancers, including extended adjuvant breast cancer. In addition, because breast cancer occurs in inly 1 in 1-million children, the pediatric population with HER2-positive breast cancer is not large enough to be able to extrapolate to specific pediatric populations.

10 Labeling Recommendations

10.1. Prescribing Information

The table below summarizes changes to the proposed prescribing information made by FDA. This labeling was under negotiation at the time of this review. See the final approved prescribing information for Nerlynx (neratinib) accompanying the approval letter for more information.

Summary of Significant Labeling Changes *(As of June 20, 2017)*		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights		
Indications and Usage	*See Full Prescribing Information, 1 Indications and Usage.*	FDA added the established pharmacological class required in the Highlights indication statement (i.e., "kinase inhibitor"). [21 CFR 201.57(a)(6).] *See Full Prescribing Information, 1 Indications and Usage for additional revisions.*
Dosage and Administration	RECOMMENDED DOSE: 240 MG GIVEN ORALLY ONCE DAILY WITH FOOD, CONTINUOUSLY FOR ONE YEAR (b) (4)	FDA added information to describe required antidiarrheal prophylaxis, dose interruptions and reductions, and dose reductions required for patients with hepatic impairment.
Warnings and Precautions	Diarrhea … Hepatotoxicity … (b) (4) monitor liver function tests, for the first (b) (4) of treatment. Withhold NERLYNX (b) (4) in patients experiencing Grade (b) (4)	FDA clarified (b) (4) discontinue (Grade 4 or Grade ≥ 2 after maximal dose reduction) Nerlynx. FDA revised the required hepatotoxicity requirements to add liver function test monitoring monthly for the first 3 months and when clinically indicated. FDA clarified that Nerlynx

	(b) (4) liver abnormalities (b) (4) (b) (4) …	should be withheld in patients experiencing Grade 3 liver abnormalities and permanently discontinued in patients experiencing Grade 4 liver abnormalities. FDA removed data proposed in the Highlights (b) (4)
Adverse Reactions	The most common adverse reactions (> 5%) were diarrhea, nausea, fatigue, vomiting, abdominal pain, rash, decreased appetite, (b) (4), stomatitis, muscle spasms, dyspepsia, alanine (b) (4) aspartate aminotransferase increased, nail disorder, dry skin, weight decreased and urinary tract infection. (6. (b) (4)	FDA reordered the adverse reactions (ARs) in descending order and revised (b) (4) to "abdominal distention" to better characterize these ARs. *See 6. Adverse Reactions below for more information.*
Drug Interactions	…	FDA revised this section to remove data and non-actionable information. FDA revised the information provided for gastric acid reducing agents to: • Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors (PPI) and H2-receptor antagonists. Separate NERLYNX by 3 hours after antacid dosing. (7.1) FDA added the following regarding drug-drug interactions: • Strong or moderate CYP3A4 inhibitors: Avoid concomitant use. (7.1) • Strong or moderate CYP3A4 inducers: Avoid concomitant

		use. (7.1) • P-glycoprotein (P gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with NERLYNX. (7.2)
Full Prescribing Information		
1. Indications and Usage	NERLYNX (b) (4) is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/ amplified breast cancer (b) (4) adjuvant trastuzumab-based therapy.	FDA removed (b) (4) and clarified the timing of initiation for this indication: "NERLYNX is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/ amplified breast cancer, to follow adjuvant trastuzumab based therapy [*see Clinical Studies (14)].*"
2. Dosage and Administration	2.1 Antidiarrheal Prophylaxis …	FDA created a new subsection 2.1 and added directions for the required antidiarrheal prophylaxis to increase the prominence of this information and promote mitigation of common and potentially serious adverse reactions. FDA and the Applicant agreed on the antidiarrheal prophylaxis regimen to mitigate these adverse reactions (vs. the two regimens originally proposed in labeling).
2. Dosage and Administration	2.2 Recommended Dose and Schedule …	FDA requested information from the Applicant and revised this section to include information restricting the ability to chew, crush, or split the tablets prior to swallowing.

2. Dosage and Administration	2.3 Dose Modifications …	In addition to the proposed dose modifications for diarrhea, FDA added dose modifications for other adverse reactions. FDA revised the dose modifications information for diarrhea (and other ARs) to include a 200 mg dose reduction consistent with dose modification guidelines in the ExteNET clinical trial. Dose reductions for severe hepatic impairment (Child Pugh C) were added by FDA. Dose reductions for concomitant use with gastric acid reducing agents were added by FDA. Non-actionable dose reduction information was removed from this section [*see Clinical Pharmacology (12*)].
3. Dosage Forms and Strengths	…	FDA added the salt equivalent (48.31 mg neratinib maleate) strength to the free-base strength (40 mg) in accordance with FDA salt labeling policies.
5. Warnings and Precautions	5.1 Diarrhea …	FDA revised the information related to diarrhea to provide addition safety results from the ExteNET trial. These include the addition of sequelae related to the diarrhea ARs such as hypotension and renal failure. FDA clarified the effects of antidiarrheal prophylaxis with loperamide and added

		additional patient management information for severe diarrhea (e.g., rule out infectious causes).
5. Warnings and Precautions	5.2 Hepatotoxicity ...	FDA revised this subsection from (b) (4) to "Hepatotoxicity" and removed the proposed statements (b) (4) as this information does not meet the requirements for a Warning and Precaution. FDA added information to report the incidence of hepatotoxicity ARs observed in Nerlynx clinical trials. FDA added details on the required liver function tests and the frequencies that they should be measured to detect and manage hepatotoxicity ARs.
6. Adverse Reactions	…	FDA added cross references to clinically significant adverse reactions described elsewhere in the labeling.
6. Adverse Reactions	6.1 Clinical Trials Experience …	FDA added dose reductions and permanent discontinuations due to ARs that occurred in Nerlynx clinical trials. FDA pooled the abdominal pain terms and added abdominal distention to the list of most common adverse reactions.

		FDA added renal failure to the list of serious adverse reactions based on the FDA safety review. *See 7.3.4 Safety Results for more information.* FDA added table footnotes to annotate the pooled AR terms listed in the common AR table (i.e., abdominal pain, stomatitis, rash, and nail disorder).
7. Drug Interactions	7.1 Effect of Other Drugs on NERLYNX …	FDA revised subsection 7.1 to use a tabular format and to include the known clinically significant drug interactions that may affect NERLYNX exposure. Clinical (b) (4) and prevention/management information were added for each relevant drug interaction. Drug interactions that are not clinically relevant were removed from this subsection [*see Clinical Pharmacology (12.3)].* FDA revised the prevention and management information for gastric acid reducing agents to avoid concomitant use of PPIs and H2-receptor antagonists; and to separate NERLYNX dosing by 3 hours after antacids. FDA added clinical impact information and prevention and management strategies for strong or moderate CYP3A4 inhibitors and for strong and moderate CYP3A4 inducers (i.e., Avoid

		concomitant use). Additional examples of strong or moderate CYP3A inhibitors and inducers were added to this subsection.
7. Drug Interactions	7.2 Effect of Nerlynx on Other Drugs <u>P-glycoprotein (P-gp) Substrates</u> …	FDA revised this section to add "Increased concentrations of digoxin may lead to increased risk of adverse reactions including cardiac toxicity." FDA added a cross reference to the digoxin prescribing information for dosage adjustment recommendations due to drug interactions.
8. Use in Specific Populations	8.1 Pregnancy …	FDA revised this section to state that Nerlynx can cause fetal harm based on findings from animal studies and the mechanism of action. The animal data is this section was revised to reflect the FDA Nonclinical Reviewer's findings. *See Section 5 Nonclinical Pharmacology/ Toxicology for more information.*
8. Use in Specific Populations	8.2 Lactation …	FDA revised the proposed information related to excretion in human milk and milk production to clarify the lack of existing data. FDA also added the following statement: "Because of the potential for serious adverse reactions in breastfed (b) (4) nfants from NERLYNX, advise a lactating women not to breastfeed while taking NERLYNX and for at least 1 month after the last dose."

8. Use in Specific Populations	8.3 Females and Males of Reproductive Potential …	FDA added the following heading and information: Pregnancy Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with NERLYNX.
8. Use in Specific Populations	8.6 Hepatic Impairment	FDA revised this section to clarify that no dose modifications are required for mild to moderate (Child Pugh A or B) hepatic impairment. FDA added the required dose reductions for severe hepatic impairment (Child Pugh C).
10. Overdosage	…	FDA revised this section to remove detailed information (b) (4)
11. Description	…	FDA added additional inactive ingredients found in the tablet coating for Nerlynx.
12. Clinical Pharmacology	12.1 Mechanism of Action …	FDA revised the proposed mechanism of action to remove subjective terminology and promotional language with unclear meaning.
12. Clinical Pharmacology	12.2 Pharmacodynamics (Not applicable)	FDA added this subsection to the labeling, moved the information related to cardiac electrophysiology, and revised this information to remove data not required for the safe use of Nerlynx.

12. Clinical Pharmacology	12.3 (b) (4) …	FDA removed the proposed labeling that concluded (b) (4) and replaced with the following statement: "Neratinib exhibits non-linear PK profile with less than dose proportional increase of AUC with the increasing daily dose over the range of 40 to 400 mg."
	<u>Absorption</u> …	FDA revised the absorption subsection and food effects study information to be consistent with the FDA Clinical Pharmacology review. FDA added the composition of the high fat food and standard breakfast used in the food effects studies. *See 6.3 Comprehensive Clinical Pharmacology Review for more information*.
	<u>Distribution</u> …	FDA revised (b) (4) to "In patients, following multiple doses of NERLYNX, the mean (%CV) apparent volume of distribution at steady-state (Vss/F) was 6433 (19%) L.
	<u>Elimination</u> …	FDA revised the proposed labeling to provide the half-life information for multiple doses and for the neratinib active metabolites. FDA added the clearance information from Nerlynx after the first dose and to provide

		the clearance at steady state.
	Specific Populations …	FDA revised this section to concisely summarize PK concerns for specific populations by adding the following statement: "Age, gender, race, and renal function do not have a clinically significant effect on neratinib pharmacokinetics." FDA revised the Patients with Hepatic Impairment subsection to provide results from the chronic hepatic impairment study and to provide the Cmax and AUC increases observed.
	Drug Interactions Studies …	The Drug Interactions subsection was revised to remove (b) (4) language [i.e., (b) (4) and to provide the changes in Cmax and AUC observed in the drug interactions studies.
13. Nonclinical Toxicology	13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility …	FDA revised this section to be consistent with the FDA Nonclinical Reviewer's findings and added clinically relevant information related to the fertility studies performed in rats and toxicity studies performed in dogs. FDA also removed the additional information (b) (4) since it was redundant to information already included (b) (4)

14. Clinical Studies	14.1 Extended Adjuvant Treatment in Breast Cancer …	FDA added the following to the description of clinical trial characteristics and enrollment: • Stratification factors used in the ExteNET clinical trial • The definition of the major efficacy outcome (iDFS) used in the ExteNET trial • "The majority of patients (81%) were enrolled within one year of completion of trastuzumab treatment." FDA removed redundant text descriptions of results (b) (4) [redacted] FDA removed (b) (4) [redacted] FDA added Table 9: Subgroup Analyses to provide descriptive information on the most clinically relevant subpopulations in the ExteNET clinical trial. FDA removed the (b) (4) proposed by the Applicant. FDA removed (b) (4) [redacted] exploratory 5-year iDFS (b) (4) and provided a general descriptive statement describing the consistency of these results. (b) (4) [redacted]

		(b) (4) [redacted]
16. How Supplied/Storage and Handling	(b) (4) [redacted].	FDA added the required information for Section 16 (i.e., information on dosage forms, identifying characteristics, special handling, and storage conditions). *[see 21CFR201.57(c)(17)]*
17. Patient Counseling Information	…	FDA revised this section to add information for antidiarrheal prophylaxis, hepatotoxicity, embryo-fetal toxicity, and gastric acid reducing agent drug interactions. FDA also revised to add counseling topic headings, cross references, and to remove (b) (4) [redacted] to be consistent with FDA labeling guidance.

10.2. Patient Labeling

At the time of this labeling review (June 22, 2017), the Patient Information is under
{See appended electronic signature page}

William PierceAssociate Director for Labeling DOP1

11 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

No REMS is recommended.

12 Postmarketing Requirements and Commitments

The following Postmarketing Requirements (PMRs) were recommended to the Applicant:

PMR #1 Description:	**Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to address the potential for excessive drug toxicity. If the PBPK modeling/simulation is not feasible, then a clinical pharmacokinetic trial will be conducted. Submit Final Report, datasets, and labeling.**	
PMR Schedule Milestones:		
	Final Report Submission:	10/2017
Comment(s): Alternatively, if it is not feasible to conduct the PBPK the timeline will change. A clinical study of moderate CYP 450 3A4 inhibitors and inducers will take approximately 5 months from 08/11/2017 to 01/11/2018.		
PMR #2 Description:	**To assess carcinogenic potential conduct a 2-year carcinogenicity study in the rat. Refer to the ICH S1A Guidance for Industry on The Need for Long Term Rodent Carcinogenicity Studies of Pharmaceuticals, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065007.htm.**	
PMR Schedule Milestones:		
	Final Protocol Submission:	Submitted/Ongoing
	Study Completion:	02/2017
	Final Report Submission:	8/2017

The following postmarketing commitments (PMCs) were recommended to the Applicant:

PMC #1 Description:	**Conduct a physiologically-based pharmacokinetic modeling/simulation study or a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Submit Final Report with datasets.**	
PMC Schedule Milestones:		
	Final Report Submission:	10/2017
PMC #2 Description:	**Conduct a clinical pharmacokinetic trial to evaluate whether separating the dosing of H2-receptor antagonists and neratinib can minimize the drug-drug interaction potential. Submit Final Report with Datasets.**	
PMC Schedule Milestones:		
	Final Report Submission:	12/2017
PMC #3 Description:	**Submit the overall survival (OS) data and results from Trial 3144A2-3004-WW, ExteNET, "A Randomized, Double-Blind, Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women with Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer"**	
PMC Schedule Milestones:		
	Study Completion:	07/2019
	Final Report Submission:	01/2020
Comment(s): The analysis is predicated on reaching (b) (4) and the dates are therefore only estimates.		

13 Appendices

13.1. References

As annotated throughout the review.

13.2. Financial Disclosure

In accordance with 21 CFR 52.3, the Applicant submitted a list of Study 3004 investigators attached to FDA form 3454 certifying that the principal investigators and sub-investigators had complied with disclosure are defined by 21 CFR 54.2. Financial disclosure information was collected for 3364/3395 (99/1%) of principal investigators and sub-investigators on Study 3004. Disclosable financial interests were recorded by 7 out of 3395 (0.21%) of principal investigators.

Table 43: List of Investigators and Sub-investigators with Information to Disclose

Principal (P) or Sub (S)	Investigator Name (Last, First)	Financial Interest or Arrangements
P	(b) (6)	On February 27,, 2015, Dr (b) (6) disclosed approximately 4,000 shares of a derivative of Pfizer common stock currently valued at $140,000.
S		On November 29, 2006, Dr. (b) (6) disclosed receipt of $250,000 grant from Pfizer to fund ongoing research.
P		On September 8, 2010, Dr. (b) (6) disclosed approximately 2,500 shares of a derivative of Pfizer stock, currently valued at approximately $100,000.
S		On June 24, 2016, 2016, Dr. (b) (6) disclosed an unknown numbers of shares of a derivative of Pfizer stock, at unknown value, but declarable as it was estimated to be valued at over $50,000.
S		On July 11, 2016, Dr. (b) (6) disclosed research funding from Pfizer in the amount of $106,950.
S		On September 14, 2011 Dr. (b) (6) disclosed Pfizer funding of a research grant to study (b) (6) The total grant was approximately $280,000 with $30,000 received by Dr. (b) (6) in 2009.
P		On August 28, 2009, Dr. (b) (6) disclosed that he owned Wyeth common stock in the $50-$100,000 range. No additional information was provided.

Reviewer's comment: ***It is unlikely that the financial bias affected the trial given the relatively few investigators with financial disclosures relative to the overall size of the trial.***

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3395		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 4 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 31		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. OCP Appendices (Technical documents supporting OCP recommendations)

13.3.1. Bioanalysis report /Summary of Bioanalytical Method Validation

Analytical Methods and Validation Reports for neratinib and active metabolites M3, M6, and M7 are summarized in Table 44- Table 47.

Table 44: Analytical Methods Validation Reports of Neratinib and Metabolites

Report Number , Title and Date	Description
RPT-62457: Validation of an LC/MS/MS Method for the Quantification of HKI-272 in Human Plasma (Protocol 05_3275)	GLP validation of neratinib from plasma (K2EDTA) with a structural analog internal standard (WAY-178357) and separation by protein precipitation and HPLC-MS/MS analysis. Stock solutions in acetonitrile: water (1:1 v/v) were stable for 9 hours at RT and up to 70 days at 2 to 8°C. Standard curves were linear from the LLOQ of 3.00 ng/mL to 250 ng/mL (mean r2 = 0.9917). Selectivity was acceptable and there was no significant carryover. The matrix effect was 14.0%. Mean precision (%RSD) and accuracy (%) for n=6 of the LLOQ were 8.8% and 104.0%, respectively. Mean inter-day and intra-day precision and accuracy for low, mid, and high QCs were acceptable. Neratinib was stable in whole blood stored for up to 2 hours at RT or in an ice bath. Plasma samples could be diluted 1:10 with acceptable accuracy and precision. Processed samples were stable after storage for up to 82 h at 2 to 8°C. The maximum batch size was 96 injections. Long term storage was extended to 2 years at -70°C and 13 months at -20°C for the low and high
RPT-68103: Cross-validation of an LC/MS/MS Bioanalytical Method for the Quantification of HKI-272 (WAY-179272) in Human Plasma and Protein-free Plasma (Protocol 05_1835), version 1.0. 23-JUL-2008	A LC-MS/MS method for determining the concentration of neratinib in 0.10 mL EDTA protein-free human plasma was cross-validated to a LC/MS/MS method for the quantitation of neratinib in EDTA human plasma. The method was linear over the range of 0.50 to 10 ng/mL using a sample volume of 0.25 mL protein-free human plasma.
RPT-72542: Validation of a LC/MS/MS Method for the Quantification of HKI-272, WYE-12159 (M3), WYE-121592 (M7), and WAY-193575 (M6) in Human K3EDTA Plasma (Protocol 08_0273), original report, 16-JAN-	A selective, accurate, and reproducible analytical method using LC-MS/MS for the quantitation of neratinib, metabolites WYE-121529 (M3), WYE-121592 (M7), and WAY-193575 (M6) in human plasma was validated (GLP). The assay was linear for neratinib, M3, and M7 from 3.00 to 250 ng/mL and for M6 from 1.50 to 125 ng/mL using 100 µL plasma. Standard curves were linear from the LLOQs of 1.50 ng/mL (M6) and 3.00 ng/mL (neratinib, M6, and M7) to 125 and 250 ng/mL, respectively (with r2 > 0.9930 for all analytes). Stock solutions of neratinib, M3, M6, and M7 were stable at nominal -70°C for 126 days.

2009; Addendum 1, 26-JAN-2009; Addendum 2, 27-FEB-2012; Addendum 3, 30-AUG-2012	Mean precision (%CV) and accuracy (%bias) at the LLOQ for 6 replicates in 3 different runs, ranged from 5.5% (M3) to 8.7% (neratinib), and from -7.7% (M7) to 7.0% (M3), respectively. Selectivity was acceptable. There was no carryover. Neratinib and metabolites were stable in whole blood for up to 2 hours at RT or in an ice bath, and there was no effect of hemolysis on the accuracy or precision. Processed samples including metabolites were stable after storage for up to 74 h at 2 to 8°C and reinjection reproducibility at all QC concentrations was acceptable for 74 h after storage at 2 to 8°C. Plasma samples were stable for 24 h on wet ice, and through 5 F/T cycles. Neratinib, M3, M6, and M7 were stable for 360, 70, 166, and 360 days, respectively, when stored at -70°C. The maximum batch size was 96 injections.
RPT-78414: The Determination of HKI-272 and Metabolites (Covance Study No. 8200244), version 1.0. 24-SEP-2009. Addendum 1 to Final Report: Bioanalytical Method Validation Report: Partial Validation of a Method for the Determination of HKI-272 in Human Plasma Ultracentrifugate by HPLC With MS/MS Detection. 27-FEB-2012.	No metabolites of neratinib were included in this partial validation (GLP) of neratinib in plasma ultracentrifugate by Covance. Six analytical batches were completed and accepted. Standard curves were linear from (LLOQ) 0.30 ng/mL to 30.0 ng/mL (mean r2 = 0.9996). Acceptable selectivity (i.e., <20% of the peak area response at the LLOQ) was demonstrated with 6 individual lots of matrix. The matrix effect for neratinib and the internal standard (calculated with post extraction samples fortified with analyte and neat solutions) was determined in 3 separate assays, and the mean %effect ranged from 21.0 to 27.9% for neratinib and from 23.3 to 25.9% for the deuterated analog. The magnitude of potential carryover was not calculated; but was judged to be acceptable based on chromatographic results. Mean precision and accuracy at the LLOQ (n=3) ranged from 7.1 to 13.1% and from 91.0 to 105.3% (intra-day) and from 11.6 to 96.0%, respectively (inter-day, n=18). Mean inter-day precision and accuracy (n=18) for QCs ranged from 3.4 to 8.5% and from 94.0 to 104.9%, respectively. Mean intra-day precision and accuracy ranged from 2.3 to 10.2% and from 88.0 to 108.4%, respectively. Samples were stable for 5 F/T cycles, and for 12 h on wet ice. Matrix stability was demonstrated for 4 h at 15 to 25°C, and processed sample stability and reinjection reproducibility were acceptable after 104 h at 2 to 8°C. Samples were stable for up to 196 days frozen at -60 to -80°C. The maximum batch size was 96 injections.
RPT-PF-05208767: Semi-Quantitation of a Neratinib Metabolite M11 in Human Plasma: a Preliminary Evaluation. 02-AUG-2011.	Concentrations of M11 in 0.1 mL plasma were determined by a non-GLP, HPLC-MS/MS assay using a provisional standard of authentic M11 and deuterated neratinib as the internal standard. Standards and QCs were prepared, but the concentrations were not reported. The LLOQ was 0.5 ng/mL using an acceptance criterion of ± 20%; however, no range, QC or standard performance, stability, or other analytical data were reported. The M11 standard was isolated by RP-HPLC from synthetic M7 and was characterized structurally by MA and 1 and 2-D 1H and 13C-NMR. Purity was determined by HPLC-UV and the concentration of M11 was determined by quantitative NMR.

Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods, Table 13, page30-37

Table 45. Mean Key Validation Parameters for the Quantitation of Neratinib in Human Plasma

	RPT-62457	RPT-72542
Range (ng/mL)	3.00 – 250	3.00 - 250
r^2	0.9920 (n=5)	0.9983 (n=3)
Batch size	96	96
Dilution QC	1:10 of 1250 ng/mL 6.7% CV and 102.4% accuracy	1:10 of 1250 ng/mL 5.2% CV and 2.4% bias
Stability		
Whole Blood	2 h RT or on ice	2 h RT or on ice
Plasma: benchtop (ambient)	ND	ND
Plasma: wet ice	ND	24 h
Plasma: long-term	ND	13 months -20°C (RPT-61797) 2 years -70°C (RPT-61798)
Plasma: freeze/thaw	ND	5 cycles
Stock solution	9 h RT and 70 days 2-8°C	6 h RT and 81 days -60 to -80°C
Injector	ND	ND
Reinjection	ND	74 h 2-8°C
Processed sample	ND	74 h 2-8°C
Interference from M3, M6, M7	ND	no interference
Hemolyzed plasma	ND	no interference
Lipemic plasma	ND	ND

Abbreviations: CV = coefficient of variation; ND = not done; QC = quality control sample; RT = room temperature
Source: Summarized from RPT-62457, RPT-61797, RPT-61798, and RPT-72542

Table 46. Mean Accuracy and Precision Validation Results for the Quantitation of Neratinib in Human Plasma

	LLOQ		QC low		QC mid		QC high	
Report (RPT-)	**62457**	**72542**	**62457**	**72542**	**62457**	**72542**	**62457**	**72547**
Concentration	**3.00 ng/mL**		**9.00 ng/mL**		**120 ng/mL**		**200 ng/mL**	
Precision, %CV								
Intra-day (n=6)	8.8	4.8-6.7	4.2-9.3	4.1-6.3	4.5-8.8	4.3-5.0	2.8-10.0	2.2-4.3
Inter-day (n=18)	NR	8.7	7.8	5.1	6.7	4.9	6.9	3.7
Accuracy, % accuracy or % bias								
Intra-day (n=6)	104.0	-2.0-14.3	98.6-106.6	3.0-6.1	98.3-100.0	0.0-5.0	96.0-102.0	1.5-4.0
Inter-day (n=18)	NR	5.3	103.2	4.7	99.2	1.7	98.5	2.5

Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods, Table 28, page 64

Table 47. Precision and Accuracy of the Quantitation of Neratinib and Metabolites M3, M6, and M7 in Human Plasma

	Neratinib	M3	M6	M7
Precision (%CV)				
intra-day	1.9 to 6.3	3.2 to 6.8	2.2 to 9.9	1.4 to 6.5
inter-day (n=18)	3.7 to 5.1	4.8 to 5.4	4.4 to 6.7	4.5 to 6.8
Accuracy (% bias)				
intra-day	-0.6 to 5.0	-6.7 to 3.0	-3.8 to 6.0	-9.7 to 1.7
inter-day (n=18)	1.7 to 4.7	-3.3 to -1.0	-0.3 to 3.3	-5.8 to -3.0

** Abbreviations: M3=WYE-121529; M6=WAY-193575; M7=WYE-121592*
Source: RPT-72542, Table 7.29, Table 7.30, Table 7.31, and Table 7.32

13.3.2. Clinical PK/PD Assessments

13.3.2.1. In vitro ADME profiles:

Plasma protein binding:
In vitro, neratinib was highly bound (~ 99 %) to human plasma proteins at clinical exposures. The ex vivo protein binding of neratinib in human plasma samples from clinical study in healthy subjects as determined using ultracentrifugation was ~88% (free fraction of ~12%).

Blood to plasma ratio: Not determined.

Transport and inhibition of P-glycoprotein:

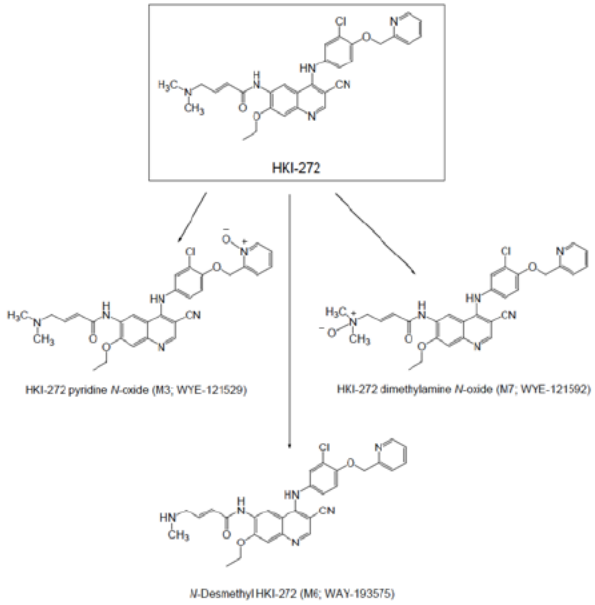
- P-gp substrate and inhibitor of P-gp with IC_{50} of 1 µM for the P-gp mediated transport of digoxin
- In vitro hepatic uptake in human hepatocyte suspensions indicated by passive diffusion.

CYP phenotyping using human liver microsomes (HLM):
Four metabolites were produced by HLM: O-desmethylpyridine HKI-272 (M2), hydroxy HKI-272 (M3), N-desmethyl HKI-272 (M6), and HKI-272 N-oxide (M7). CYP3A4 is responsible for the HLM metabolism of neratinib to M3 and M6 and to a small degree M7. M7 is mainly formed by Flavin-dependent monooxygenases (FMO).

Metabolite profiles in human PK study in healthy subjects:

After a single 240 mg or 800 mg dose of neratinib (HKI-272), intact parent was the most predominant species in plasma. Three metabolites were also present; the pyridine N-oxide of neratinib (M3, WYE-121529), the N-desmethyl HKI-272 (M6, WAY-193575), and the dimethylamino N-oxide of HKI-272 (M7, WYE-121592). The structures of these metabolites are shown in Figure 15 below:

Figure 15. Neratinib Metabolites in the Plasma of Healthy Subjects Given a Single 240 or 800 mg Oral Dose of Neratinib



Source: Applicant's Summary of Clinical Pharmacology, Figure 1, page 39

In vitro CYP interactions:

- Neratinib was not a mechanism-based inhibitor of CYP2C9, 2C19, 2D6, or 3A4 at concentrations up to 100 µM.
- Not an inducer for CYP1A2, 2B6, 2C9 or 3A4 at concentrations up to 1 µM, which is >10-fold of the total C_{max} at steady state following the therapeutic dosing regimen.

13.3.2.2. PK in healthy subjects:

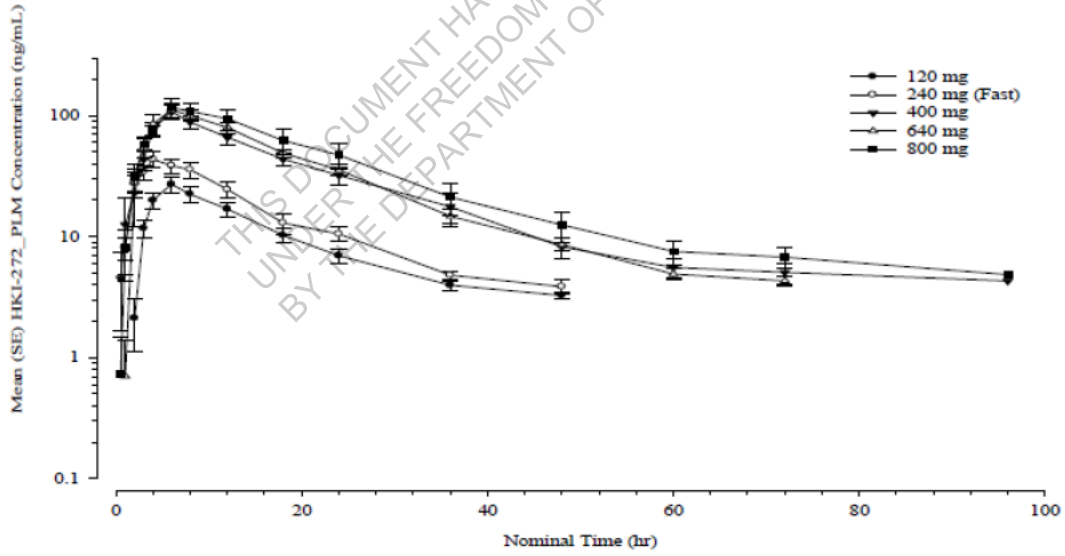
Single oral doses (capsules) of HKI-272 ranging from 120 to 800 mg (120, 240, 400, 640, and 800 mg) were evaluated in healthy subjects after an overnight fast of at least 10 hours. The PK parameters and concentration time profiles are summarized in Table 48 and Figure 16 below

Table 48. Single Dose PK Parameters of HKI-272 in Healthy Subjects

Mean ± SD (CV%) [Geometric Mean]	Treatment				
	120 mg (n=6)	240 mg (Fast) (n=6)	400 mg (n=6)	640 mg (n=6)	800 mg (n=6)
C_{max} (ng/mL)	27.28 ± 9.30 (34) [25.88]	44.62 ± 14.99 (34) [41.81]	110 ± 32.58 (30) [106]	115 ± 37.97 (33) [110]	121 ± 47.08 (39) [113]
t_{max} (hr)	6.00 (4.00 , 6.20)	4.00 (3.00 , 8.00)	6.01 (4.00 , 6.27)	6.00 (3.00 , 8.00)	7.00 (3.00 , 12.00)
$t_{1/2}$ (hr)	11.19 ± 3.08 (28) [10.84]	9.75 ± 2.97 (31) [9.34]	17.39 ± 6.95 (40) [16.28]	13.67 ± 2.20 (16) [13.52]	15.03 ± 4.64 (31) [14.55]
AUC_T (ng*hr/mL)	389 ± 135 (35) [371]	585 ± 275 (47) [515]	1919 ± 702 (37) [1811]	2053 ± 435 (21) [2014]	2516 ± 1296 (52) [2262]
AUC (ng*hr/mL)	453 ± 137 (30) [436]	667 ± 268 (40) [605]	2018 ± 740 (37) [1904]	2141 ± 438 (20) [2102]	2624 ± 1330 (51) [2368]
t_{lag} (hr)	1.50 (1.00 , 2.00)	0.50 (0.50 , 0.50)	1.00 (0.00 , 2.00)	1.00 (0.50 , 2.00)	0.50 (0.00 , 1.00)
CL/F (L/hr)	286 ± 84.09 (29) [275]	456 ± 310 (68) [397]	223 ± 83.56 (38) [210]	310 ± 65.21 (21) [304]	374 ± 190 (51) [338]
CL/F (L/hr/kg)	4.09 ± 1.63 (40) [3.85]	6.27 ± 4.63 (74) [5.36]	2.79 ± 1.00 (36) [2.63]	3.74 ± 0.65 (18) [3.69]	4.74 ± 1.77 (37) [4.46]
V_z/F (L)	4553 ± 1678 (37) [4301]	5681 ± 2301 (41) [5345]	5122 ± 1470 (29) [4933]	6147 ± 1838 (30) [5940]	7424 ± 2751 (37) [7089]
V_z/F (L/kg)	64.61 ± 26.98 (42) [60.11]	78.56 ± 36.39 (46) [72.27]	63.12 ± 14.36 (23) [61.80]	74.30 ± 21.48 (29) [71.97]	95.49 ± 21.44 (22) [93.67]

Source: Applicant's CSR 3144A1-107-US, Table 7-1, page 47

Figure 16. Plasma Concentration - Time Profile of HKI-272 Following Single Oral Doses in Healthy Subjects



Source: Applicant's CSR 3144A1-107-US, Figure 7-1, page 38

13.3.2.3. Mass balance and contribution of the major metabolites in healthy subjects:

Mass Balance Study

A phase 1, open-label, single dose was conducted in healthy subjects (n=6) to characterize the mass balance, metabolic disposition, and to identify the metabolites and general metabolic pathways after administration of a single oral dose of [^{14}C]-neratinib. Subjects received neratinib 200 mg containing 0.099 µCi ^{14}C- neratinib. Total radioactivity in blood, plasma, urine, and feces was determined by Accelerated Mass Spectrometry (AMS) technology using a National Electrostatics Corporation (NEC) 1.5SDH Compact AMS System.

The mean recovery of radioactivity was 98.2% of the total dose. Fecal excretion accounted for approximately 97.1% and urine accounted for 1.13% of the total dose. The unchanged parent drug percentages in the fecal excretion or urine were unknown due to the low sensitivity of the assay. The excretion of total radioactivity is summarized in Table 49.

Table 49. Mean Recovery of Radioactivity in Healthy Subjects

Excreta	% of Dose (0-216 h)	SD (0-216 h)	CV (0-216 h)
Urine (Range)	1.13 (0.91 – 1.47)	0.262	23
Feces (Range)	97.1 (87.3 – 106.5)	8.52	9
Total (Range)	98.2 (88.7 – 107.4)	8.34	8

Abbreviations: CV=coefficient of variation expressed as a percent; h=hour; SD=standard deviation.
Note: N=6.

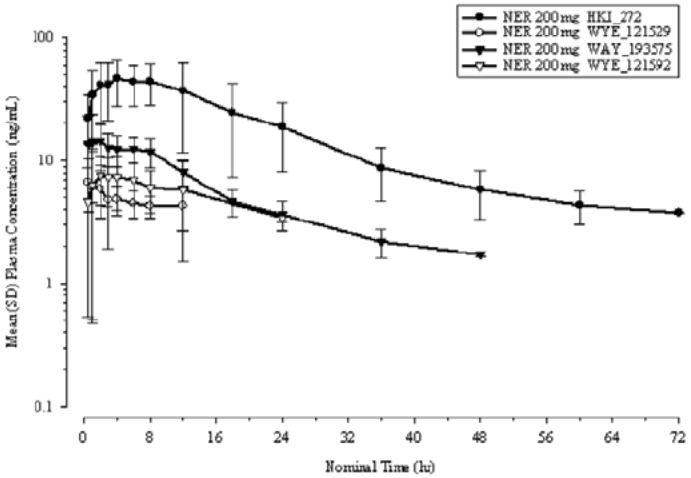
Source: Summary of Clinical Pharmacology, Table 37, page 83.

Active Metabolites in Healthy Subjects after single dose

In the mass balance study 1108, plasma concentrations of neratinib and metabolites M3, M6, and M7 were measured by a validated HPLC-MS/MS assay with LLOQs of 3 ng/mL for neratinib, M3, and M7, and 1.5 ng/mL for M6. The concentration-time profiles are shown in Figure 17 and PK parameters are summarized in Table 50.

The mean AUC_T ratio of metabolites to parent drug was 3.8% for M3, 26% for M6, and 7.5% for M7. The mean C_{max} ratio of metabolites to parent drug was 0.15 for M3, 0.36 for M6, and 0.17 for M7 (Table 51)

Figure 17. Plasma Concentration-Time Profiles of Neratinib, M3 (WYE-121529), M6 (WAY-193575), and M7 (WYE-121592) After in Healthy Subjects



Source: CSR 3144A1-1108-US, Figure 8-1, page 26

Table 50. Single Dose PK Parameters of Neratinib and Metabolites M3 (WYE-121529), M6 (WAY-193575) and M7 (WYE-121592) in Healthy Subjects

Mean ± SD	Analyte Comparison			
	Neratinib 200 mg			
Analyte	Neratinib	WYE-121529	WAY-193575	WYE-121592
N	6	6	6	6
C_{max} (ng/mL)	53.7 ± 24.9	8.26 ± 5.73	17.7 ± 7.93	8.58 ± 4.12
t_{max}[a] (h)	7.00 (2.00 - 12.00)	1.00 (0.50 - 4.03)	2.00 (0.50 - 6.00)	2.00 (0.50 - 4.03)
$t_{½}$	16.15 ± 5.57	13.30 ± 6.49b	13.37 ± 2.44	10.70 ± 4.01
AUCT (ng•h/mL)	1100 ± 563	40.9 ± 28.9	251 ± 61.7	92.9 ± 77.6
AUC (ng•h/mL)	1190 ± 573	141 ± 74.7[b]	285 ± 63.6	147 ± 92.0
% Extrapolated (%)	8.7 ± 5.1	56 ± 16b	13 ± 3.5	45 ± 21

Notes: a. Median (Min - Max). b. n=4, Subject 5, 6 not included in calculation of summary statistics. AUC=total area under the concentration-time curve; AUCT= area under the concentration-time curve to the last measurable concentration at time T (CT);

Source: CSR 3144A1-1108-US, Table 8-1, page 27

Table 51. Mean Plasma Exposure Ratios of Metabolites M3 (WYE-121529), M6 (WAY-193575), and M7 (WYE-121592), to the Parent (Neratinib) After Single Oral Dose in Healthy Subjects

	Analyte Comparison (Metabolite/Parent)					
	Plasma Neratinib					
	WYE-121529 vs Neratinib		WAY-193575 vs Neratinib		WYE-121592 vs Neratinib	
	Neratinib 200 mg		Neratinib 200 mg		Neratinib 200 mg	
Subject	C_{max} (ng/mL)	AUC_T (ng•h/mL)	C_{max} (ng/mL)	AUC_T (ng•h/mL)	C_{max} (ng/mL)	AUC_T (ng•h/mL)
N	6	6	6	6	6	6
Mean	0.152	0.0377	0.363	0.262	0.166	0.0746
SD	0.0617	0.0285	0.161	0.0997	0.0519	0.0373
Min	0.0877	0.00968	0.196	0.167	0.124	0.0185
Median	0.134	0.0317	0.322	0.238	0.151	0.0727
Max	0.238	0.0891	0.628	0.428	0.262	0.120
CV%	41	76	44	38	31	50
Geometric Mean	0.142	0.0296	0.336	0.248	0.160	0.0641

Notes: AUCT=area under the concentration-time curve to the last measurable concentration at time T (CT); Cmax=peak concentration; CV%=coefficient of variation; h=hour; Max=maximum; Min=minimum; SD=standard deviation.

Source: CSR 3144A1-1108-US, Table 8-2, page 28

Contributions of Neratinib and Active Metabolites to Pharmacological Activity at steady state:

In a phase 1 study conducted in healthy subjects (Study 1116), 240 mg oral doses of neratinib were administered as capsules with a standard meal for 14 days (n=25). The mean relative exposure (AUC) to parent at steady-state (Day 7) was 15%, 33%, 22%, and 4% for M3, M6, M7, and M11, respectively. Steady state exposure at day 7 (mean AUCss) and potency data (inhibition of phosphorylation by ERBB2) for parent and active metabolites were used to calculate the contributions to total plasma pharmacological activity provided by neratinib and each metabolite according to the following formula:

$$AUC_{activity\ combined} = AUC_{neratinib} + \sum \left[AUC_{metabolite} \times \frac{IC_{50neratinib}}{IC_{50metabolite}} \right]$$

Contribution % =AUCactivity / AUC activity combined *100

This calculation and comparison also assumes that the fraction unbound for all parent and active metabolites are the same, since it is generally accepted that only free drug combines with receptors. As summarized in Table 52, neratinib provides the majority of pharmacological activity (73%), with 20% provided by exposure to M6, 6% provided by M3, and negligible contribution (<1%) from M7 and M11 AUC.

Table 52. Contributions by Neratinib and Metabolites to Pharmacological Activity after Multiple 240-mg Oral Doses of Neratinib

Compound	IC_{50} nM	AUC_{SS} ng•h/mL	AUC_{SS} µM•h	$AUC_{activity}$ µM•h	Contribution %
neratinib	17#	1060	1.90	1.90	73.2
M3	32#	162	0.283	0.150	5.8
M6	21	350	0.645	0.522	20.1
M7	330#	233	0.407	0.021	0.8
M11	560#	66*	0.112	0.003	0.1

Source: Summary of clinical pharmacology, table 50, page 106.
Notes: AUC values for neratinib and M3, M6, M7 were taken from Day 7 PK in Study 1116.
*AUC value for M11 was estimated from single dose data (33 ng•h/mL) and assuming 50% accumulation with multiple dosing.
IC50 values taken from RPT-100023348 and RPT-54307 (M6 phosphorylation).

13.3.2.4. PK in patients:

Initial Dose escalation study (Study 102) in cancer patients

Study 102 was conducted with neratinib being supplied as 10 mg and 40 mg capsules. Neratinib was taken orally once daily in the morning with food. Subjects initially received a single dose of the test article, followed by a 1-week observation period, during which PK samples were collected and AEs were monitored. One week after the single dose, the same dose level of neratinib was administered orally once daily in the morning with food.

Diarrhea was the primary DLT in this study. The MTD was determined to be 320 mg as four subjects at the 400-mg dose level had grade 3 diarrhea. The 320-mg dose level was expanded to include an additional 39 subjects to confirm the safety and tolerability. The concentration time profiles are shown in Figure 18 and the PK parameters are summarized in Table 53.

Table 53. PK Parameters of HKI-272 in Patients on Day 1 and Day 21 in Dose Escalation Study

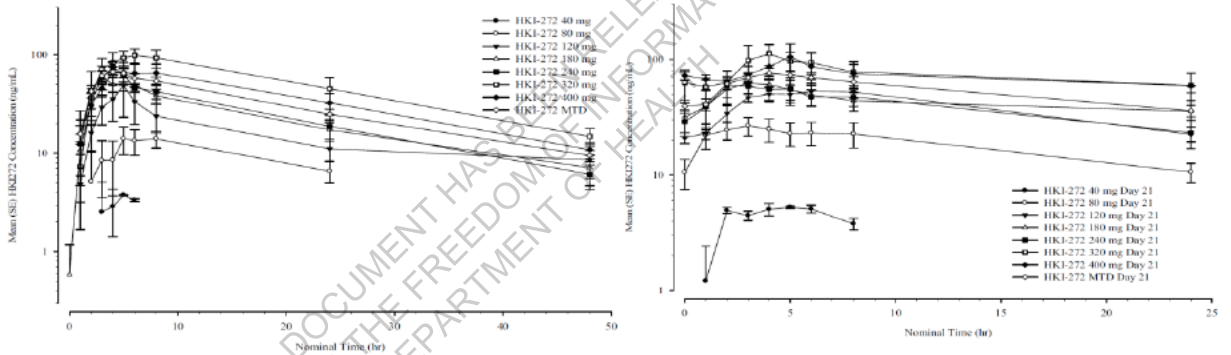
Dose (mg)		Day 1					Day 21				
		C_{max}	T_{max}	$T_{1/2}$	AUC_t	AUC_{inf}	C_{max}	T_{max}	$T_{1/2}$	AUC_t	AUC_{ss}
40	n	3	3	2	3	2	3	3	1	3	1
	GeoMean	4.73	3.91	7.29	9.51	52.27	5.8	4.9	11.7	28.6	76
	CV%	44	25	65	59	37	8	20	NC	26	NC
80	n	4	4	2	4	2	4	4	3	4	4
	GeoMean	16	5	14.5	212	453	32.6	2.38	21.2	416	416
	CV%	42	50	18	46	45	16	95	90	36	36
120	n	4	4	3	4	3	4	4	2	4	4
	GeoMean	34	5	16.2	444	874	48	7.7	12	778	778
	CV%	71	39	15	78	55	44	92	52	30	30
180	n	6	6	6	6	6	6	6	4	6	6

	GeoMean	58.4	3.2	15.5	886	1065	60.6	3.6	12.65	765	834
	CV%	53	31	29	45	44	48	52	41	72	65
240	n	3	3	3	3	3	3	3	3	3	3
	GeoMean	75.2	4.3	13.9	1043	1160	69.6	3.1	16.5	899	899
	CV%	17	13	8	38	39	37	46	33	34	34
320	n	7	7	7	7	7	5	5	5	5	5
	GeoMean	109	4.5	14.8	1972	2270	107	4.1	13.8	1272	1328
	CV%	40	48	18	54	53	51	26	64	64	62
400	n	6	6	6	6	6	2	2	1	2	2
	GeoMean	69.1	4.8	16.5	1452	1723	100	5	21	1687	1687
	CV%	52	40	25	48	42	43	0	NC	20	20
MTD(320)	n	39	39	38	39	38	31	31	25	31	31
	GeoMean	69.7	4	14.4	1074	1334	75.6	4.1	16.3	1123	1123
	CV%	62	43	27	65	66	52	81	38	58	58

*Notes: NC, not calculated; Units: C_{max} (ng/mL) T_{max} (hr) $T_{1/2}$ (hr) AUC (ng*hr/mL)*

Source: Adapted from data of Applicant's CSR 3144A1-102-US.

Figure 18. Plasma Concentration- Time Profiles in Patients on Day 1 and Day 21 in Dose Escalation Study.



Source: Applicant's CSR 3144A1-102-US, Figure 11-1 and 11-2, page 108-109

<u>Dose escalation study (Study 104) in Japanese patients with advanced solid tumors:</u>

Twenty-one subjects were enrolled in a dose escalation study (Study 104) for neratinib given once daily in the morning with food in Japanese subjects with advanced solid tumors (3 subjects in the neratinib 80-mg cohort, 3 subjects were in the 160-mg cohort, 10 subjects in the 240-mg cohort, and 5 subjects in the 320-mg cohort).

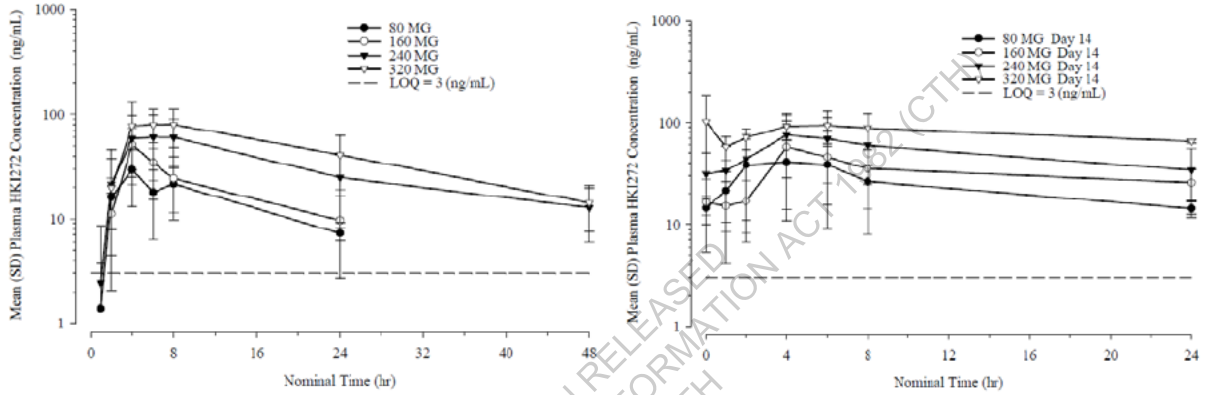
Neratinib had an acceptable safety profile and was generally well tolerated as a continual oral daily dose up to 240 mg. Diarrhea of any grade was the most common TEAE and was reported for 20 subjects (95.2%).

Neratinib 240 mg was determined to be the MTD and the recommended dose for the expanded MTD cohort as there were grade 2 diarrhea, grade 3 diarrhea, and grade 3 anorexia were reported as DLTs for 2 subjects in the neratinib 320-mg cohort and no subjects in the neratinib

80-mg, 160-mg, and 240-mg cohorts had DLTs. The primary DLT, diarrhea, was managed with clinical intervention, that may include antidiarrheal medication, dose reduction, and/or temporary dose interruption.

The PK profiles are indicated in Figure 19 and Table 54. After single or multiple daily oral doses of neratinib, Cmax and AUC increased with increasing dose. There was no major accumulation of neratinib after repeated daily administration (mean accumulation ratios were 1.19 to 1.45 at the doses of 80 to 320 mg). Mean apparent oral clearance ranged from 2.5 to 12 L/h/kg. Mean half-life following a single dose on day 1 ranged from 11 to 16 hours.

Figure 19 . Plasma Concentration- Time Profiles in Japanese Patients on Day 1 and day 14 in Dose Escalation Study.



Source: Applicant's CSR 3144A1-102-US, Figure 11-1, page 108

Table 54. PK Parameters of HKI-272 in Japanese Patients on Day 1 and Day 14 in Dose Escalation Study

Day 1:

	Plasma neratinib (Mean ± Standard Deviation)			
	80 mg N=3	160 mg N=3	240 mg N=10	320 mg N=5
C_{max} (ng/mL)	33.3 ± 14.2	51.4 ± 21.9	76.3 ± 31.3	93.2 ± 37.1
t_{max} [a] (hr)	4.00 (2.00 - 8.00)	3.92 (3.92 - 3.98)	5.88 (1.98 - 8.03)	3.95 (3.93 - 7.90)
$t_{1/2}$ (hr)	NC ± NC [b]	11.11 ± 3.17	14.25 ± 2.68 [c]	15.95 ± 2.03
AUC_T (ng•hr/mL)	301 ± 176	544 ± 388	1330 ± 680	1960 ± 880
AUC_{0-24} (ng•hr/mL)	400 ± 61.9 [d]	462 ± 260	960 ± 441	1350 ± 587
AUC_{∞} (ng•hr/mL)	NC ± NC [b]	638 ± 424	1640 ± 792 [c]	2290 ± 1040

Day 14:

	Plasma neratinib (Mean ± Standard Deviation)			
	80 mg N=3	160 mg N=3	240 mg N=10	320 mg N=3
C_{max} (ng/mL)	41.9 ± 26.0	57.4 ± 45.9	81.5 ± 45.9	143 ± 48.6
t_{max} [a] (hr)	3.98 (2.02 - 6.00)	3.92 (1.97 - 3.95)	3.97 (2.03 - 7.88)	3.92 (0.00 - 5.92)
$t_{1/2}$ (hr)	17.61 ± 8.82	12.65 ± 3.37	22.69 ± 19.94 [b]	22.10 ± 2.72 [c]
AUC_T (ng•hr/mL)	575 ± 259	667 ± 560	1160 ± 645	1840 ± 323
AUC_{∞} (ng•hr/mL)	581 ± 267	688 ± 546	1110 ± 660 [b]	2040 ± 205 [c]

13.3.2.5. Single versus multiple dose PK in patients:

Accumulation index in patients:

Multiple dose escalation study in subjects with cancer indicated no accumulation for Cmax and 14% accumulation for AUC at dose 240 mg at steady state (n=3, day 21). In the expansion cohort of 320 mg at steady state (day 21, n=31), the accumulations were 1.2 and 1.5 for C_{max} and AUC respectively (Table 55).

Table 55. Accumulation Index of HKI-272 PK After Daily Oral Doses in Patients

Mean ± SD (CV%) [Geometric Mean]	Treatment = HKI-272 40 mg	HKI-272 80 mg	HKI-272 120 mg	HKI-272 180 mg
	Day 21 vs. Day 1	Day 21 vs. Day 1	Day 21 vs. Day 1	Day 21 vs. Day 1
C_{max}	1.27 ± 0.38 (30) [1.23]	2.24 ± 1.20 (54) [2.04]	2.45 ± 3.05 (125) [1.40]	1.36 ± 1.11 (82) [1.04]
R	1.98 ± NC (NC) [1.98]	2.09 ± 0.86 (41) [1.97]	2.66 ± 2.20 (83) [2.06]	1.40 ± 0.68 (49) [1.22]
Mean ± SD (CV%) [Geometric Mean]	HKI-272 240 mg	HKI-272 320 mg	HKI-272 400 mg	HKI-272 MTD (320 MG)
	Day 21 vs. Day 1	Day 21 vs. Day 1	Day 21 vs. Day 1	Day 21 vs. Day 1
C_{max}	0.99 ± 0.39 (39) [0.93]	1.18 ± 0.43 (37) [1.11]	1.04 ± 0.16 (15) [1.03]	1.20 ± 0.50 (42) [1.09]
R	1.18 ± 0.42 (36) [1.14]	1.24 ± 0.73 (59) [1.07]	1.17 ± 0.42 (36) [1.13]	1.52 ± 0.71 (47) [1.37]

R = Accumulation Ratio (AUC_{ss} Multiple-Dose/AUC_{tau} Single-Dose).

Source: Applicant's CSR 3144A1-102-US, Supportive Table 15.22, page 481

Time-independent PK

A phase 2, open-label study was conducted to evaluate the 16 week PFS rate for neratinib given as a continual oral 240 mg dose daily in women with ERBB2 positive advanced breast cancer (Study 201). Single 240 mg oral doses of neratinib (3×80 mg capsules) were to be taken once daily in the morning preferably with food. The mean C_{trough} plasma concentrations on Day 1 of months 2 through 6 are summarized in Table 56. C_{trough} measured through cycle 6 did not show any significant changes with protracted treatment.

Table 56. Mean Steady-State Neratinib Trough Plasma Concentrations Following Daily Oral Dose in Patients with Breast Cancer

PK Visit (month)	Neratinib Trough Plasma Concentration (ng/mL)				
	2	3	4	5	6
N	117	103	92	87	81
Mean ± SD	52.6±32.2	58.0±33.7	56.8±30.6	53.3±28.8	59.2±34.1
Min	3.2	3.2	5.1	10.6	8.2
Median	45.7	54.5	55.1	48.6	52.4
Max	217.0	169.0	188.0	137.0	153.0
CV%	61.2	58.2	53.9	54.1	57.5

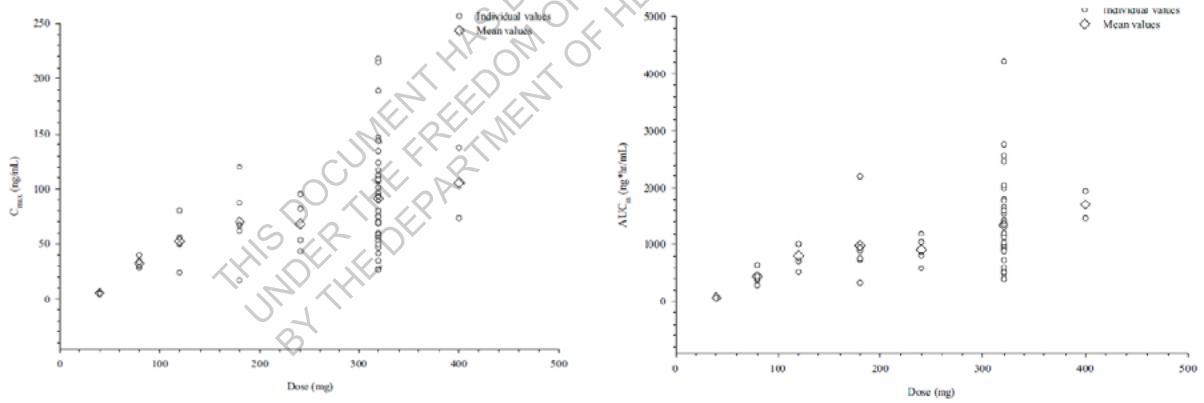
Source: Applicant's Summary of clinical pharmacology, Table 21, page 59

13.3.2.6. Dose proportionality assessment:

Dose escalation in Patients:

In the dose escalation study 102, after multiple oral daily doses, HKI-272 Cmax and AUC_{ss} appear to increase with increasing dose (Figure 20). However, the relation of HKI-272 C_{max} and AUC_{ss} to dose does not appear to be linear.

Figure 20. Dose Proportionality Assessment on Day 21 after Ascending Daily Doses in Patients



Source: Applicant's CSR 3144A1-102-US, Figure 11-1, page 109

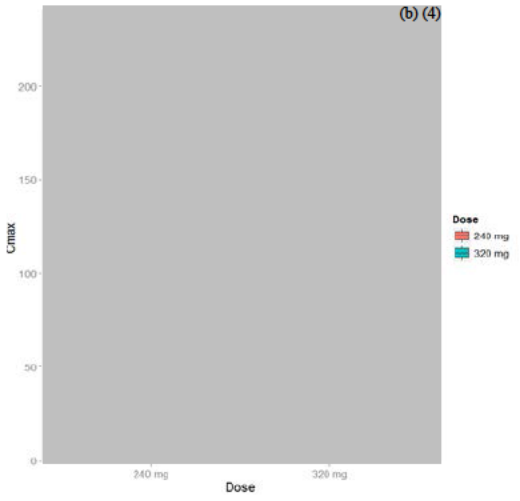
Sparse PK (C_{max} and C_{min}) at steady state after multiple doses in patients:

In another phase 2 clinical trial, neratinib was administered as a single-agent to evaluate the ORR in subjects with advanced NSCLC (Study 200). Predose blood samples were collected prior to the day 1 dose of neratinib in months 1 through 6, and postdose samples were collected at 2, 7, and 21 to 24 hours after oral administration of neratinib on day 1 of month 2.

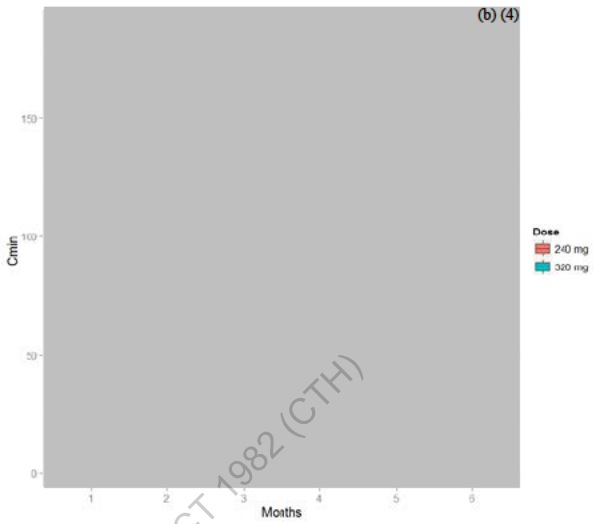
The steady state C_{max} and C_{min} indicated apparently higher values at 320 mg dose group than those values in 240 mg dose group but not in a dose proportional manner (Figure 21).

Figure 21. C_{max} and C_{min} at Steady State after Daily Oral Doses of HKI-272 in Patients

C_{max} at Day 1 Month 2



C_{min} in Month 2-6

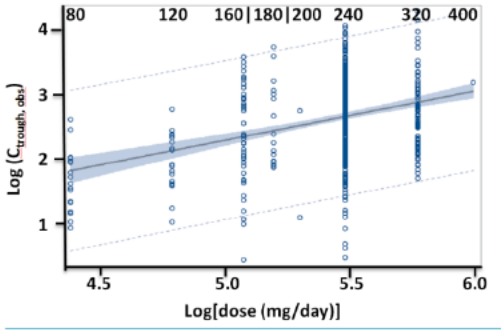


Source: Reviewer's analysis based on raw data from Clinical Pharmacology Information Request for CSR 3144A1-200-WW

Observed C_{min} from pooled PK data sets in PPK analysis:

The observed C_{min} at 24 hours after single dose of neratinib in the pooled PK data sets from healthy subjects and patients used for the PPK analysis indicated less than dose proportional increase when dose increased in the range of 80-400 mg. Power modeling of the log transformed data indicated the slope of 0.765 with 95% confidence interval of 0.58-0.95, which is less than one (Figure 22).

Figure 22. Less Than Dose Proportional Increase of Cmin in Dose of 80-400 mg in Healthy Subjects and Patients.



13.3.3. Population PK and Exposure-Response Analysis

13.3.3.1. Sponsor's Population Pharmacokinetics Analysis

Objectives

Perform population PK modeling of neratinib in healthy subjects and patients with solid tumors from Phase 1/2 clinical studies.

Data, Software, Methods

7713 quantifiable plasma neratinib concentrations from 596 subjects in 11 clinical trials were included in the initial PPK analysis. Demographic information of PPK study population is summarized in Appendix 13.3.3.3.

Study ID	Title
3144-A1-102-US (102)	An Ascending Single and Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Neratinib Administered Orally to Subjects with Her2/neu or Her1/EGFR-Positive Tumors
3144-A1-2206-WW (2206)	A Phase 1/2, Open-label Study of Neratinib in Combination With Capecitabine in Subjects With Solid Tumors and ErbB-2 Positive Metastatic or Locally Advanced Breast Cancer
3144-A2-3003-WW (3003)	A Phase 2, Randomized, Open-Label Study of Neratinib Versus Lapatinib Plus Capecitabine for the Treatment of ErbB-2-Positive Locally Advanced or Metastatic Breast Cancer
3144-A1-104 (104)	An Ascending Single and Multiple Dose Study of the Safety, Tolerability, and Pharmacokinetics of Neratinib Administered Orally to Japanese Subjects with Advanced Solid Tumors
3144-A1-201-WW (201)	Phase 2 Study of Neratinib in Subjects with Advanced Breast Cancer
3144-A1-105-US (105)	A Single Dose, Crossover, Placebo- and Moxifloxacin-Controlled Study of the Effects of Neratinib on Cardiac Repolarization in Healthy Adult Subjects
3144-A1-107-US (107)	Ascending Single Dose Study of The Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Neratinib Administered Orally To Healthy Subjects
3144-A1-1116-US (1116)	A Double-Blind, Sponsor-Unblinded, Randomized, Multiple-Dose, Parallel Group Study to Characterize the Occurrence of Mild to Moderate Diarrhea After Administration of Neratinib Either 240 mg Once Daily or 120 mg Twice Daily for 14 Days Healthy Subjects
3144-A1-1117-US (1117)	A Single Dose Relative Bioavailability Study of a New Tablet Formulation (2 Dose Strengths) and a Reference Capsule of Neratinib in Healthy Adult Subjects
3144-A1-1127-US (1127)	A Single Dose Bioequivalence Study Comparing the Commercial Tablet Formulation to the Clinical Tablet of Neratinib in Healthy Subjects
PUMA-NER-4201 (4201)	A Phase 2 Study of Neratinib and Neratinib Plus Temsirolimus in Patients with Non-Small Cell Lung Cancer Carrying Known Her2 Activating Mutations

All data manipulation and graphical presentation was performed using R software, Version 3.2.1. PopPK analysis was executed using NONMEM 7.3 with Intel(R) Visual Fortran or GNU Fortran. First order conditional estimation with interaction was used exclusively.

Concentration-time data of neratinib was modeled using first-order compartmental models. Linear elimination processes were tested. First order and mixed first order, zero order, with and without absorption lag, were tested to optimally characterize the absorption. Weight effects were included on clearance and volume terms during base model development. Model evaluation and selection was based on model stability, standard model diagnostics and goodness-of-fit criteria (log-likelihood difference, precision of parameter estimates), and pertinent graphical representations of goodness-of-fit.

Covariate analysis was performed using a full model approach to identify sources of variability in PK parameters of neratinib. No hypothesis testing was conducted. Parameter estimation was emphasized. Pre-specified covariate-parameter relationships include age (years), total bilirubin (mg/dL), ALT (U/L), concomitant trastuzumab exposure (yes/no) and concomitant capecitabine exposure (yes/no) on CL/F, and age effect on apparent central volume of distribution (Vc/F). The effect of continuous and categorical covariates was modeled by a power function or an exponential factor relative to the reference category, respectively. The effect of race, renal and hepatic function measures, and category, healthy vs. patient status, cancer type, and concomitant administration of loperamide or other anti-diarrheal drugs were explored graphically. The Final Model was validated using nonparametric bootstrapping (1000 resampled datasets stratified on study) and posterior predictive check where five hundred data sets were simulated and systematically compared to the observed data using quantile-quantile plots of subject-level exposure measures.

After the Final model was developed, Any Grade and Grade 3/4 Diarrhea AE were incorporated to indicate whether the time of each PK record falls within the date range of qualifying diarrhea event. The full covariate model approach was attempted to evaluate the effect of diarrhea on PK as a time-varying covariate.

Results

Plasma neratinib PK was described by a 2-compartment model with first-order absorption, first-order elimination, and absorption lag (**Table 57**). Bootstrap 95% confidence intervals (183 of 500 runs minimizing normally) indicate that estimates for covariate effects of age, bilirubin, ALT, trastuzumab, and capecitabine on central clearance are indistinguishable from null effect. Concomitant trastuzumab could have a clinically relevant effect but is poorly estimated from this data, whereas concomitant capecitabine is well estimated and has an effect that is probably clinically-negligible conditional on this analysis. Ketoconazole is well-estimated and reduces clearance by more than 80%. The age effect on absorption rate constant is well-estimated and meaningfully large (greater than one). Covariate effects are expressed relative to a reference individual with no concomitant medications, bilirubin=10 umol/L, ALT=20 U/L, age=53 y, and weight=70 kg.

Inter-individual random effects were estimated for central clearance, central volume, and absorption rate constant; variance (CV%) were 0.19 (46), 0.595 (90), and 0.717 (102) respectively. Shrinkage for inter-individual random effects on clearance, central volume, and absorption rate constant were about 5.4%, 22%, and 30%, respectively.

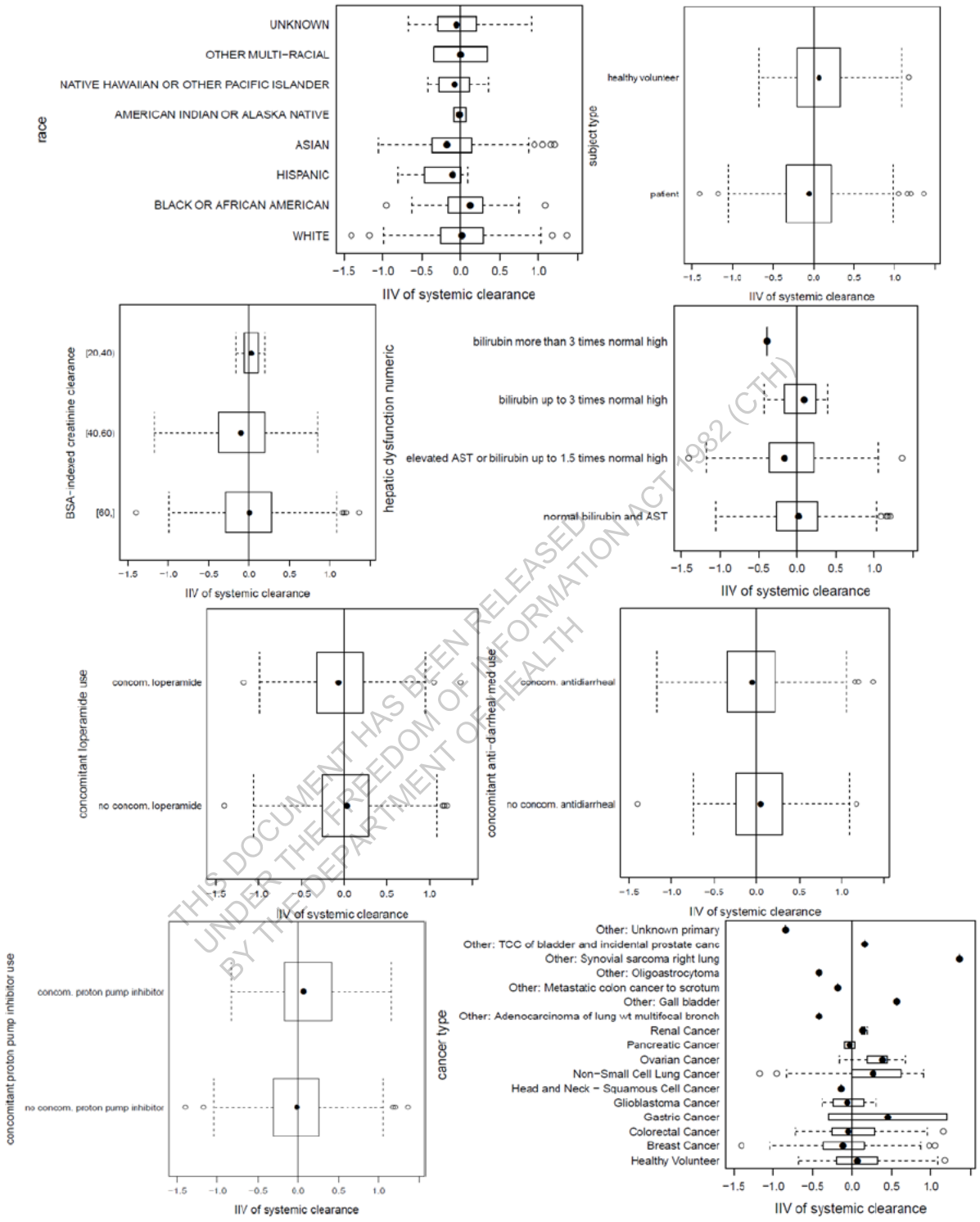
Race, renal and hepatic function category, healthy vs. patient status, cancer type, and concomitant administration of loperamide showed no strong relationship with post-hoc model random effects and are not a likely covariate for PK (**Figure 23**).

Table 57**. Sponsor's Model Parameters**

Parameter	Base Model (Mod. 1340)	Final Model (Mod. 1360)		Diarrhea Model (Mod. 1450)
	Estimate	Estimate (RSE)	Bootstrap CI	Estimate / (RSE)
CL/F	179	195 (2.79)	(185, 205)	190 (2.6)
Vc /F	2620	4430 (7.51)	(3860, 5060)	4130 (5.67)
Ka	0.251	0.391 (11.7)	(0.311, 0.481)	0.394 (6.85)
WT_CL/F	0.322	0.381 (27)	(0.195, 0.591)	0.379 (23.11)
WT_Vc /F	0.255	0.462 (19.9)	(0.113, 0.764)	0.458 (40.61)
Q/F	41.2	52 (9.64)	(45, 62.2)	50.2 (5.44)
Vp /F	1160	1440 (11.3)	(1160, 1960)	1440 (8.13)
Absorption Lag Time	0.74	0.727 (3.04)	(0.677, 0.764)	0.728 (1.41)
AGE_CL/F	.	-0.102 (56.4)	(-0.186, 0.015)	-0.112 (-59.64)
AGE_Ka	.	1.42 (11.8)	(1.04, 1.85)	1.42 (14.08)
AGE_Vc	.	1.67 (8.48)	(1.29, 2.03)	1.64 (8.23)
ALT_CL/F	.	0.0559 (102)	(-0.117, 0.269)	0.0563 (195.38)
BILI_CL/F	.	-0.00805 (483)	(-0.096, 0.074)	-0.00175 (-1971.43)
CAPE_CL/F	.	0.986 (7.07)	(0.838, 1.14)	0.978 (6.21)
KETO_CL/F	.	0.172 (12)	(0.137, 0.23)	0.166 (5)
TRAS_CL/F	.	0.882 (36.1)	(0.507, 1.99)	0.898 (31.07)
DIAR_F	.	.	.	0.943 (0.91)
DIAR_V2/F	.	.	.	1.14 (2.02)
cov_CL * K_a	0.0686	.	.	.
cov_CL * V_c	0.282	.	.	.
cov_V_c * K_a	0.396	.	.	.
IIVCL/F	0.298	0.19 (6.87)	(0.162, 0.213)	0.193 (6.74)
IIVVc /F	1.33	0.595 (12.6)	(0.46, 0.719)	0.64 (8.73)
IIVKa	0.403	0.717 (14.6)	(0.486, 0.917)	0.735 (10.59)
Proportional Error	0.12	0.104 (4.32)	(0.0966, 0.112)	0.103 (1.04)
Additive Error	2.62	2.7 (37.9)	(0.538, 4.46)	2.69 (2.12)
OFV		48962		48904

Source: POPPK report: an update, Table 7 and 8; POPPK report: update II, Table 1

Figure 23. Post-hoc Analysis of Covariate Effect on the Random Effect for CL/F



Source: POPPK report: an update, Figure 19, 23, 27, 28, 31, 34, 37, and 40.

Of the 7713 PK observations that were analyzed, 2996 occurred during an incident of Any Grade diarrhea and 26 out of the 2996 were of Grade 3 or 4. Including effects of Grade 3/4 diarrhea on bioavailability (F) or on Vc/F had no effect on the model, consistent with the very

small number of qualifying observations. Grade 3/4 diarrhea was not further explored. Including effects of Any Grade diarrhea on Vc/F and F led to a well-conditioned, reasonably stable model with well-estimated diarrhea effects (Table 57, Model 1450). PK parameter point estimates were similar to those for the previously-reported model. Representative diagnostic plots were reasonably similar to those previously reported. Random effects were well-centered and symmetrical. The objective function of this nested model decreased substantially, indicating a better fit. The parameter estimate (95% CI) for effect of diarrhea on F is 0.94 (0.93, 0.96), a well-estimated but modest decrease. The parameter estimate (95% CI) for effect of diarrhea on Vc/F is 1.14 (1.09, 1.19), a well-estimated but modest increase.

Reviewer's Comments:

1. *In the analysis dataset, subjects labeled with concomitant loperamide took varying amounts of loperamide throughout the PK sampling period, and the loperamide dose and time were not collected with sufficient detail to support a robust evaluation as a time-varying covariate. The effect of loperamide use on PK is not conclusive as it is confounded by differences in loperamide dose, time of dosing, and the presence of diarrhea events. Similar issue exists for the evaluation of other anti-diarrhea treatments, proton pump inhibitor use, and CYP3A4 inhibitor/inducer use (other than ketoconazole) on neratinib PK.*
2. *Sponsor's analysis dataset contains data from 596 subjects, however, sponsor summarized baseline characteristics of 592 subjects only (Table 59, Table 60). The reviewer repeated sponsor's analysis with the submitted dataset (N=596), and results were similar to those presented in sponsor's PPK report.*
3. *The reviewer conducted independent stepwise covariate modeling using NONMEM 7.3 and Pirana 2.9.0. Consistent with sponsor's analysis, reviewer's analysis suggests that there is no need for dose adjustment based on age, sex, race, trastuzumab, or capecitabine. Ketoconazole reduces neratinib clearance by more than 80% and therefore should be avoided. There is no clinically meaningful difference in PK between patients with mild renal impairment (n=34, BSA-indexed creatinine clearance ≥ 40 and <60 mL/min) and patients with normal renal function (n=556, BSA-indexed creatinine clearance > 60 mL/min), or between patients with mild hepatic impairment (n=125, elevated AST or bilirubin up to 1.5 times normal high) and patients with normal hepatic function (n=465, normal AST and bilirubin). There is limited data on patients with moderate renal impairment (n=3, BSA-indexed creatinine clearance ≤ 20 mL/min), moderate hepatic impairment (n=4, bilirubin up to 3 times normal high), or severe hepatic impairment (n=1, bilirubin more than 3 times normal high).*
4. *Consistent with sponsor's analysis, reviewer's analysis suggests that the event of Any Grade diarrhea does not have a clinically meaningful impact on neratinib exposure (i.e. approximately 10% decrease in bioavailability). Therefore, a clinically meaningful difference in exposure is not expected between the registration study where anti-diarrhea medication was employed as needed and the proposed usage where prophylaxis loperamide is mandated.*

13.3.3.2. Sponsor's E-R Analysis

Objectives

Conduct E-R analysis (logistic regression) on efficacy with data from breast cancer patients on neratinib monotherapy and on safety with data from breast cancer patients on neratinib therapy.

Data, Software, and Methods

Data from Phase 1/2 studies, 3144-A1-102, 3144-A1-104, 3144-A1-201, and 3144-A2-3003, were included in the E-R analysis. SAS software was used to generate K-M plot and to conduct logistic regression analysis.

Results

E-R analysis on efficacy was conducted based on data from 284 breast cancer patients using average daily exposure (simulated $C_{trough,ss}$, AUC_{ss}, and $C_{max,ss}$ adjusted by the average daily dose from the time of first dose to the time of event as the exposure metrics), in studies A1-102, A1-104, A1-201 and A2-3003 who received neratinib monotherapy. 108 (39%) patients had confirmed complete response/partial response (CR/PR, ORR) and 169 (61%) patients did not. The odds ratios (95% CI) of having any ORR for exposure were between 1.001 and 1.025 and p-values were < 0.001 (Table 58, Figure 5). Baseline LDH, baseline tumor burden, and baseline ECOG status were not significant covariates, based on multivariate analysis.

Table 58. Analysis of ORR and Steady State Exposures Adjusted by Average Daily Dose of Neratinib (Neratinib Arm in Studies A1-102, A1-104, A1-201, and A2-3003)

	AUC_{ss} (ng*h/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)
Odds Ratio	1.001 (1.001, 1.001)	1.017 (1.008, 1.026)	1.025 (1.012, 1.038)
P-Value	<.001	<.001	<.001

The odds are defined as the odds of having any ORR for each additional unit of exposure measures; 95%CI and P-value are from Wald test result.

Source: Response to Population Pharmacokinetic Information Request, Table 1-3

E-R relationships between safety endpoints of any Grade diarrhea (≥ Grade 1), ≥ Grade 2 diarrhea, ≥ Grade 3 diarrhea, ≥ Grade 3 fatigue, elevated liver enzyme levels, and ≥Grade 1 rash, and average daily exposure (simulated Ctrough,ss, AUCss, and Cmax,ss adjusted by the average daily dose up to the time of the event of interest), was evaluated for the 345 patients on neratinib therapy in Studies A1-102, A1-104, A1-201, and A2-3003 (Figure 6, Table 61).

Reviewer's Comments:

E-R analysis for efficacy and safety in the target patient population (early stage HER2+ patients) is not available as PK data was not collected in the registration study. Sponsor's E-R analysis, conducted in advanced / metastatic breast patients, showed a positive correlation between the objective response rate and steady sate neratinib exposure and flat relationships between systemic toxicities and steady state exposure. The median starting dose and the median average daily dose in the E-R datasets are 240 mg, similar to what was observed the registration study. According to PPK analysis, mandatory use of anti-diarrhea treatment is expected to minimize Any Grade diarrhea events and increase bioavailability by approximately 10% at most (assuming no DDI between neratinib and the anti-diarrhea drug). Such an increase in neratinib exposure should not be of concern given the flat E-R relationship on systemic toxicity. On the other hand,

E-R analysis for efficacy in advanced / metastatic breast patients suggests a risk of losing activity when neratinib exposure is significantly reduced. For instance, the probability of response decreases from 37% in a typical patient (i.e. body weight=70 kg, age=53 y.o., bilirubin=10 mg/L, and ALT=20.09 IU/L) taking 240 mg neratinib QD to 20% in a patient taking 80 mg neratinib QD (i.e. a 67% reduction in exposure).

13.3.3.3. Appendix

Table 59. Summary of Baseline Demographic Information (Categorical) in the PPK Dataset.

Property	Type	Count	%	Property	Type	Count	%
[*] Renal Impairment	Normal	553	93.4	[#] Hepatic Impairment	Normal	462	78
	Mild	33	5.6		Mild	124	20.9
	Moderate	3	0.5		Moderate	4	0.7
	Missing	3	0.5		Severe	1	0.2
Cancer Type	Healthy Volunteer	200	33.8		Missing	1	0.2
	Breast Cancer	307	51.9	Race	American Indian / Alaska Native	2	0.3
	Colorectal Cancer	21	3.5		Asian	141	23.8
	Gastric Cancer	2	0.3		Black for African American	61	10.3
	Glioblastoma Cancer	4	0.7		Hispanic	4	0.7
	HNSCC	1	0.2		Pacific Islander	5	0.8
	NSCLC	39	6.6		Other Multi-racial	2	0.3
	Ovarian Cancer	6	1		Unknown	13	2.2
	Pancreatic Cancer	2	0.3		White	364	61.5
	Renal Cancer	3	0.5	Sex	Female	369	62.3
	Other	7	1.4		Male	223	37.7

[*] Renal Impairment: defined by BSA-indexed creatinine clearance, as Normal (> 60 mL/min), Mild ([40, 60) mL/min), Moderate (([20, 40) mL/min), and Missing.
[#] Hepatic Impairment: defined as Normal (Bili ≤ ULN & AST ≤ ULN), Mild (Bili ≤ ULN & AST ≥ ULN, or, 1x ULN < Bili < 1.5x ULN), Moderate (1.5x ULN < Bili < 3x ULN), Severe (Bili >3x ULN), and Missing.
Source: POPPK report: an update, Table 4

Table 60. Summary of Baseline Demographic Information (Continuous) in the PPK Dataset.

covariate	N	minimum	1st Quartile	median	3rd Quartile	maximum
age	592	18.000	37.00	47.00	56.00	90.00
alkaline phosphatase	592	28.000	65.00	82.00	126.00	1090.00
body mass index	592	16.000	22.60	25.10	28.50	50.50
body surface area	592	1.300	1.64	1.80	1.98	2.55
BSA-indexed creatinine clearance	589	30.600	81.90	97.60	114.00	213.00
creatinine	589	0.400	0.70	0.80	1.00	1.55
height	592	146.000	159.00	165.00	174.00	198.00
ideal body weight	592	45.500	50.10	57.00	68.40	91.40
lean body weight	592	32.400	43.50	49.10	58.20	84.50
plasma AST	592	7.000	19.00	24.00	33.00	239.00
SGPT_ALT	592	5.000	16.00	22.00	32.00	380.00
total bilirubin	592	0.171	5.56	8.55	10.60	53.00
weight	592	39.000	60.40	70.60	82.30	130.00

Source: POPPK report: an update, Table 5

Table 61. Analysis of Safety Endpoints and Steady State Exposures Adjusted by Average Daily Dose of Neratinib (Neratinib Arm in Studies A1-102, A1-104, A1-201, and A2-3003)

	$C_{trough,ss}$ (ng/mL)		AUC_{ss} (ng*h/mL)		$C_{max,ss}$ (ng/mL)	
	Odds Ratio	**P-Value**	**Odds Ratio**	**P-Value**	**Odds Ratio**	**P-Value**
>Grade 1 Diarrhea	1.018 (1.000, 1.037)	0.055	1.001 (1.000, 1.001)	0.033	1.013 (1.001, 1.025)	0.034
>Grade 2 Diarrhea	1.000 (0.990, 1.010)	0.956	1.000 (1.000, 1.000)	0.537	0.997 (0.990, 1.004)	0.368
>Grade 3 Diarrhea	1.003 (0.992, 1.014)	0.632	1.000 (1.000, 1.000)	0.901	0.998 (0.991, 1.006)	0.655
>Grade 3 Fatigue	1.002 (0.975, 1.029)	0.901	1.000 (0.999, 1.001)	0.969	1.000 (0.982, 1.018)	0.993
Rash	0.996 (0.983, 1.009)	0.521	1.000 (0.999, 1.000)	0.475	0.997 (0.988, 1.006)	0.474
Elevated Liver Enzyme Level	0.998 (0.987, 1.008)	0.646	1.000 (1.000, 1.000)	0.770	0.999 (0.992, 1.006)	0.799

Source: Adapted from Response to Population Pharmacokinetic Information Request, Table 4-21

14 Division Director (DHOT)

{See appended electronic signature page}

John Leighton, PhD

15 Division Director (OCP)

{See appended electronic signature page}

Nam Atiqur Rahman, PhD

16 Division Director (OB)

{See appended electronic signature page}

Rajeshwari Sridhara, PhD

17 Division Director (Clinical)

{See appended electronic signature page}

Julia Beaver, MD

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

{See appended electronic signature page}

Richard Pazdur, MD

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

/s/

PAMELA I BALCAZAR
07/17/2017

XIANHUA W CAO
07/17/2017

QI LIU
07/17/2017

NAM ATIQUR RAHMAN
07/17/2017
I concur.

KIMBERLY R RINGGOLD
07/17/2017

JOHN K LEIGHTON on behalf of TODD R PALMBY
07/17/2017

JOHN K LEIGHTON
07/17/2017

JOYCE H CHENG
07/17/2017

SHENGHUI TANG
07/17/2017

RAJESHWARI SRIDHARA
07/17/2017

WILLIAM F PIERCE
07/17/2017

B HARPREET SINGH

07/17/2017

AMANDA J WALKER
07/17/2017

LALEH AMIRI KORDESTANI
07/17/2017

JULIA A BEAVER
07/17/2017

RICHARD PAZDUR
07/17/2017

Clinical Review – Memo

NDA:	208051
Drug Name:	NERLYNX (neratinib)
Indication:	Extended adjuvant treatment of adult patients with early stage ERBB2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy
Applicant:	Puma Biotechnology
Receipt Date:	July 19, 2016
PDUFA Goal Date:	July 19, 2017
Review Priority:	Standard
Medical Division:	OHOP/DOP1
Clinical Team:	Amanda Walker, M.D., Clinical Reviewer Harpreet Singh, M.D., Clinical Reviewer Laleh Amiri-Kordestani, M.D., Clinical Review Team Leader Julia Beaver, M.D., Division Director
Project Manager:	Pamela Balcazar, M.S.

The clinical safety review is complete and has been added to the Multi-disciplinary Review and Evaluation. My recommendation for this application is to approve.

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

/s/

AMANDA J WALKER
07/05/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208051 **Applicant: Puma Biotechnology** **Stamp Date: July 19, 2016**

Drug Name: Neratinib **NDA/BLA Type: NME**

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 common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
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)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159 htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:				
EFFICACY					

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
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 3004 Indication: Extended adjuvant therapy of HER2+ breast cancer with prior adjuvant trastuzumab-based therapy	X			
17.	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?	X			
18.	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.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	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?	X			

[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
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	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)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
42.	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?	X			

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.

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

Harpreet Singh/ Amanda Walker	9/17/2016
Reviewing Medical Officer	Date
Clinical Team Leader	Date

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/s/

B HARPREET SINGH
07/03/2017
Uploaded 7/3/17, however completed at time of filing meeting, 9/15/16

AMANDA J WALKER
07/05/2017

LALEH AMIRI KORDESTANI
07/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

NONCLINICAL STUDIES – MEMO

Application number:	208051
Supporting document/s:	1
Applicant's letter date:	7/18/2016
CDER stamp date:	7/19/2016
PDUFA goal date:	7/19/2017
Product:	Nerlynx (neratinib maleate)
Indication:	Extended adjuvant treatment of adult patients with early stage ERBB2-positive breast cancer who have received prior trastuzumab-based therapy
Applicant:	Puma Biotechology, Inc. 10880 Wilshire Blvd Los Angeles, CA United States
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewers:	Kimberly Ringgold, PhD
Supervisor:	Todd Palmby, PhD
Division Director:	John Leighton, PhD, DABT (DHOT) Julia Beaver, MD (DOP1, acting)
Project Manager:	Pamela Balcazar

Disclaimer

The Pharmacology/Toxicology review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no nonclinical findings that would preclude the approval of NERLYNX for the proposed indication.

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/s/

KIMBERLY R RINGGOLD
06/29/2017

TODD R PALMBY
06/30/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA-208051
Drug Name:	Neratinib Maleate
Indication:	Indicated for the Exyended Adjuvat Treatment of Patients with (b) (4) Stage (b) (4) HER2 (b) (4) /Amplified (b) (4) Breast Cancer who have received prior Adjuvant Trastuzumab Therapy.
Studies:	26 Weeks Mouse Carcinogenicity Study
Applicant:	Sponsor: Puma Biotechnology, Inc. 10880 Wilshire Blvd., Suite 2150 Los Angeles, CA 90024 United States Testing Facility: (b) (4)
Documents Reviewed:	Electronic submission: Submitted on Feb 2 2017 Electronic data: Submitted on Feb 2 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Hematology Oncology Toxicology
Reviewing Pharmacologist:	Kimberly Ringgold Ph.D.
Date Submitted:	Feb 20 2017
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included a carcinogenicity study report in mice. This study was intended to determine the potential carcinogenicity of Neratinib maleate when administered to mice by oral gavage for 6 months.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Study Design and Analysis

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups, one vehicle control group, and one water group. One hundred twenty-five CByB6F1/Tg rasH2 hemizygous (transgenic) mice of each sex were assigned randomly to the treated, vehicle control, and water control groups in equal size of 25 mice per group. The dose levels for treated groups were 8, 20, and 50 mg/kg/day for male mice and 20, 50, and 125 mg/kg/day for female mice, respectively. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The mice in the vehicle control group (Group 2) and the water control group (Group 1) were administered with the reference item [0.5% polysorbate 80 NF; 0.5% methylcellulose (4000 cps), (final concentrations) and purified (Type I) water (b) (4)] and (b) (4) water, respectively, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Mice Study

Group No.	No. of Toxicity Animals[a]		Test Material	Dosae Level (mg/kg/day)[b]	
	Male	Female		Male	Female
1	25	25	Water control	0	0
2	25	25	Vehicle control	0	0
3	25	25	low	8	20
4	25	25	mid	20	50
5	25	25	mid	50	125

The animals were observed for general health/mortality and moribundity twice daily, once in the morning and afternoon, throughout the study. Cage side observations were performed once daily, beginning during Week -1 and continuing throughout the dosing period. During the dosing phase, these observations were performed 1 to 3 hours postdose. The animals were removed from the cage and a detailed clinical observation was performed weekly, beginning during Week -1. A necropsy was conducted for carcinogenicity animals that died on study and specified tissues were saved. When necessary, animals were refrigerated before necropsy to minimize autolysis. If necessary for humane reasons, carcinogenicity animals were euthanized as per Testing Facility SOPs. These animals underwent necropsy and specified tissues were retained. When necessary, animals were euthanized and refrigerated before necropsy to minimize autolysis. When possible, the animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied at similar times throughout the day.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's report, Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. A log-rank test for survival was used to make the following comparisons: I) pairwise comparisons of groups 2-5 with water control group I; and 2) pairwise comparisons of groups 3-5 with vehicle control group 2. All tests were 2-sided and conducted at the 0.05 significance level. Survival times in which the status of the animal's death was classified as an accidental death or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 23 (92%), 24 (96%), and 23 (92%) in the water control, the vehicle control, and the low, mid, and high dose groups (Groups 1, 2, 3, 4, and 5) for male mice, respectively, and 24 (96%), 24 (96%), 23 (92%), 25 (100%), and 23 (92%) for female mice, respectively. There were no statistically significant findings among male or female mice for survival rates.

2.1.2. Tumor data analysis

In the sponsor's report, the tumor incidence data was conducted in accordance with the FDA draft Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.

The incidence of tumors in groups 1-5 were analyzed by Peto's method (Peto et, 1980), without continuity correction, incorporating the context (incidental, fatal, or mortality-independent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: Weeks 1-18 and 19-end of study (EOS) including scheduled terminal sacrifice. There were no incidental tumors detected prior to week 19 and a minimum exposure of 19 weeks was considered sufficient to be included with animals surviving through scheduled termination. Tumors that were detected after the first animal of that sex was terminally sacrificed were considered incidental for the purpose of statistical analysis.

Tumors classified as mortality-independent were analyzed with Peto's onset rate method incorporating the day of detection.

Each diagnosed tumor type was analyzed separately and, at the discretion of the Study Director, analysis of combined tumor types was performed as described by McConnell (see Table 4.2.1). Grouping of tissues was performed for analysis purposes. In addition, all leukemias or other systemic tumors were grouped under "hemolymphoreticular tissue". Finally, all metastases and invasive tumors were considered secondary and not included in the analyses unless the primary tumor could not be identified.

All analyses were conducted separately for each sex. For each tumor type, the following analyses were conducted: 1) 1-sided pairwise comparison of groups 2-5 with water control group 1; 2) 1-sided pairwise comparison of groups 3-5 with vehicl control group 2; and 3) 1-sided trend test with groups 2-5 utilizing ordinal coefficients.

An exact permutation test was conducted for tumor types with small numbers of total tumor bearing animals across treatment groups.

Adjustment for multiple testing:

In the sponsor's report, statistical significance was determined according to the following level of significance: all pairwise tests were made at the 0.05 significance level; trend tests were made at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Sponsor's findings:

In the sposor's report, there was one finding in male mice with a p-value less than 0.05 (trend test with vehicle control p=0.0279 for hemangiosarcoma in the spleen). Because this is a common tumor it was not considered statistically significant. Therefore there were no statistically significant tumor findings among both male and female mice.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of mice in all five groups (Groups 1, 2, 3, 4, and 5) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across groups using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female mice, respectively. The intercurrent mortality data of all five groups, and the results of the tests for dose response relationship and homogeneity of survivals for Groups 2, 3, 4, and 5 are given in Tables 1A and 1B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 23 (92%), 24 (96%), and 23 (92%) in the water control, the vehicle control, and the low, mid, and high dose groups (Groups 1, 2, 3, 4, and 5) for male mice, respectively, and 24 (96%), 24 (96%), 23 (92%), 25 (100%), and 23 (92%) for female micerespectively. No statistically significant findings in mortality were noted in male and female mice.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups Groups 2, 3, 4, and 5 and pairwise comparisons of each of the three treated groups (Groups 3, 4, and 5) and the water control group (Group 1) against the vehicle control group (Group 2), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^*_i is defined as $R^*_i = \sum w_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / t_{sacr})^k$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and t_{sacr} is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned w_{ij} =1 since $t_{ij} = t_{sacr}$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the t_{sacr} should not be affected by the unplanned early terminations. The t_{sacr} should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than t_{sacr}, regardless their actual terminal sacrifice time, t_{sacr} was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. The present study is a 26 week study. For this kind of medium or short term study no such suggested value of k in the literature is known to this reviewer. Following the suggested value for long term studies, this reviewer analyzed the tumor data using k=3. Therefore, any significant finding form this analysis should be interpreted more carefully, including pathological consideration.

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female mice, respectively.

Adjustment for multiple testing:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the

FDA guidance for statistical design and analysis of carcinogenicity studies (2001). In order to keep the overall false-water rate at the nominal level of approximately 10%, for both of the dose response relationship tests and the multiple pairwise comparisons of treated group with control group, the guidance suggests the use of a significance level α=0.01 for common tumors and α=0.05 for rare tumors (background rate of 1% or less) for a submission with one species,

Reviewer's findings:

The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and combined control are reported in Table 2.

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Mice

Organ name	Tumor name	Water (NC) 0 mg P – VC vs. WC	Vehicle (VC) 0 mg P - Trend	Low (L) 8 mg P - VC vs. L	Mid (M) 20 mg P - VC vs. M	High (H) 50 mg P - VC vs. H
Male-Spleen	Hemangiosarcoma	2/25 (25) 0.5156	1/25 (24) 0.0245 @	1/25 (24) NC	3/25 (25) 0.3202	5/25 (25) 0.1039
Male-Whole Body	Hemangiosarcoma	2/25 (25) 0.5156	1/25 (24) 0.0090*	1/25 (24) NC	3/25 (25) 0.3202	6/25 (25) 0.0551

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
@: not statistically significant at 0.01 for common tumors for test of dose response relationship;
*: statistically significant at 0.01 for common tumors for test of dose response relationship;
NC = Not calculable.

The results of the reviewer's analysis given in Table 2 above showed that p-value of 0.0245 (>0.01) and 0.0090 (<0.01) were noted for the dose response relationship of the hemangiosarcoma in spleen and in the whole body for male mice, respectively. Based on the criteria of adjustment for multiple testing discussed previously, the trend for the hemangiosarcoma in spleen was not statistically significant as this tumor was considered to be common, whereas the trend for the hemangiosarcoma in the whole body can be considered as statistically significant regardless whether this tumor was treated as rare or common.

No other observed tumor types were noted to be statistically significant for the dose response relationships or pairwise comparisons in both male and female mice.

3. Summary

In this submission the sponsor included a carcinogenicity study report in mice. This study was intended to determine the potential carcinogenicity of Neratinib maleate when administered to mice by oral gavage for 6 months.

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one vehicle control group, and one water group. One hundred twenty-five CByB6F1/Tg rasH2 hemizygous (transgenic) mice of each sex were assigned randomly to the treated, vehicle control, and water control groups in equal size of 25 mice per group. The dose levels for treated groups were 8, 20, and 50 mg/kg/day for male mice and 20, 50, and 125 mg/kg/day for female mice, respectively.

This reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 23 (92%), 24 (96%), and 23 (92%) in the water control, the vehicle control, and the low, mid, and high dose groups (Groups 1, 2, 3, 4, and 5) for male mice, respectively, and 24 (96%), 24 (96%), 23 (92%), 25 (100%), and 23 (92%) for female micerespectively. No statistically significant findings in mortality were noted in male and female mice.

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Hepei Chen.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, DBVI

Cc: Archival NDA-208051

Dr. Kimberly Ringgold
Dr. Lillian Patrician
Dr. Mohammad Atiar Rahman

4. Appendix

Table 1A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low		Mid		High		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
1 - 13							1	4.00		
14 - 27	1	4.00	2	8.00	1	4.00	1	8.00		
Terminal sacrifice	24	96.00	23	92.00	24	96.00	23	92.00	25	100.00
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.3646	0.2298	0.6175	0.2322
Homogeneity (Log-Rank)	0.5721	0.2081	0.6063	0.2129

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low		Mid		High		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
14 - 27	1	4.00	2	8.00			2	8.00	1	4.00
Terminal sacrifice	24	96.00	23	92.00	25	100.00	23	92.00	24	96.00
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.6499	0.4987	0.2010	0.5019
Homogeneity (Log-Rank)	0.5013	0.4847	0.3149	0.4896

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Water (NC) 0 mg P – VC vs. WC	Vehicle (VC) 0 mg P - Trend	Low (L) 8 mg P - VC vs. L	Mid (M) 20 mg P - VC vs. M	High (H) 50 mg P - VC vs. H
Gland, Harderian	Adenocarcinoma	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (24)	0/25 (24)
		0.5102	NC	NC	NC	NC
	Adenoma	0/25 (25)	0/25 (24)	1/25 (24)	0/25 (24)	0/25 (24)
		NC	0.7500	0.5000	NC	NC
	Adenocarcinoma/Adenoma	1/25 (25)	0/25 (24)	1/25 (24)	0/25 (24)	0/25 (24)
		0.4898	0.5000	0.5000	NC	NC
Gland, Zymbals	Papilloma	0/18 (18)	0/20 (19)	1/23 (22)	0/23 (22)	0/23 (22)
		NC	0.7765	0.5366	NC	NC
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (24)	1/25 (24)
		NC	0.2500	NC	NC	0.5000
Large Intestine, Cecum	Hemangioma	1/25 (25)	0/25 (24)	0/24 (23)	0/25 (24)	0/25 (24)
		0.5102	NC	NC	NC	NC
Lung	Bronchioloalveolar Adenoma	1/25 (25)	3/25 (24)	2/25 (24)	0/25 (24)	0/25 (24)
		0.9498	0.9951	0.8262	1.0000	1.0000
	Bronchioloalveolar Carcinoma	0/25 (25)	2/25 (25)	2/25 (24)	1/25 (24)	0/25 (24)
		1.0000	0.9458	0.6798	0.8752	1.0000
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	1/25 (25)	5/25 (25)	4/25 (24)	1/25 (24)	0/25 (24)
		0.0947	0.9971	0.4725	0.8961	0.9721
Pancreas	Hemangiosarcoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (24)	1/25 (24)
		NC	0.2500	NC	NC	0.5000
Spleen	Hemangiosarcoma	2/25 (25)	1/25 (24)	1/25 (24)	3/25 (25)	5/25 (25)
		0.5156	0.0245*	NC	0.3202	0.1039
Whole Body	Hemangiosarcoma	2/25 (25)	1/25 (24)	1/25 (24)	3/25 (25)	6/25 (25)
		0.5156	0.0090*	NC	0.3202	0.0551

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Water (NC) 0 mg P - VC vs. NC	Vehicle (VC) 0 mg P - Trend	Low (L) 20 mg P - VC vs. L	Mid (M) 50 mg P - VC vs. M	High (H) 125 mg P - VC vs. H
Gland, Harderian	Adenoma	0/25 (25)	0/25 (24)	0/25 (24)	3/25 (25)	2/25 (25)
		NC	0.0847	NC	0.1248	0.2551
Hemolymphoreticular Tissue	Lymphoma, Malignant	1/25 (25)	0/25 (24)	2/25 (25)	1/25 (25)	0/25 (25)
		0.5102	0.7429	0.2551	0.5102	NC
Lung	Bronchioloalveolar Adenoma	1/25 (25)	1/25 (24)	1/25 (24)	4/25 (25)	0/25 (25)
		0.7653	0.7311	NC	0.1871	1.0000
	Bronchioloalveolar Carcinoma	0/25 (25)	1/25 (24)	2/25 (24)	0/25 (25)	2/25 (25)
		1.0000	0.3649	0.5000	1.0000	0.5156
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	1/25 (25)	2/25 (24)	3/25 (24)	4/25 (25)	2/25 (25)
		0.4844	0.5731	0.5000	0.3535	0.3202
Muscle, Skeletal	Hemangiosarcoma	0/25 (25)	1/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)
		1.0000	1.0000	1.0000	1.0000	1.0000
Spleen	Hemangiosarcoma	1/25 (25)	1/25 (24)	2/25 (24)	0/25 (25)	2/25 (25)
		0.7653	0.3649	0.5000	1.0000	0.5156
Thymus	Thymoma, Malignant	0/25 (25)	1/25 (24)	0/25 (24)	2/25 (25)	0/24 (24)
		1.0000	0.6914	1.0000	0.5156	1.0000
Tongue	Squamous Cell Carcinoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (25)	1/25 (25)
		NC	0.2551	NC	NC	0.5102
Whole Body	Hemangiosarcoma	1/25 (25)	2/25 (25)	2/25 (24)	0/25 (25)	2/25 (25)
		0.8827	0.5172	0.6798	1.0000	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Mice

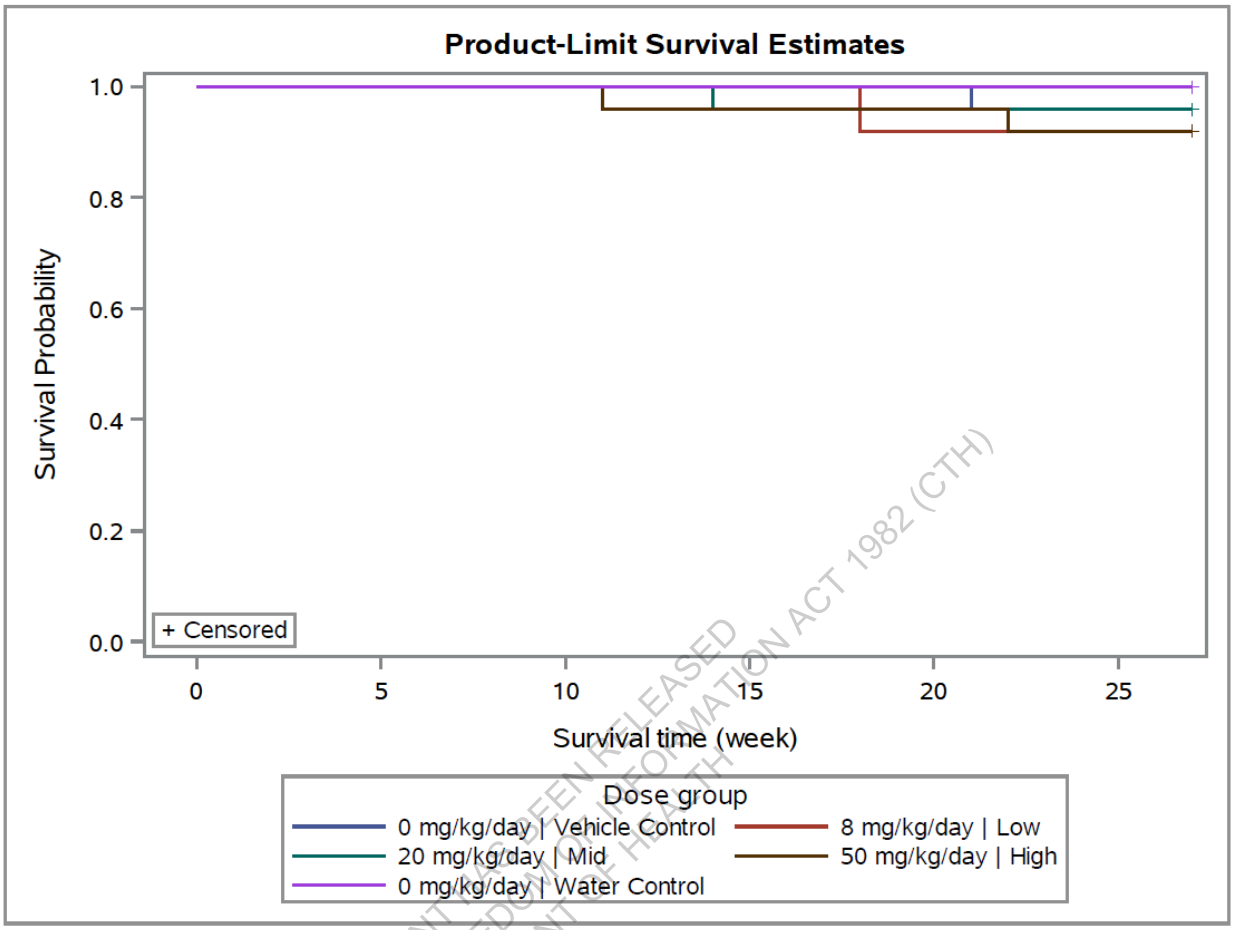
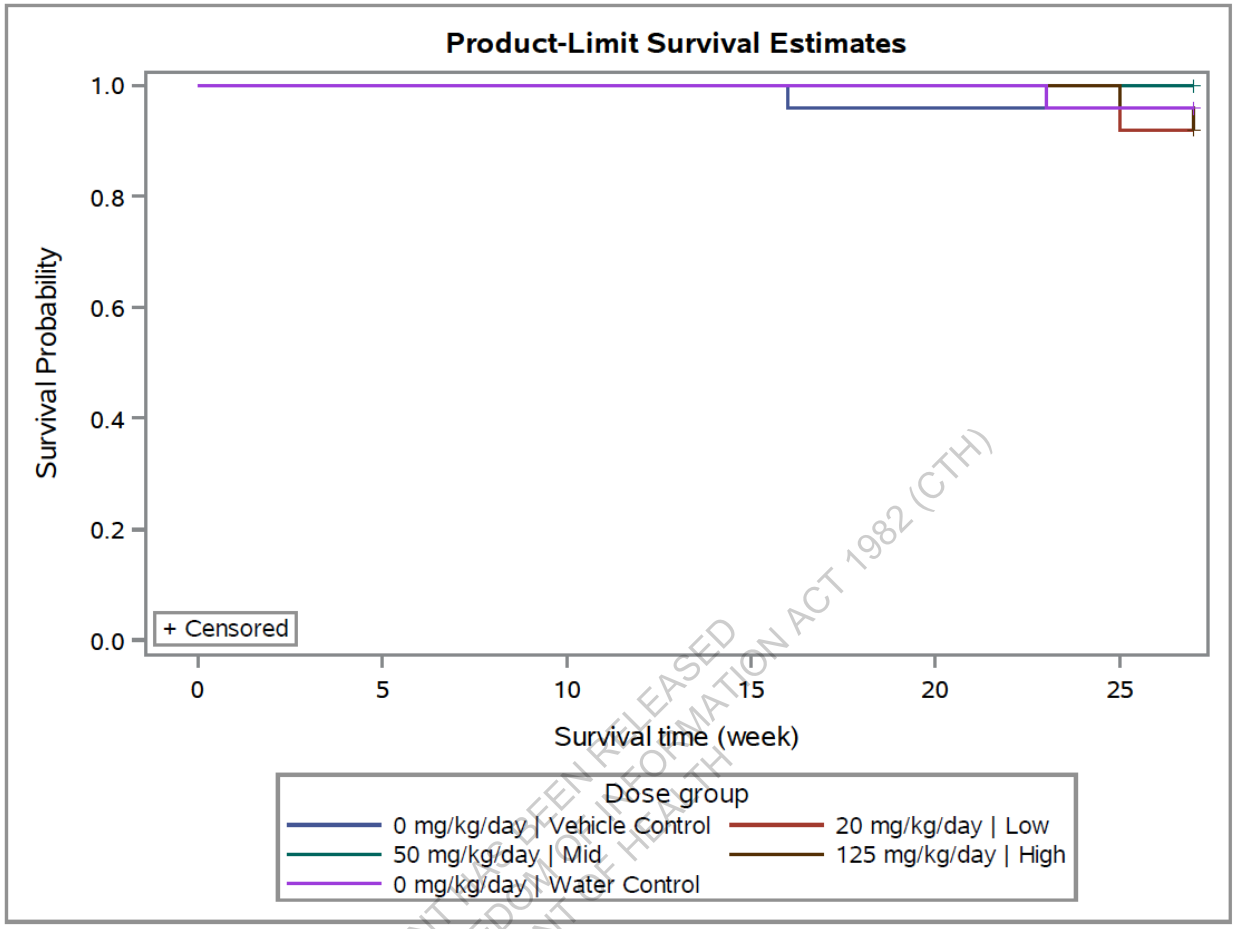


Figure 1B: Kaplan-Meier Survival Functions for Female Mice



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Rahman, A.M., and Lin, K.K. (2009), "Design and Analysis of Chronic Carcinogenicity Studies of Pharmaceuticals in Rodents", in “Design and Analysis of Clinical Trials with Time-to-Event Endpoints", K.E Peace, Editor, Chapman & Hall/CRC, Taylor & Francis Group, LLC, Boca Raton, FL, London, and New York.

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/s/

HEPEI CHEN
06/29/2017

KARL K LIN
06/29/2017
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translation Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES- MEMO

NDA:	208051
Drug Name:	NERLYNX (neratinib)
Indication:	Extended adjuvant treatment of adult patients with early stage ERBB2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy
Applicant:	Puma Biotechnology
Receipt Date:	July 19, 2016
PDUFA Goal Date:	July 19, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Primary Reviewers:	Joyce Cheng, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Statistical Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	OHOP/DOP1
Clinical Team:	Harpreet Singh, M.D., Clinical Reviewer Amanda Walker, M.D., Clinical Reviewer Laleh Amiri-Kordestani, M.D., Clinical Review Team Leader Julia Beaver, M.D., Division Director
Project Manager:	Pamela Balcazar, M.S.

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the ExteNET study met its primary endpoint.

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/s/

JOYCE H CHENG
06/19/2017

SHENGHUI TANG
06/19/2017

RAJESHWARI SRIDHARA
06/19/2017

Office of Clinical Pharmacology Memo

NDA/SDN	NDA 208051/1
Link to EDR	\\cdsesub1\evsprod\nda208051
Submission Date	July 19, 2016
Submission Type	NME, original NDA
Brand Name	Nerlynx
Generic Name	Neratinib
Dosage Form and Strength	Tablets (40 mg)
Route of Administration	Oral
Dosing Regimen	240 mg once daily with food, continuously for one year
Proposed Indication	Extended adjuvant therapy of HER2+ breast cancer with prior adjuvant trastuzumab-based therapy
Applicant	Puma Biotechnology, Inc.
Associated IND	IND 066783
OCP Review Team	Xianhua (Walt) Cao, Ph.D., Nan Zheng, Ph.D., Jingyu (Jerry) Yu, Ph.D., Qi Liu, Ph.D.
OCP Final Signatory	Nam Atiqur Rahman, Ph.D. Division Director Division of Clinical Pharmacology V

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the primary review in the Multi-disciplinary Review and Evaluation for additional details. From a Clinical Pharmacology standpoint, the NDA is approvable provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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/s/

XIANHUA W CAO
06/02/2017

NAN ZHENG
06/02/2017

JIANG LIU
06/02/2017
On behalf of Jerry Yu

QI LIU
06/02/2017

NAM ATIQUR RAHMAN
06/03/2017
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208051 **Applicant:** Puma **Stamp Date:** 7/19/16

Drug Name: Neratinib **NDA/BLA Type:** NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for NDA_208051

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/s/

JOYCE H CHENG
08/31/2016

SHENGHUI TANG
09/15/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208051	**SDN**	1
Applicant	Puma Biotechnology, Inc.	**Submission Date**	July 19, 2016
Generic Name	Neratinib	**Brand Name**	Nerlynx
Drug Class	Tyrosine kinase inhibitor		
Indication	Extended adjuvant therapy of HER2+ breast cancer with prior adjuvant trastuzumab-based therapy		
Dosage Regimen	240 mg once daily QD with food, continuously for one year		
Dosage Form	40 mg Tablets	**Route of Administration**	oral
OCP Division	DCPV	**OND Division**	DOP1

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Xianhua (Walt) Cao, Ph.D.	Qi Liu, Ph.D.
Pharmacometrics	Nan Zheng, Ph.D.	Jingyu (Jerry) Yu, Ph.D.
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	9/17/2016	**74-Day Letter Date**	10/1/2016
Review Due Date	3/29/2017	**PDUFA Goal Date**	7/19/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☑ Metabolism Characterization	5	
☑ Transporter Characterization	3	
☑ Distribution	4	
☑ Drug-Drug Interaction	4	

In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		1	
☑ Bioequivalence		2	
☑ Food Effect		2	
☑ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	11	
	☑ Multiple Dose	1	PK/diarrhea effects
Patients	☑ Single Dose	2	
	☑ Multiple Dose	11	
☑ Mass Balance Study		1	
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☑ Hepatic Impairment		1	
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug		3	
☑ Effects of Primary Drug		1	
Pharmacodynamics			
☑ Healthy Subjects		1	
☑ Patients		1	
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☑ QT		1	
Pharmacometrics			
☑ Population Pharmacokinetics		1	
☑ Exposure-Efficacy		1	
☑ Exposure-Safety		1	

Total Number of Studies	**In Vitro**	16	**In Vivo**	24
Total Number of Studies to be Reviewed		16		24

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	To-be-marketed formulation was used in the pivotal trial
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Requested for waiver of pediatric studies
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

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/s/

XIANHUA W CAO
09/06/2016

QI LIU
09/08/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208051 **Applicant: Puma Biotechnology** **Stamp Date: 7/19/2016**

Drug Name: Neratinib **NDA Type: Standard Review** **PDUFA Date: 7/19/2017**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Applicant submitted final report for 6-month carcinogenicity study in transgenic mice and report from 1-year repeat-dose toxicology study in rats.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Labeling is a review issue.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The acceptability of impurity levels and specifications is a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?			NA
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

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

None

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

KIMBERLY R RINGGOLD
09/01/2016

TODD R PALMBY
09/06/2016

s 22

From: s 22
Sent: Friday, 6 December 2019 6:28 PM
To: s 47F
Subject: FW: FW: FW: s 47E [SEC=OFFICIAL]
Attachments: s 47E s 47F .docx

s 47F

Forwarding without reading. I will read myself in case you wish to discuss.

s 47E

s 47E

s 22

Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 47F
Sent: Thursday, 5 December 2019 7:14 PM
To: s 22
Cc: s 22
Subject: Re: FW s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E