13 July 2018
EMA/CHMP/525204/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nerlynx

International non-proprietary name: neratinib

Procedure No. EMEA/H/C/004030/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE(s)	adverse event(s)
aITT	amended ITT
Akt	protein kinase B
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCS	Biopharmaceutics Classification System
CBR	clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	oral clearance
Cmax	peak plasma concentration
CMPH	Committee for Medicinal Products for Human Use
CNS	central nervous system
CRO	contract research organization
CV	coefficient of variation
CYP	cytochrome
DDFS	distant disease-free survival
DFS	disease-free survival
DFS-DCIS	disease-free survival including ductal carcinoma in situ
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EQ-5D	EuroQol 5-Dimension Questionnaire
ER	estrogen receptor
ERBB	erythroblastic leukemia viral oncogene homolog; also termed HER
ExteNET	Extended Adjuvant Treatment of Breast Cancer with Neratinib
FACT-B	Functional Assessment of Cancer Therapy-Breast
FMO	flavin-containing monooxygenase
GI	gastrointestinal
HER	human epidermal growth factor receptor
HERA study	HERceptin Adjuvant study
HR	hazard ratio
HRc	hormone receptor
IC50	half-maximal inhibitory concentration
iDFS	invasive disease-free survival
IDMC	independent data monitoring committee
I-SPY study	Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and moLecular Analysis study
ITT	intent-to-treat
IV	intravenous
LVEF	left ventricular ejection fraction
M3	pyridine N-oxide

M6	N-desmethyl 272
M7	dimethylamine N-oxide
M11	bis-N-oxide
MAPK	mitogen-activated protein kinases
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PD	progressive disease
PFS	progression-free-survival
P-gp	P-glycoprotein
PgR	progesterone receptor
PK	pharmacokinetic(s)
PPI	proton pump inhibitors
QTc	corrected QT interval (corrected for heart rate)
RR	relative risk
SAE(s)	serious adverse event(s)
SD	standard deviation
SOC(s)	system organ classe(s)
T-DM1	ado-trastuzumab emtansine
TEAE(s)	treatment-emergent adverse event(s)
t½	half-life
Tmax	time to peak concentration
TTDR	time to distant recurrence
ULN	upper limit of normal
US	United States
Vz/F or Vzss/F	apparent distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Puma Biotechnology Limited submitted on 23 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Nerlynx, through the centralised marketing authorisation procedure falling within the scope of Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility of the medicinal product for authorisation to the centralised marketing authorisation procedure was agreed upon by the EMA/CHMP on 22 May 2014.

The applicant initially applied for the following indication:

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 legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that neratinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance neratinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 15 November 2007 and 19 March 2009. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Bruno Sepodes

- The application was received by the EMA on 23 June 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 17 November 2016.
- During the meeting on 15 December 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 May 2017.
- The following GCP inspection was requested by the CHMP and its outcome was taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
    - A GCP inspection at two sites: Clinical Investigator site in Croatia and CRO in the US between 12-16 December 2016 and 13-17 February 2017 respectively. The outcome of the inspection carried out was issued on 31 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 26 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 10 January and 19 January 2018.
- During a meeting of a SAG on 11 January 2018, experts were convened to address questions raised by the CHMP. The CHMP considered the views of the SAG as presented in the minutes of this meeting.
- During the CHMP meeting on 23 January 2018, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- During the meeting on 19-22 February 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Nerlynx on 22 February 2018.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Filip Josephson

- The applicant submitted written notice to the EMA on 7 March 2018 to request a re-examination of Nerlynx CHMP opinion of 22 February 2018.
- During its meeting on 22 March 2018, the CHMP appointed Paula Boudewina van Hennik as Rapporteur and Filip Josephson as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 30 April 2018 (Appendix 2 of Final Opinion). The re-examination procedure started on 1 May 2018.
- The CHMP rapporteur's and PRAC rapporteur's joint re-examination assessment report was circulated to all CHMP members on 5 June 2018. The co-rapporteur's assessment report was circulated to all CHMP members on 29 May 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 15 June 2018.
- During the PRAC meeting on 14 June 2018, the PRAC agreed on a PRAC Assessment Overview and Advice.
- During the CHMP meeting on 26 June 2018, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 25-28 June 2018, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for Nerlynx as single therapy is the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy).

2.1.2. Epidemiology, screening tools / prevention

Breast cancer is the most frequently diagnosed malignancy in women and the leading cause of cancer mortality in women worldwide. In 2012, the estimated age-adjusted annual incidence of breast cancer

in 40 European countries was 94.2/100 000 and the mortality was 23.1/100 000[1]. There is a steep age gradient, with about a quarter of breast cancers occurring before age 50, and <5% before age 35. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection. However, breast cancer is still the leading cause of cancer-related deaths in European women. Ten-year survival of breast cancer exceeds 70% in most European regions, with 89% survival for local and 62% for regional disease. 25% of women with HER2+ early breast cancer will suffer a recurrence or die within 10 years of initiation of adjuvant therapy. Human epidermal growth factor 2 (HER2) over-expressed/ amplified breast cancer is a subset of early breast cancer in which there is amplification of the HER2 gene and overexpression of its product in breast tumour tissue. HER2-positive breast cancer comprises 20 to 25% of the entire breast cancer population[2].

2.1.3. Biologic features

The HER2 biomarker is both prognostic and predictive. HER2 positivity is associated with an increased tendency to metastasise, and poorer outcomes, but also predicts response to HER2 targeted therapy such as trastuzumab, pertuzumab, lapatinib, and ado-trastuzumab emtansine.

HER2-positive breast cancer is a heterogeneous disease. There is concurrent expression of oestrogen receptor (ER) or progesterone receptor (PgR) in nearly 50% of patients. Data derived from prospective cohorts demonstrate different outcomes for hormone receptor (HRc)-positive and HRc-negative cancers that are HER2-positive; the latter are associated with a higher risk of early recurrence and the former characterised by a relatively consistent risk of relapse over time.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment of the primary tumour and axillary nodes. Final pathological diagnosis is made according to the WHO classification and the tumour–node–metastases (TNM) staging system. The stage grouping is the basis for prognostication. The pathological report includes the histological type, grade, immunohistochemical (IHC) evaluation of oestrogen receptor (ER) status and progesterone receptor (PgR). HER2 gene expression is also routinely assessed using *in situ* hybridisation (fluorescent, chromogenic or silver), or IHC.

2.1.5. Management

Early breast cancer is treated with a combination of loco-regional surgery ± radiotherapy, and systemic (neo-) adjuvant therapy. Patients with HER2 receptor positive disease are generally treated with combination chemotherapy including an anthracycline and a taxane, with concomitant or sequential trastuzumab for one year. For those at high risk, neo-adjuvant pertuzumab may be given in combination with trastuzumab and chemotherapy. Those with HRc-positive disease are also treated with endocrine therapy, generally tamoxifen or an aromatase inhibitor, for at least 5 years. Following adjuvant treatment, patients are followed-up to detect recurrence.

[1] Tinoco G, Warsch S, Glück S, Avancha K, Montero AJ. Treating breast cancer in the 21st century: emerging biological therapies. *J Cancer* 2013; 4(2):117-132.
[2] Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365:1273–1283.

In the extended adjuvant setting, following trastuzumab, endocrine therapy is standard treatment for HR+ disease. There is no standard treatment for HR- disease. The annual hazard of recurrence peaks in the second year after diagnosis but remains at 2%–5% in years 5–20. No HER2 targeted agent has been approved in Europe for extended adjuvant therapy following treatment with trastuzumab.

About the product

Neratinib (HKI-272) has been developed as extended adjuvant treatment of HER2 positive early breast cancer in patients who have already received trastuzumab, in order to further reduce the risk of recurrence. Neratinib is an orally bioavailable small molecule that irreversibly binds at the intracellular tyrosine kinase domain of the epidermal growth factor receptor (EGFR) (ERBB1), HER2 (ERBB2), and HER4 (ERBB4) receptors. Neratinib binding reduces EGFR and HER2 auto-phosphorylation, downstream signalling, and growth of EGFR- and HER2-dependent cell lines, with cellular half-maximal inhibitory concentration (IC50) <100 nM. *In vivo*, neratinib is active in HER2- and EGFR-dependent tumour xenograft models when administered orally once-daily. The inhibition of ERBB2 downstream phosphorylation by neratinib may render neratinib effective despite development of trastuzumab resistance. Recent *in vitro* studies showed that neratinib can overcome trastuzumab resistance in ERBB2-amplified cell line models of acquired trastuzumab resistance as well as in innately resistant cell lines. The main hypothesis behind the development of neratinib in this indication is that a sustained anti-ERBB blockade with a non-cross resistant drug after one year of adjuvant trastuzumab could increase sustained cure rates with acceptable toxicity.

The applicant initially applied for the following indication: “Nerlynx as a single agent is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer at high risk of recurrence who have received prior adjuvant trastuzumab based therapy.” The Applicant proposed the following restricted indication during the procedure: “Nerlynx as a single agent is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy.”

Neratinib is a class 4 Biopharmaceutics Classification System (BCS) molecule with low solubility and low permeability and absorption is decreased at more alkaline gastric pH. The proposed commercial formulation is an immediate-release film-coated 40 mg tablet of the maleate salt. The recommended dose is 240 mg orally once daily with food.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing neratinib maleate, equivalent to 40 mg neratinib as active substance.

Other ingredients are:

Tablet core: mannitol, microcrystalline cellulose, crospovidone, povidone, colloidal anhydrous silica, and magnesium stearate.

Tablet coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, and iron oxide red (E172)

The product is packed in high density polyethylene (HDPE) round bottle with child-resistant, polypropylene closure and foil induction inner seal as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of neratinib maleate is (E)-N-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate corresponding to the molecular formula $C_{30}H_{29}ClN_6O_3 \bullet C_4H_4O_4$. It has a relative molecular mass of 673.11g/mol and the following structure:

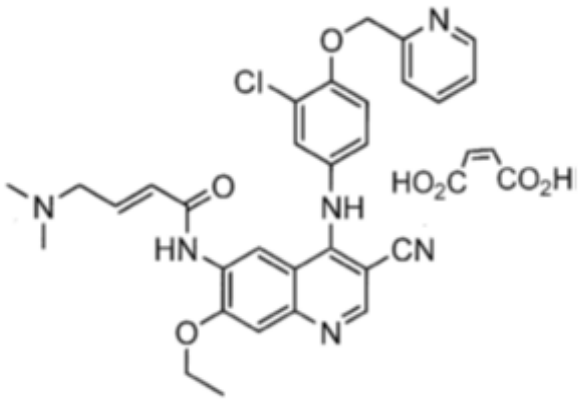


Figure 1 Active substance structure

The chemical structure of the active substance was elucidated by a combination of proton and carbon nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (ATR-IR), mass spectroscopy by electrospray ionization (ESI-MS), elemental analysis (C,H,N, and Cl), and single crystal X-Ray diffraction (SC-XRD).

The active substance is off-white to yellow powder, the solubility in aqueous media increases dramatically as neratinib becomes protonated at acidic pH. The maximum solubility of neratinib maleate is at pH 1.2 and falls at approximately pH 5.0 and above. It is hygroscopic.

Neratinib has a non - chiral molecular structure.

Manufacture, characterisation and process controls

The proposed commercial manufacturing process of the active substance uses well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD. However, no design space was claimed. A criticality analysis to assess the critical steps and controls for the active substance manufacturing process was performed. This criticality analysis was performed using a two-tiered approach. Tier 1 analysis was an evaluation of each of the synthetic steps to assess the impact of each step on the CQAs of the active substance. Tier

2 analysis was an evaluation of individual process parameters within each step based on Design of Experiments (DOE) studies.

As mentioned, Tier 1 of the criticality analysis was an evaluation of the process steps of the active substance synthesis to assess their potential impact on the CQAs (appearance, identification, assay, impurities, residual platinum, heavy metals, maleic acid content, residual solvents, water content and particle size) of the active substance. For the purposes of this criticality analysis, a critical step is defined as a processing step that impacts any CQA of the active substance. The following principles were used as criteria to identify the critical steps:

- a synthetic step is considered critical if it impacts a CQA of the active substance.
- a synthetic step is considered critical if impurities that are specified in the active substance specifications are formed or removed in that step.

In Tier 2 of this criticality analysis, the individual process parameters within each of the synthetic steps were evaluated to define their proven acceptable ranges (PARs) and normal operating ranges (NOR), and to assess their potential impact as Critical Process Parameters (CPPs) on the CQAs of the active substance. The process parameters studied were chosen based on previous process knowledge gained from process development and manufacturing of batches used in clinical development. Design of Experiments (DOE) studies were performed to define the PARs and subsequently set the NORs of the process within the PARs. The process parameters are variables of the process which can be measured and controlled and must be within a pre-established range, such as temperature, time, solvent ratios, etc. Once the PARs for the process parameters were established, and the effects on the CQAs were known, they were classified as either a CPP or non-CPP. The classification was based on the NOR relative to the PAR (the likelihood and detectability of excursion from the established limits, and the potential impact on either the manufacturing process (i.e., yield, robustness, etc.), or the quality of the final active substance.

DOEs studies were conducted to identify potential CPPs within each synthetic step of the manufacturing process. PARs were identified for each of the process parameters studied within each of the teps. As a result, the NORs were defined inside the PARs to ensure a robust manufacturing process. The DOE studies indicate that the individual process parameters studied for each of the manufacturing steps are easy to control and have a low risk of impacting the CQAs of the DS. Therefore, no CPPs were identified during Tier 2 DOE studies.

However, in spite of the ease of control of these parameters within the PAR, the step in which they appear and affect a CQA of the active substance will be deemed ‘critical’ according to the two principles indicated in the Tier 1 analysis.

Process validation has been performed on three commercial scale batches. The data is not provided. It is stated that all batches met intermediate specifications and IPC limits. It is acceptable that data is not provided for a non-sterile active substance. Certificates of analysis are provided for the three process validation batches, which show compliance with the proposed specification.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in an inner transparent linear low-density polyethylene (LLDPE)/low-density polyethylene (LDPE) bag, which is secured appropriately with a twist-tie or equivalent which complies with the EC directive 2002/72/EC and Directive 94/62/EEC.

Specification

The active substance specification includes tests for appearance and description (visual), identification (IR, HPLC UV), assay (HPLC UV), impurities (HPLC UV), water content (KF), heavy metals - platinum (colorimetry), residue on ignition (Ph. Eur.), residual metals (IPC MS), maleic acid content (HPLC UV), residual solvents (GC HS), and particle size (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (20 pilot scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in transparent linear low-density polyethylene (LLDPE)/low-density polyethylene (LDPE) film which is representative to the one used for storage of the proposed commercial active substance for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Supportive stability data for two representative clinical batches and three process validation batches stored from 9 to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) were provided

The following parameters were tested*:* description, assay, purity, and water content. The analytical methods used were the same as for release and were stability indicating.

An increasing trend for water content, and purity is observed under long term conditions, however all parameters are in compliance with the shelf life specification. All tested parameters were within the specifications under accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. Based on the results of these studies, the appearance of the active substance could fail to meet the acceptance criteria. Thus the storage conditions will include a statement: “Protect from light”.

A forced degradation study was conducted on neratinib maleate as part of the validation for the analytical method for chromatographic purity. The stress conditions evaluated included thermal (100°C and 110°C), acid, base, oxidation, and photolysis. The highest degradation was observed when the active substance is exposed to a combination of hydrolytic and extreme heat.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months, protected from light. Keep well closed in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Nerlynx have been developed as an orally administered, immediate-release film coated tablet. The tablet is red film coated, oval shaped, and debossed with 'W104' on one side and plain on the other side. The nominal tablet dimensions are 10.5 mm x 4.3 mm with a nominal thickness of 3.1 mm.

The finished product was developed and characterized in the context of the quality target product profile (QTPP) presented in Table 1. The finished product attributes required to ensure the safety, efficacy, and quality of the tablet dosage form were identified and targeted. The QTTP identified were dosage form and strength, bioavailability, appearance and description, specifications to assure safety and efficacy during the shelf life of the product and tablet hardness and packaging.

Table 1 Quality Target Product Profile

Drug Product Attribute	Target Profile
Dosage form and strength[a]	Immediate release tablet taken orally to deliver 40 mg of neratinib as the free base.
Bioavailability	Adequate bioavailability to provide efficacy with acceptable safety/tolerability/PK characteristics
Appearance and Description	Film-coated tablet of suitable size and shape to aid patient compliance and acceptability. Debossed with unique identifying markings.
Specifications to assure safety and efficacy during the shelf life of the product	Upon release and/or over the shelf life of the product: Assay remains NLT 90% of label claim Degradation products remain within those outlined in ICH Guidance for Industry Q3B(R2): Impurities in New Drug Products Uniformity of dosage units meet pharmacopeial limits Rapid dissolution Microbial tests meet pharmacopeial limits for a non-sterile product. Water content has no impact on critical quality attributes.
Tablet Hardness and Packaging	Robust tablet able to withstand transport and handling. Packaging protects and uniquely identifies product.

[a] The 40-mg tablet was chosen to allow for potential dose modification by physicians based on known adverse events

The active substance is presented as maleate salt.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The excipients were studied for their compatibility with the active substance. To evaluate compatibility, each excipient was mixed with neratinib maleate in a ratio based on the typical level of the excipient in a solid dosage form. The sample mixtures were stored in induction sealed high density polyethylene (HDPE) bottles for 4 weeks at 51°C/70% RH. Samples were tested at initial and up to 4 weeks storage for purity. The compatibility study demonstrates that the quantities of degradants in the various sample mixtures after four weeks storage at 51°C/70% RH are below the limits of currently proposed impurity

specifications for finished product. Therefore, the excipients intended for use in solid oral formulation development are compatible with the active substance.

Preliminary formulations employed the anhydrous neratinib maleate dry blended with conventional excipients then filled into hydroxypropyl methylcellulose capsules of 40 mg and 80 mg strength. The capsule formulations exhibited poor powder flow that worsened when the drug load was increased. As a consequence, further finished product development focused on the tablet as the preferred solid oral dosage form. Three tablet manufacturing approaches were evaluated using 80 mg formulations appropriate for each process: dry blending with direct compression, dry granulation via roller compaction, and wet granulation via fluid bed processor

The formulations were evaluated in terms of final blend density, compressibility, powder flow, and tablet dissolution. Wet granulation was selected as the preferred method of tablet manufacture based on formulation processing characteristics, final blend physical properties, and tablet dissolution performance. The wet granulation formulation prototype was then modified to improve processing and performance characteristics. An aesthetic film coating was also added. Then, the tablet formulation was optimized to overcome processing issues related to poor powder flow and tablet sticking. The levels of colloidal silicon dioxide and magnesium stearate were increased, and quantities of the diluents microcrystalline cellulose and mannitol were decreased correspondingly. The resulting tablet was ultimately selected for commercialisation This accounting change to the quantitative composition did not translate to any difference in the actual composition of the tablets manufactured.

Dissolution method development was conducted in parallel with formulation and process development of the current 40 mg finished product. The dissolution method used was the one applied for the routine analysis of the finished product. The justification for the selection of the dissolution apparatus, dissolution medium, dissolution volume and agitation speed were provided and considered satisfactory. Discussion on the suitability of dissolution method with respect to discrimination is presented for a slow formulation tablet core with reduced disintegrant level and increased binder and lubricant levels to compare against the target formulation tablet core. The data obtained showed that the proposed dissolution method is able to potentially identify non-conforming batches. The selected dissolution conditions are therefore appropriate for the routine release testing of the finished product.

Fluid bed wet granulation was selected as the preferred method of tablet manufacture based on formulation processing characteristics, final blend physical properties, and tablet dissolution performance. The wet granulation formulation was then optimized (disintegrant and lubricant levels were increased) to further improve processing and performance characteristics. The fluid bed granulation process was scaled up for Phase 2 clinical manufacture. Other than minor changes to operating ranges and limits for specific process parameters, the finished product manufacturing process has not changed since manufacture of the first clinical batch.

The primary packaging is high density polyethylene (HDPE) round bottle with child-resistant, polypropylene closure and foil induction inner seal.The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of the finished product uses a conventional aqueous fluid bed granulation and drying, screening/delumping, blending, compression and film coating. The process is considered to be a standard manufacturing process.

The manufacturing process control was developed in the context of the QTPP, CQAs, Risk Assessment, and the CPPs. The defined CQAs, established as release specifications include: description, identification, assay, chromatographic purity, uniformity of dosage units, dissolution, water content, and microbiological limits. The manufacturing process risk assessment and control strategy was provided and considered satisfactory.

The finished product manufacturing process was evaluated to identify critical process parameters. Dried granulation moisture content was identified as the only CPP of the manufacturing process.

As the manufacturing process is considered a standard process, only validation protocol of manufacturing process of the finished product was provided which is acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification if the active substance ((HPLC (UV spectra), HPLC (retention time)), identification of colourants in film coat (PH. Eur), assay (HPLC), uniformity of dosage units (Ph Eur), impurities (HPLC) water content (KF), dissolution (Ph. Eur.), and microbiological limits (Ph. Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 17 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 4 pilot scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability data for 4 representative full scale clinical batches are provided. Two clinical batches were packaged in a comparable container/closure system: 60-cc HDPE bottles with child-resistant (CR) closure and foil induction seal, with an HDPE desiccant canister with silica gel. These batches and this packaging presentation are representative of the finished product used in the pivotal study. These two batches were stored for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH). The other two clinical batches were packaged using the proposed commercial primary packaging configuration and were stored for 12 and 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH).

Samples were tested for description, assay, chromatographic purity, water content, dissolution, microbiological limits. The analytical procedures used are stability indicating.

Under long term and accelerated conditions, all parameters are in compliance with the shelf life specification.

An in-use study was conducted on one bulk batch in order to understand the influences of moisture and temperature on finished product stability. The test was conducted by placing 100 tablets in a petri dish covered with a watch glass, and exposing the tablets to 30°C/75% RH for 0, 15, and 31 days. These in-use stability samples were tested for description, assay, chromatographic purity, water content, and dissolution. There were no changes to the description, assay, unspecified impurities, total impurities or dissolution. An increase in moisture content was observed, but given the hygroscopic nature of neratinib maleate, this was expected. An increase in a specified degradation product was also observed, but the results remained well within specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photo stability study showed no deleterious changes due to exposure to UV-light. The results of this study met the proposed commercial specifications. Based on the results of the photo stability study, no special labelling requirements are needed for the finished product.

Based on available stability data, the proposed shelf-life of 24 months and keep the bottle tightly closed in order to protect from moisture as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product. However, no design spaces were claimed for the manufacturing process of the active substance, or for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way and there are no unresolved quality issues which might have negative impact on the benefit/risk balance.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development programme for neratinib consisted of a range of primary pharmacology, safety pharmacology, pharmacokinetic (PK) and toxicology studies. Toxicity studies were conducted primarily in rats and dogs (up to 26 weeks in rats and up to 39 weeks in dogs), including a full battery of genotoxicity, carcinogenicity, reproductive toxicity, local tolerance and phototoxicity studies. No juvenile toxicity studies were conducted by the Applicant as neratinib is intended only for the treatment of adults. All pivotal studies are stated to be conducted according to Good Laboratory Practice (GLP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Table 2 Overview of primary pharmacodynamic studies with neratinib

Overview			Test Article: Neratinib maleate	
Type of Study	**Test System**	**Method of Admin**	**Testing Facility**	**Study Number**
Primary Pharmacodynamics				
Inhibition of ERBB2 and EGFR kinases	Purified enzyme preparations	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Kinase inhibition panel	Purified enzyme preparations	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Cell proliferation assay panel	3T3, 3T3/neu, A431, SK-BR-3, BT-474, MDA-MB-435, and SW620 cell lines	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Receptor phosphorylation assays (cell lines)	BT-474 and A431 cells	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Irreversible binding to ERBB2	BT-474 and A431 cells	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Effects on ERBB2 mediated signal transduction	Purified enzyme preparations	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Effects on cell cycle progression	BT-474 and A431 cells	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Receptor phosphorylation assays (human breast cancer tumor xenografts)	Nude mice bearing BT-474 tumor xenografts	Oral	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272

Pharmacology Overview (Continued)			Test Article: Neratinib maleate	
Type of Study	**Test System**	**Method of Admin**	**Testing Facility**	**Study Number**
Efficacy in xenograft models	Female athymic nude mice (nu/nu) bearing tumors (3T3/neu, BT-474, SK-OV-3, A431, MCF7, MX-1)	Oral	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49430

Primary pharmacology studies have been performed *in vitro* and *in vivo* and demonstrated that neratinib is a potent tyrosine kinase inhibitor of 3 epidermal growth factor receptors EGFR, ERBB2, and ERBB4. *In vitro* studies, including autophosphorylation assays confirmed the specificity of this

inhibition demonstrating that neratinib is a highly selective inhibitor of the ERBB kinases. Neratinib preferentially inhibits proliferation of cells expressing ERBB2 and EGFR. This was demonstrated in a variety of cell lines. Neratinib blocks the function of the ERBB receptor in ERBB2- and EGFR-overexpressing cells through decreased ligand-independent ERBB2 phosphorylation. Neratinib affects downstream signal transduction by ERBB2 and EGFR and blocks cell cycle progression in those cells. Neratinib inhibited the growth of high or moderately ERBB2- and EGFR-dependent tumor xenograft models. *In vitro* study RTP-49272 and in vivo study RTP-49430 were also conducted with tumour cell lines that are low expressers of ERBB2 and EGFR confirming the specificity of neratinib. As a result, neratinib may be considered to be specific for ERBB2 overexpressing tumours. ERBB4 has also been identified to have anti-proliferative activity (Chuu *et al*, 2008). However, other reports suggest ERBB4 may also function as an oncogene.The pharmacological effects on the human metabolites M3, M6, M7 and M11 were determined. Although M10 was also identified as a human metabolite, the low exposures observed in man justified the absence of further evaluation. When compared to neratinib, the M6 metabolite inhibited the activity of all ERBB2, EGFR and ERBB4 kinases. On the basis of this finding, the Applicant conducted further studies to characterise the pharmacological profile of M6. In vitro, M6 inhibited the proliferation of tumour cell lines which overexpressed ERBB2 (IC50 3 to 40 nM) and EGFR (A431 cell line; IC50 69nM). However, no significant effects on tumour growth were evident following treatment of mice bearing 3T3/neu or BT-474 xenografts with up to 100 mg/kg/day of M6.

Given that the observed inhibition of ERBB2 kinase was substantially less pronounced with M7 and M11 (330 nM and 560 nM, respectively when compared to neratinib (17 nM), the absence of further pharmacological characterisation of these metabolites is accepted. The Applicant provided as rationale for not providing additional pharmacology data on M3 that neratinib provides the majority pf the pharmacological activity.

Secondary pharmacodynamic studies

Table 3 Overview of secondary pharmacodynamic studies with neratinib

Pharmacology Overview (Continued)			Test Article: Neratinib maleate	
Secondary Pharmacodynamics				
Receptor screen (side effect profile)	NovaScreen® receptor binding	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49659
Effect on cystic fibrosis transmembrane conductance regulator	HEK-293 cells transfected with hCFTR	*in vitro*	Eurofins Pharma Bioanalytical Services, St. Charles, MO	PUM061715-1
Melanin binding	Melanin, bovine serum albumin, IgG	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-49272
Kinase inhibition (metabolites)	Purified enzyme preparations	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-54307
Cell proliferation assay panel (metabolites)	3T3, 3T3/neu, A431, SK-BR-3, BT-474, and SW620 cell lines	*in vitro*	Oncology Research, Wyeth Research, Pearl River, NY	RPT-54307

Pharmacology Overview (Continued)			Test Article: Neratinib maleate	
Type of Study	**Test System**	**Method of Admin**	**Testing Facility**	**Study Number**
Efficacy in allograft model (metabolites)	Female athymic nude mice (nu/nu) bearing 3T3/neu tumors or BT-474 tumors	Oral	Oncology Research, Wyeth Research, Pearl River, NY	RPT-54307
Binding, enzyme and uptake, and cellular and nuclear receptor functional assay panels Compound binding was calculated as a % inhibition of the binding of a radioactively labeled ligand specific for each target.	M3 and M7 metabolites of neratinib	*in vitro*	Eurofins Cerep Celle l'Evescault France	100025180
Binding, enzyme and uptake, and cellular and nuclear receptor functional assay panels Compound binding was calculated as a % inhibition of the binding of a radioactively labeled ligand specific for each target.	M6 and M11 metabolites of neratinib	*in vitro*	Eurofins Cerep Celle l'Evescault France	100026477
Binding, enzyme and uptake, and cellular and nuclear receptor functional assay panels with compounds tested at several concentrations for IC_{50} or EC_{50} determination.	M3, M6, M7, and M11 metabolites of neratinib	*in vitro*	Eurofins Cerep Celle l'Evescault France	100027486
Neratinib maleate was tested at several concentrations in binding assays to determine the IC_{50} or EC_{50}.	neratinib	*in vitro*	Eurofins Cerep Celle l'Evescault France	100023347
M3, M7, and M11 metabolites of neratinib were tested at several concentrations in binding assays to determine the IC_{50} or EC_{50}.	M3, M7, and M11 metabolites of neratinib	*in vitro*	Eurofins Cerep Celle l'Evescault France	100023348

The potential for neratinib to interact with secondary targets including neurotransmitters, ion channels, prostaglandins, growth factors, steroids, second messengers, peptides, and various enzymes was investigated. At the highest dose tested (10 µM), significant inhibition was detected at the following receptors: adrenergic alpha 1, histamine H2, histamine H3, muscarinic M1, muscarinic M2, calcium channel type L, sodium site 2, nitric oxide synthase neuronal-binding, oxytocin, platelet activating factor, neurokinin NK1, neurokinin NK2, neurokinin NK3, and vasopressin 1. The IC_{50} values ranged from 0.83 µM (for the NK1 receptor) to 31 µM (for the NK3 receptor). Given that the Cmax for neratinib is estimated to be 0.14 µM, the potential for neratinib to interact with any of the secondary targets is low but could not be completely ruled out.

Diarrhoea was the most commonly reported treatment-emergent adverse event (see clinical safety). A study was conducted *in vitro*, to determine whether neratinib affected the cystic fibrosis transmembrane conductance regulator (CFTR), as this target is a major cyclic adenosine monophosphate (cAMP)-regulated Cl- channel activated in diarrhoea. Neratinib had no effect on CFTR Cl^- current. Hence, neratinib induced diarrhoea is not mediated via the CFTR Cl^- channel. There is evidence to suggest that ERBB4 is induced in colonic epithelial cells in the inflamed mucosa of inflammatory bowel disease patients (Bernard *et al,* 2012). Selective activation with the ERBB4 ligand and neuregulin-4 (NRG-4) is said to represent a survival pathway in colon epithelial cells and thus ERBB4 activation could be protective in the colon.

The potential for the human metabolites M3, M6, M7 and M11 to interact with secondary targets revealed IC_{50} values of 0.31 µM (inhibition of src kinase) to 7.3µM (binding to N-type calcium channel) for M6. The clinical exposures to M6 were not expressed in nM and the molecular weight for M6 could not be located at the time of assessment. Nevertheless, based on the cited exposure of 26 ng/mL and the similarity in structure and hence molecular weight of M6 (when compared to neratinib), the potential for interaction of M6 (or the other metabolites at lower clinical exposures) with the secondary targets listed should be relatively low.

Safety pharmacology programme

Table 4 Overview of safety pharmacology studies with neratinib

Pharmacology Overview (Continued)			Test Article: Neratinib maleate	
Type of Study	Test System	Method of Admin	Testing Facility	Study Number
Safety Pharmacology				
hERG assay[b]	HEK293 cells transfected with hERG	*in vitro*	ChanTest, Cleveland, OH	RPT-59094[a]
Respiratory[b]	Rat	Oral	Drug Safety, Wyeth Research, Chazy, NY	RPT-47595[a]
Central nervous system[b]	Rat	Oral	Drug Safety, Wyeth Research, Chazy, NY	RPT-47592[a]
Cardiovascular[b]	Dog	Oral	Bioresources, Wyeth Research, Pearl River, NY	RPT-48164[a]

The potential for neratinib to inhibit the hERG (human ether-a-go-go-related gene) channel current (IK_r, the rapidly activating, delayed rectifier cardiac potassium ion current) was evaluated using an *in vitro* preparation of hERG-transfected HEK293 human embryonic kidney cells. The calculated IC_{50} for the effect of neratinib on hERG potassium ion current was determined to be 1.9 µM (1.3 µg/mL) which was more than 900-fold higher than the proposed free clinical Cmax for the parent compound.

The potential for effects on the central nervous and respiratory systems were evaluated in the male rat. Single doses of up to 100 mg/kg had no effect on the sensory, motor and the behavioural endpoints evaluated. Likewise, no significant effects on the respiratory system deemed to be treatment-related were observed. In a 2-week repeated-dose study in the CD VAF rat, where doses of 100 mg/kg/day were administered, the Cmax was 3818 ± 656 ng/mL which is substantially in excess of the proposed clinical Cmax for neratinib (73.5 ng/mL). Following repeated daily doses of neratinib at 240 mg to healthy subjects, Cmax (mean ± SD, n=20) on Day 7 for metabolite M3 was 15.4 ± 5.53, for M6 was 28.3 ± 8.16 and for M7 was 19.6 ± 12.6 ng/mL. In the rat, at 10 mg/kg, the exposures to M6 and M7 were either similar or exceeded that observed clinically. Thus at the maximum dose evaluated i.e. 100 mg/kg/day, these metabolites should be considered qualified. However at 10 mg/kg, the exposures to M3 were below the limit of quantification. Separate toxicology studies have been conducted with the human metabolite M3. However, the evaluations did not include the relevant central nervous system endpoints.

The potential for effects on the cardiovascular system were evaluated in the dog. Emesis was dose-limiting and hence only 2 animals were treated at the maximum dose of 20 mg/kg. No effects on electrocardiogram (ECG) were noted at this dose. At the lower doses of 5 and 10 mg/kg, no toxicologically significant effects on MAP, heart rate or ECG parameters were noted. Firm conclusions should only be based on the more robust dataset of n=4/group where doses of up to 10 mg/kg were administered. In a separate study in the dog at 6 mg/kg, the exposures to M6 and M7 were essentially similar to that proposed clinically. During the evaluation the Applicant provided additional studies examining the hERG channel inhibition due to metabolites M3, M6 and M7. These new reports indicate similar IC_{50} values to the parent compound and are present to sufficiently high safety margins to be of limited concern. In order to fully evaluate the safety pharmacology endpoints for the metabolite M3, a new set of studies has been conducted to examine effects of this metabolite on the CNS (study 20130868), respiratory (study 6901562) and cardiovascular (study 20130869) systems. Taking into account the final results from the new studies 20130868 and 6901562, the findings observed demonstrate that the metabolite M3 does not raise any safety concern.

Pharmacodynamic drug interactions

No such studies were performed. Considering the specific binding of neratinib, the absence of pharmacodynamic drug interactions studies was considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

In vivo oral (gavage) and intravenous (IV) single and repeat dose pharmacokinetic (PK) studies were performed in the mouse, rat, and dog, the species used in supportive pharmacology and toxicology studies. Tissue distribution studies were performed in the male rat following administration of a single dose using both liquid scintillation counting (LSC) and whole body autoradiography (WBA) methods. Similar studies were conducted in male mice following single and repeat doses of neratinib using the LC/MS/MS method. *In vitro* studies included red blood cell distribution and plasma protein binding studies (rat, dog, and human). Biotransformation and metabolism studies were performed with neratinib using liver microsome preparations from nude mice, rats, dogs, and humans and HepG2 cells transfected with the CYP3A4 promoter. Other pharmacokinetic studies included PK assessment of pyridine N-oxide metabolite (M3) in the rat and *in vitro* covalent binding of neratinib to human serum albumin and human plasma proteins.

Absorption

Single-dose pharmacokinetics of neratinib was characterised in the mouse, rat and dog after oral and intravenous (IV) administration. Repeated-dose studies with neratinib of up to 6 months duration have been conducted in the mouse and rat. Studies of up to 9 months duration were conducted with neratinib in the dog.

In rodents, the PK profile following a single dose was characterised by moderate clearance, a high volume of distribution and a short half-life. In male dogs, clearance was high relative to the liver blood flow. The plasma elimination half-life ($t_{1/2}$) ranged from 1.4 (mouse) to 10.7 (dog) hours in the species evaluated. Neratinib exhibits low to moderate oral bioavailability in mice, rats, and dogs (11 to 39%). The observed low oral bioavailability of neratinib is justified by a strong contribution of neratinib's profound pH-dependent solubility and modest-poor intrinsic permeability.

After oral administration, neratinib was absorbed at a moderate rate, with the time to peak concentration (Tmax) occurring between 2 to 4 hours after dosing in all species.

In short term (10-and 14-day) repeat dose studies, exposure was 2-3 fold greater in females when compared to males rats. In longer term studies (1-6 month) this was more variable. In the rat, exposure increased with increasing doses generally in a dose proportional manner. In the dog, there were no gender-related differences. In the dog, exposure to neratinib increased with dose in both male and female dogs with minimal accumulation (ratios of 2.73 in study of 39 weeks duration). The exposure ratio of the major metabolite in dogs to parent was 24% (males) and 35% (females) for M6 and 20% (males) and 18% (females) for M7.

Exposure to metabolites N-desmethyl neratinib (M6) and neratinib dimethylamine N-oxide (M7) at the no-effect levels within the pivotal toxicology studies in the rat and dog were either similar to or greater than exposure in humans (exposure ratios of 1.3 to 3.4-fold). The metabolite neratinib pyridine N-oxide (M3) was not observed at appreciable levels in rats and dogs; therefore, additional studies were conducted with M3 including a 2-week study in the rat. The potential toxicity of these metabolites has been thoroughly investigated. However, further clarifications with respect to the qualification of these metabolites was sought with respect to the safety pharmacology (see section 2.3.2 Pharmacology above) and genotoxicity aspects (see section 2.3.4 Toxicology below).

Distribution

Neratinib was highly bound to plasma proteins and this binding was independent of concentration in male mouse, rat, rabbit, and dog plasma. Because of instability issues in human plasma, the binding of neratinib to plasma proteins in human plasma was determined indirectly in solutions of the main drug-binding proteins in plasma, HSA and AAG, at 37°C for up to 3 hours. Neratinib was highly bound to HSA (99.1%) and AAG (98.5%) when incubated with these plasma proteins in solution at physiological concentrations and binding was independent of neratinib concentration. Based on the binding of neratinib to HSA, the major plasma protein, the *in vitro* binding of neratinib in human plasma was estimated to be greater than 99%.

The distribution of [14C]neratinib-derived radioactivity to tissues was evaluated in the rat and monitored after a single oral administration of [14C]neratinib (10 mg/kg). The time to peak concentration of radioactivity in whole blood and plasma was 4 hours in both albino and pigmented rats. In albino rats; tissue Tmax was achieved at 1 to 8 hours post-dose. Tissue-to-plasma AUC ratios were greater than 10 for the small intestine and large intestine (indicative of elimination route and possibly toxicity profile) along with the adrenal gland, renal cortex, liver (identified target organ) and pituitary gland.

In the albino rat, with the exception of the skin, the levels of drug-related radioactivity were below the limit of quantification by 720 hours post-dose and the brain and eye were below the quantification limit at all time-points. In both albino and the Long-Evans rat, drug-related radioactivity was well distributed to the skin (which suggests that the presence in skin is not solely due to binding with melanin). The rate of elimination from the skin was slow in the albino rat, but even slower in the pigmented rat. The uptake of drug-related material to the uveal tract was extensive in the Long Evans rat and was slowly eliminated over a 26-week (4320-hour) period. These findings therefore demonstrate a high affinity the skin and uveal tract.

In the 28-day and 39-week toxicity studies with neratinib, in pigmented (beagle) dogs, ophthalmoscopic examination (including the uveal tract) and microscopic examination of the eyes revealed no neratinib-related changes in the eye. Similarly, results of a phototoxicity study in rats revealed no findings indicative of skin or ocular phototoxicity. Covalent binding most likely contributes to the observed retention by the skin and uveal tract and it is evident that that the extent of covalent binding is more pronounced in the monkey and human than it is for the rat and dog, the primary toxicological species used.

Following single and multiple oral (gavage) administration of neratinib in mice, the 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 into the brain. Data provided from study 3144A-3005 (NEfERT-T) suggested that neratinib may have clinically meaningful activity in the treatment of brain metastases when used in the extended adjuvant setting. In view of the presently claimed indication, the issue of poor brain penetration and its clinical consequences is not discussed further.

Metabolism

Following incubation of liver microsomes from mouse, rat, dog, and humans with neratinib, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and uridine diphosphate glucuronic acid (UDPGA), the predominant metabolites observed were M6 and M7. No glucuronide conjugates were detected. Incubation with glutathione produced the glutathione conjugate of neratinib M5. Overall, the metabolic profiles for all species were similar, except that microsomes from the dog produced more of the N-oxide metabolite but did not generate the more polar metabolites.

CYP3A4 and flavin-containing monooxygenase (FMO) are involved in the Phase I metabolism of neratinib, with CYP3A4 forming O-desmethyl pyridine metabolite (M2), pyridine N-oxide (M3), N-desmethyl (M6), and small amounts of dimethylamine N-oxide (M7). The FMO formed the majority of the N-oxide metabolite.

In vivo, neratinib was not extensively metabolised in the rat or the dog. The parent drug was the major circulating entity in both species, and the major route of excretion was via faeces, where the parent compound was the major compound observed. N-demethylation and glutathione conjugation occurred in both species, while N-oxidation was only observed in the dog.

Following a single IV administration of neratinib to bile duct-cannulated monkeys, bile was the major excretion route for neratinib and its metabolites. Neratinib, neratinib pyridine N-oxide (M3), and N-desmethyl neratinib N-oxide (M13) were the major peaks observed in bile samples, representing up to 45.9%, 18.1%, and 14.0% of the radioactivity, respectively.

Excretion

After single oral administration of [14C]neratinib to male rats, beagle dogs and *Cynomolgus* monkeys, the primary route of excretion of radioactivity was via the faeces. In rats, mean recovery of radioactivity in urine and faeces after 5 days was 1.6% and 90.7%, respectively. Corresponding values were 0.80% (urine) and 66.2% (faeces) after 7 days in dogs and 0.34% (urine) and 71.6% (faeces) after 14 days in monkeys. Likewise, in healthy male human subjects, after oral administration of a single 200 mg dose of [14C]neratinib (100 nCi), faecal excretion was the major route of elimination of radioactivity. Mean recovery of radioactivity in urine and faeces was 1.1% and 97.1%, respectively, with a mean total recovery of radioactivity of 98.2% after 9 days. Excretion of radioactivity was rapid with the majority (61%) of the dose recovered within 96 hours after oral dose.

2.3.4. Toxicology

Single dose toxicity

Single-dose GLP acute toxicity studies were conducted by the oral (gavage) and intraperitoneal (IP) routes in rats and mice.

Table 5 Single dose toxicity studies with neratinib

Study ID	Species/ Sex/Number/Group	Dose (mg/kg)/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
RPT-48221 GLP	Mouse/ 3M:3F/Group	0, 200, 2000 – oral	>2000/2000	None
RPT-48223 GLP	Mouse 3M:3F/Group	0, 200, 700, 2000 - IP	700/200	Mortality at 2000 & 700 mg/kg. 200 mg/kg: Soft faeces. No weight loss or macroscopic findings.
RPT-48224 GLP	Rat 3M:3F/Group	0, 200, 700, 2000 - oral	2000/700	2000 mg/kg: animals euthanized with changes to adrenals, GI tract, spleen, thymus, pancreas, kidneys, liver, and ovaries. Hepatic necrosis in 1/3 females. 700 mg/kg: no evidence of macroscopic changes.

RPT-48225 GLP	Rat 3M:3F/Group	0, 200, 700, 2000 - IP	700/200	Mortality at 2000 & 700 mg/kg, with changes to adrenal gland, GI tract, and kidney. Renal tubular ectasia at 2000 mg/kg. <u>200 mg/kg:</u> enlarged liver, fibrosis of stomach, small/large intestine, spleen, pancreas.

In mice, no adverse effects were seen in doses of neratinib up to 2000 mg/kg. Single intraperitoneal dosing at 2000 and 700 mg/kg caused death, significant changes were noted as ptosis, soft faeces, mucoid faeces, decreased faeces, dehydration, coolness to the touch, decreased motor activity (grade 1), low carriage, paleness, and tremors. Kidneys changes were significant in the mid and high doses.

In rats, following oral dosing, mortality was noted in animals treated with 2000 mg/kg, accompanied by changes to the gastrointestinal tract, spleen, thymus, pancreas, kidney, liver and ovaries. Following intraperitoneal dosing, death occurred at doses of 700 mg/kg and above with significant effects to adrenals, and stomach, and findings of slight to moderate tubular ectasia in the kidney of all males and one female treated with 2000 mg/kg neratinib.

Repeat dose toxicity

Neratinib has undergone extensive examination in toxicological studies in rats and dogs treated orally for up to 6 months (rats) and up to 9 months (dogs) in duration. In addition a number of studies were completed in both rats and dogs using the intravenous route for up to 28 days utilising twice weekly dosing.

Treatment with neratinib has drawn up a number of toxicological findings ranging featuring increased mortality associated with hepatotoxicity and gastrointestinal changes, to findings of weight loss, skin toxicity, faecal changes, reproductive organ atrophy and changes in haematology and biochemical chemistry parameters. Other drugs known to inhibit EGFR and/ or ERBB2 have shown signs of toxicity to liver and lungs, as well as the skin. Neratinib was tolerated in rats for up to 6 months with a NOAEL of 10 mg/kg/day. In dogs, neratinib was tolerated for up to 9 months, and although findings related to faecal disturbance were found the NOAEL for dogs is suggested as 6 mg/kg/day.

During examination of covalent binding to human serum albumin, neratinib was shown to bind through α, β unsaturated amide binding to the ε amino group of Lysine190 via a protein-enhanced Michael addition. This binding was species dependent and occurred in human serum albumin and not in rat serum albumin. In study RPT-79001 it was demonstrated that covalent binding is higher in monkey and human than dogs, rats, and mice. Approximately 100%, 94%, 89%, 29%, and 38% of total radioactivity were recoverable from mouse, rat, dog, monkey, and human plasma, respectively, suggesting that binding occurred mainly in primates. The results of the *in vitro* covalent binding study (study RPT-79001) do not conclusively reveal definitive results of tissue binding. Binding to dog plasma with neratinib occurs at a slower rate than observed with human or monkey plasma, however there is adduct formation that does not eliminate the dog as a species of choice for the general toxicity studies.

Mortality

Neratinib treatment resulted in deaths in rats treated with oral doses ≥30 mg/kg/day and IV doses of 25 mg/kg. These deaths were attributed to gastrointestinal toxicity such as ulceration, mixed cell inflammation, soft/liquid faeces and atrophy of spleen and thymus. In the earlier 14 days study, rats treated with 100 mg/kg/day neratinib in addition to the above effects suffered bile duct hyperplasia reproductive organ and skin atrophy. Male rats experienced decreased motor activity, ataxia, and pale appearance shortly after receiving 25 mg/kg neratinib IV before death.

Dogs treated orally with up to 9 mg/kg/day showed increased toxicity, however there were no cases of neratinib-related death. 1 male dog in the 39-week study treated with 2 mg/kg/day died due to cardiopulmonary thromboembolism, secondary to spontaneous renal membranous glomerulonephritis, however this was a single event and considered not dose-related. Three other dogs in the same dose group showed limited similar signs of toxicity so the signal is weak. In the IV treated dogs, death occurred at 9 mg/kg and as a result both male and female animals were euthanised due to neratinib-related toxicity, crackling in the lung, decreased motor activity, salivation, emesis and decreased or no faeces.

Skin effects

Rats were more adversely affected by skin toxic reactions. Focal lesions around the mouth and nose were apparent in doses ≥30 mg/kg/day, animals also experienced abrasions, alopecia and red pigmentation were seen around the mouth, nose and eye areas. No notable skin effects were observed in the dog.

The presence of skin lesions has previously been associated with other EGFR inhibitors and the consequence of exaggerated pharmacology may result in the adverse skin reaction seen in the rat. It is noted that in the animal distribution studies there was migration of neratinib to the skin and to other melanin containing tissues (eye), although no ocular changes were noted in the general toxicity studies and neratinib was negative for phototoxicity in a Long Evans rat study.

Gastrointestinal effects

The gastrointestinal tract was identified as one of the target organs of toxicity with neratinib. Both rats and dogs experienced gastrointestinal changes, although this was also seen in the mouse in earlier studies completed with neratinib. The adverse effects presented mainly as soft, liquid faeces and in some cases absence of faeces. Emesis was also seen in dogs. The faecal alterations were normally associated with mucosal/villous atrophy, inflammation, and with erosions/ulcers in the intestine and the stomach. In rats this was observed in doses ≥15 mg/kg/day, and in dogs this was at ≥6 mg/kg/day. Severity of adverse effects was more pronounced in the rat. However this could be related to lower tolerable doses in the dog.

Gastrointestinal toxicity has been observed with neratinib treatment and may be a result of an effect on epidermal cell growth.

Liver and haematological changes

Changes to clinical chemistry and haematological parameters were observed in both rats and dogs following both oral and intravenous neratinib. The main clinical chemistry changes were of increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and signs of hepatic inflammation and necrosis. There were moderate increases in fibrinogen, white blood cells (WBC), neutrophils, lymphocytes, and monocytes, and decreases in cholesterol, total protein and albumin.

Other findings

High doses in the earlier dose-range finding studies in rats showed evidence of reproductive organ toxicity, prostatic and uterine atrophy leading to reduced prostate and uterus weights. In addition male rats experienced mammary gland atrophy (neratinib doses of ≥15 mg/kg/day). These findings were observed in early dose-range finding studies however were absent from the definitive chronic rat studies and also absent from the reproductive toxicity studies.

Bone changes were limited to findings of slight to mild physeal thickening of the tibia in rats (12 male and 6 female) treated with 15 and 45 mg/kg/day, although this finding is somewhat confounded and may simply be due to animal growth.

Genotoxicity

The Applicant has completed a full battery of *in vitro* and *in vivo* genotoxicity studies with neratinib. Neratinib was negative in the battery of genotoxicity tests, including *in vitro* bacterial reverse mutation (Ames) and a chromosome aberration assay using human peripheral blood lymphocytes (PBLs) cells and an *in vivo* mouse bone marrow micronucleus assay.

In addition a number of standard genotoxicity studies were conducted with neratinib metabolites M3 and M6. Metabolites M3, M6, M7, M10 and M11 were examined for genotoxicity using *in silico* studies. These were negative for structural alerts for mutagenic or carcinogenic potential. A number of *in vitro* and *in vivo* studies have also been conducted to qualify a number of neratinib process impurities.

Carcinogenicity

Two studies have been conducted to examine the potential carcinogenicity of neratinib: a transgenic mouse TgRAS.H2 study and a 2-year carcinogenicity study in the rat.

Results from the 26-week transgenic mouse study have not identified evidence of neoplastic or non-neoplastic changes in the treated mice. There was evidence of increased incidence of hemangiosarcoma in male animals. These cases were reviewed by the Applicant and pathologists and considered unlikely to be due to neratinib treatment. The incidence was not significant compared with the one observed in the control groups.

The final results of the 2-year carcinogenicity study in rats examined the effects of oral neratinib treatment in male and female SD rats at doses of 1, 3 and 10 mg/kg/day. There were no significant changes observed in the treated animals over the control groups for the extent of mortality, survival or clinical signs. Some changes in body weight and body weight gain were observed, more predominantly seen in the high dose group (10 mg/kg/day). In terms of gross pathological changes, there were no significant differences between control and treatment groups for male rats. In female rats there were higher incidences of pituitary gland adenomas in the 3 mg/kg/day group, higher than vehicle control but consistent with levels in the water control group. Adrenal glands were also observed to be dark, pale or focused in females treated with 10 mg/kg/day neratinib. Overall it can be concluded that the changes observed between treatment and control population were of limited significance for increased carcinogenic potential. The pituitary and adrenal glands appear to be a target following extended exposure to neratinib. However there is no clear differentiation between treated and control animals to trigger a potential signal for carcinogenicity.

Reproduction Toxicity

Two GLP studies have been completed to evaluate the potential of neratinib to affect male and female fertility. In the definitive rat fertility and early embryonic development study, rats were dosed orally with neratinib at 3, 6, and 12 mg/kg/day. There were no significant effects observed in terms of male fertility endpoints: sperm motility, density or morphology, or to male reproductive organs. In females, no effects were detected in oestrous cycling or on mating and embryo survival. The NOAEL was determined to be 12 mg/kg/day. Based on exposure established in the rat 26 week general toxicity study, where a NOAEL of 10 mg/kg/day gave a safety margin of 29-fold based on exposure, the fertility NOAEL provides for a sufficient margin for expected human doses (>29-fold). A statement has been proposed to section 4.6 of the SmPC to reflect that no significant changes in fertility parameters in male and female rats were detected in dosing up to 12 mg/kg/day.

Neratinib has been studied in embryo-foetal developmental oral toxicity studies in both rats and rabbits. In the definitive studies, pregnant rats were administered up to 15 mg/kg/day from gestation day 7 to 17 (GD7 to GD17), and pregnant rabbits were administered up to 9 mg/kg/day from GD7 to GD19.

In rats, no changes in embryo-foetal viability were detected and there was no evidence of teratogenicity in exposed foetuses. Adverse finding in dams treated with 15 mg/kg/day constituted as reductions in mean body weight, with no effect on litter number, early deliveries, or abortion. In the dose range-finding study, rats experienced poor conditioning in the high dose group (45 mg/kg/day), experiencing reduced body weight, food consumption, increased embryo-foetal loss, loose and discoloured faeces, with red pigment around mouse, nose and genitalia. 1 death occurred in 10 mg/kg/day toxicokinetic group although this was attributed to the blood collection procedure so cannot be considered treatment-related. The only change of note experienced in 1 pup from the 15 mg/kg/day group was of a soft tissue abnormality, situs inversus, although this was in line with historical control incidence so this is unlikely to be a treatment-related finding. The NOAEL for maternal toxicity is 10 mg/kg/day, corresponding to a C_{max} of 505 ng/mL and AUC of 5150 ng·h/mL. The NOAEL for foetal toxicity is 15 mg/kg/day, corresponding to a C_{max} of 786 ng/mL and AUC of 8550 ng·h/mL (9.1-fold anticipated clinical exposure, based on 240 mg/day, AUC 939 ng·h/mL).

In rabbits, adverse effects with neratinib were more apparent than with rats although this is generally expected. In the dose-range finding study there were two deaths, 1 animal from the control group and 1 given neratinib 6 mg/kg/day, found dead on GD 17 and 29, respectively. Both females displayed clinical signs of loose, mucoid faeces, and there was no mortality in the high dose treated rabbits (20 mg/kg/day) so a neratinib treatment effect is unlikely. In the 20 mg/kg/day group pregnant rabbits experienced increased embryo-foetal loss (28.9 to 31.8%), two females were electively euthanised following abortion on GD22, and another female had an interruption of pregnancy at the time of euthanasia. The foetal loss is attributed to neratinib. In addition dams experienced loss of body weight and reduced food consumption and gravid uterine weights. Reductions in body weight and embryo-foetal viability were noted in the 6 mg/kg/day treatment group. Foetal changes were notable in the 20 mg/kg/day group, 10 foetuses experienced flexure/rotation anomalies, 3 foetuses from 1 litter displayed anasarca (generalised oedema) and 3 foetuses from another litter had abdominal discolouration and distention. In the 6 mg/kg/day group 1 foetus displayed a flexure/rotation anomaly which given the findings seen in the higher dose this can be considered to be a treatment related effect.

In the rabbit study there were four unscheduled deaths/abortions associated with neratinib treatment, three were observed in the high dose level of 9 mg/kg/day and one at 6 mg/kg/day, these occurred between GD19 and GD19. These neratinib-treated rabbits presented with thin appearance and reduced body weight and food consumption. Pregnant rabbits in the high dose level experienced much of the effects seen in the earlier dose-range finding study, namely reduced body weight and food consumption, loose/liquid faeces and red staining to fur and increased embryo-foetal loss. Effects were reduced in the 6 mg/kg/day, and these findings were absent at the low dose of 3 mg/kg/day.

In offspring, at a dose of 9 mg/kg/day in addition to the earlier mentioned abortion cases, there was one incident of domed head, one case of dilation of the lateral ventricles of the brain and a ventricular septal defect, low levels of incidence of misshapen anterior fontanelles, as well as moderate enlargement of the anterior and/or posterior fontanelles. In the mid-dose level of 6 mg/kg/day there were no indications of foetal malformations however due to one case of abortion and reduced embryo-foetal viability this cannot be considered to be a NOAEL. The NOAEL for maternal and foetal toxicity is agreed to be 3 mg/kg/day, corresponding to a C_{max} of 50.4 ng/mL and AUC of 162 ng·h/mL (0.17-fold

of anticipated clinical exposure). This represents lower exposure than to be expected in humans and identifies the potential for embryotoxic effects during pregnancy.

There was no evidence of teratogenicity in rats, however embryotoxic and potentially malformative changes were seen in exposed foetuses in rabbits treated with neratinib exposures considered to be lower than that expected in humans. As the effects in offspring are present at doses close to those seen for the mother, this clearly demonstrates that there are treatment-related effects during pregnancy.

The pre- and post-natal development study has been completed in female pregnant rats administered 5, 10 or 15 mg/kg/day neratinib over gestation day 7 through to day 20 of lactation. Reduction in weight and food consumption was observed in F0 generation at 10 and 15 mg/kg/day groups. However this had limited effects on development and growth to the F1 generation offspring. There was no clear evidence of adverse effects to pups in terms of mortality, sexual maturation or ability to mate. It is noted that some changes were observed for number and development of male pups. There was a significant reduction in numbers of male pups in the 5 and 10 mg/kg/day groups compared to controls. In addition male F1 generation pups from all dose groups demonstrated decrease latency to trial, although this is unlikely to be due to any developmental effect due to neratinib.

Toxicokinetic data

Toxicokinetic data has been obtained from completed repeat-dose toxicity studies in mice, rats and dogs, and measurements were provided in 28 day studies, and from the pivotal 26 week (rat) and 39 week (dog) studies. Exposure was generally similar across sexes with the notable exception of the 26 week rat study where exposure was more than twice in female rats than males at doses of 10 and 30 mg/kg/day, and in the 39 week dog study where exposure in male dogs was 1.5 times that seen in females. There was little evidence of dose accumulation. Exposure to neratinib in male rats was consistently below that seen with females, and this is not reflected in terms of increased adverse findings in males. The observed differences in exposure as potentially due to increased sensitivity in male rats over females or that these effects were mediated more at a local level than through simply exposure levels.

In rats, the NOAEL following 6 months dosing was 10 mg/kg/day, AUC at this dose level was 27100 ng.hr/mL (combined), giving a human safety margin of 28.86. In dogs the NOAEL following 9 months dosing was 6 mg/kg/day, AUC at this dose level was 722.5 ng.hr/mL (combined), giving a human safety margin of 0.77. There is little to no clinical safety margin for the adverse gastrointestinal and liver toxicity findings observed in the dog. Exposure data from the completed rat embryo-fatal development study gives a safety margin of 9.118 for foetal effects at the proposed maximum daily dose of 240 mg dose level. In rabbits the safety margin is 0.17, and results in clinically relevant concerns for embryo-toxicity and potential teratogenicity (see section above on Reproductive toxicity).

Local Tolerance

Local tolerance has been investigated as part of the general toxicity studies, as described above. Two dedicated studies were conducted in rabbits to investigate the effects of neratinib on dermal or ocular exposure. In the dermal study, rabbits were exposed to 0.5 g of neratinib in a dermal formulation for a period of 4 hours. There was some evidence of dermal irritation (Grade 1 and 2, erythema) within 1 hour of administration, however this resolved within 48 hours. Yellow staining of skin also was noted but also recovered. In the ocular study, rabbit eyes were exposed to up to 0.1 g of neratinib for 7

days. Immediate irritation such as redness and discharge was observed within an hour but resolved within 2 days. A single incident of conjunctival oedema was considered to be isolated.

Other toxicity studies

Phototoxicity

Neratinib was negative for skin and ocular reactions in an *in vivo* phototoxicity study. Skin reaction such as erythematous rash is noted in humans, likely related to treatment and has been observed in other EGFR inhibitors previously, however evidence of potential phototoxicity has not been observed.

Metabolites

A number of genotoxicity studies have been completed with the metabolites of neratinib. *In vitro* Ames and chromosome aberration studies in human PBLs have been completed with metabolites M3, M6, M7 and M11. In addition an *in silco* screen in accordance with ICH M7 'guideline on the assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk' was conducted with these four metabolites, plus a fifth metabolite, hydroxyl neratinib N-oxide (M10). The *in silico* examination was negative for potential genotoxicity of all five human metabolites. Metabolite M3 was tested in two Ames studies, the initial test was positive (batch of M3 with 2.56% impurities), a subsequent study was negative when tested with a purer batch (batch with 0.67% impurities). An *in vitro* chromosome aberration study in PBLs was negative, and an *in vivo* intravenous toxicity study in the rat demonstrated tolerability of the metabolite of levels well in excess of that expected clinically. The standard screen for genotoxicity as detailed in ICH S2 'guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use' recommends that the *in vivo* study test for chromosomal damage using rodent hematopoietic cells, either for micronuclei or for chromosomal aberrations in metaphase cells. Negative results of a micronucleus genotoxicity assay study for M3. Metabolites M6, M7 and M11 were confirmed to be non-genotoxic from completed *in vitro* genotoxicity tests. *In vivo* examination of metabolites M6 and M7 will not be conducted. This was adequately addressed in the micronucleus study with the parent compound (study RPT-48593) and therefore M6 and M7 are considered adequately reviewed and concluded to be non-mutagenic at doses up to 2000 mg/kg in mice. The *in vitro* mutagenicity studies were negative for each of M6, M7 and M11 metabolites, so the findings related to the parent at such a high dose can be taken on board. The omission of genotoxicity studies with metabolite hydroxyl neratinib N-oxide (M10) were justified as levels detected in human plasma were very low and are not expected pose a risk for safety.

Impurities

Various drug substance impurities were qualified using limits established from toxicological *in vitro* and *in vivo* studies conducted with batches of neratinib. The following impurities; 3638, 3570, 3495, 3641, 3578, 3963, and 3636 were present at low concentrations in one or more of the API batches tested. Each impurity has been tested at least using *in vitro* Ames, and several were also examined using human PBL chromosome aberration study and qualified in a 14 day intravenous toxicity study in rats. All but two can be considered to be non-genotoxic: impurity 3641 is not present in the final drug substance and impurity 3963 is present at levels below the threshold of toxicological concerns (TTC). Further clarifications of the levels of potential genotoxic impurities involved in the drug substance manufacture were requested as part of the quality assessment (see section 2.2.2 Active substance above). Two impurities in the drug substance are specified and exceed qualification limits. Impurities 3638 and 3570 have been qualified to levels of 5.86% and 0.94%, respectively. A number of residual solvents have been highlighted, 1-Propanol, and Toluene, and adequate justification for their limits

have been provided. In the specification for the drug product, the only specified impurity is 3638, which is below the qualified level of 5.86% (NMT 1.5%). Excipients in the final drug product have been characterised and no concerns are raised over their use in this drug product.

Other toxicity studies

Two additional supportive studies were submitted, one to examine the gastrointestinal effects of using an immediate release tablet compared to a delayed release capsule of neratinib, and the other to explore the effects of neratinib from a gene expression level. There is limited evidence to suggest neratinib to be more susceptible to causing gastrointestinal effects when administered as an immediate release formulation. The results from the gene expression profiling study indicated that treatment with neratinib elicits an intestinal tract immune response related to inflammatory processes.

2.3.5. Ecotoxicity / environmental risk assessment

Table 6 Summary of main study results

Substance (INN / Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD107	Log Pow at pH 6 = 2.98 ± 0.02 Log Pow at pH 8 = 4.41 ± 0.07			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	N/A see above			B/not B
	BCF	N/A			B/not B
Persistence	DT50 or ready biodegradability	N/A			P/not P
Toxicity	NOEC or CMR	4.8 µg/L (≤10 µg/L) in green algae			Potential T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.024	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption **Non-conducted**					List all values
Ready Biodegradability Test **Non-conducted**					
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 1.3 days $DT_{90\ water}$ = 6.1 and 6.5 days $DT_{50, sediment}$ = 45% $DT_{50, whole\ system}$ = Not defined % shifting to sediment = Not defined			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	4.8	µg/L	Species: *Pseudokirchneriella Subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	510	µg/L	Species: *Daphnia*

					magna
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	29	µg/L	Species: Fathead Minnow
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	1000	mg/L	
Biodegradation in Sludge	OEDC 314B	DT_{50}	402.8	h	not readily biodegrade in the presence of sludge
Adsorption coefficient (Log Koc)	OECD 121	Log(Koc ads)	silty clay loam sediment :4.99 Sand: 5.58 L kg^{-1} Sludge: 4 .17	L/kg	Log adsorption coefficient >4.5 very strong sorption to soil and sediment
Phase IIb Studies					
Bioaccumulation **Not conducted**	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil **Not conducted**	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test **Not conducted**	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth **Not conducted**	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests **Not conducted**	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test **Not conducted**	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism	OECD Guideline 218	NOEC	25	mg/kg	species *Chironomus riparius*

Phase 1

As the log Pow was found to be below 4.5 at pH 8 (and below 3 for pH 6) an evaluation of persistence, bioaccumulation and toxicity (PBT) in Phase II testing was not considered necessary.

Predicted Environmental Concentration (PEC)

$PEC_{SURFACEWATER}$: = 1.2 µg/L

The calculated $PEC_{SURFACEWATER}$ exceeded the 0.01 µg/L (equivalent to 0.00001 mg/L) limit outlined in the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) and so further testing and analysis was conducted (Phase II tier A testing).

Phase II Tier A

Outcome of Phase II, Tier A Fate and Effects Analysis – PEC/PNEC Ratios

$PEC_{SURFACEWATER}/PNEC_{SURFACEWATER}$ = 0.012 µg/L / 0.48 µg/L
= 0.025

$PEC_{GROUNDWATER}/PNEC_{GROUNDWATER}$ = 0.003 µg/L / 51 µg/L
= 5.88×10^{-5}

$PEC_{SURFACEWATER}/PNEC_{MICROORGANISMS}$ = 0.012 µg/L / 100 mg = 1.2×10^{-4}

The PEC/PNEC ratios with respect to surface water, groundwater and microorganisms are all substantially less than one. Based on these data, the impact of the introduction of this active drug substance is considered to be low based on the available data.

Phase II Tier B

A study was conducted to determine the effects of sediment-incorporated test substance. The measured endpoints of the test were total number of emerged adult midges, and the development time. Groups of midges (first instar chironomid larvae) were exposed to a series of five nominal test concentrations in sediment (2.5, 5.0, 10, 20 and 40 mg/Kg, dry weight) a negative control, and a solvent control for 28 days under static test conditions. Four replicate test chambers were maintained in each treatment and control group, with 20 midges in each test chamber, for a total of 80 midges per test concentration. Adults that emerged appeared normal. The LC_{50} value, based on mortality of midges exposed to sediment-incorporated neratinib maleate, was >25 mg/Kg, the highest concentration tested. Therefore, the NOEC for development time was determined to be 25 mg/Kg, and the LOEC for development time was determined to be >25 mg/Kg.

The submitted ERA is considered incomplete as OECD study 106 (batch equilibrium method) is missing. In addition, if the adsorption/desorption data indicates the affinity for the drug substance to bind to sewage sludge in the STP (KOC > 10 000 L/kg) an environmental assessment of the drug substance in the terrestrial compartment should have been conducted, unless the substance is readily biodegradable (which was not shown to be the case in OECD study 308). Terrestrial fate and effects studies (OECD 307, 216, 208, 207 and ISO 11267) should have been conducted. Furthermore OECD 123, 106 and 218 studies should also have been conducted. The following statement is being proposed in section 6.6 of the SmPC 'Any unused medicinal product or waste material should be disposed of in accordance with local requirements.' considering that the ERA is currently incomplete.

2.3.6. Discussion on non-clinical aspects

Neratinib is a highly selective inhibitor of the EGFR, ERBB2 and ERBB4 kinases. It has been shown to bind irreversibly to EGFR and ERBB2 and blocks the function of the ERBB2/EGFR receptor in ERBB2- and EGFR-overexpressing cells. Neratinib treatment of tumour cells which overexpress ERBB2 or EGFR inhibits cell proliferation in cells overexpressing ERBB2 and induces cell cycle arrest. ERBB4 has also been identified to have anti-proliferative activity (Chuu *et al*, 2008). However, other reports suggest ERBB4 may also function as an oncogene.

It is noted that in one of the studies which aimed to demonstrate a lack of anti-tumour effect where expression of EGFR or ERBB2 was low, the maximum doses of neratinib (20 mg/kg) utilised was lower than that used for all of the other *in vivo* studies conducted. Although it would have been preferred to see the effects of 40 mg/kg evaluated (the dose often associated with maximum tumour growth inhibition) to fully establish the possibility whether tumour growth inhibition is possible *in vivo* even under conditions of low level expression of EGFR or ERBB2, at this stage of clinical development, no further *in vivo* studies are required.

Diarrhoea was the most commonly reported treatment-emergent adverse event and it is noted that more than 16% of patients discontinued neratinib due to diarrhoea (see section 2.6 Clinical safety below). There is evidence to suggest that ERBB4 is induced in colonic epithelial cells in the inflamed mucosa of inflammatory bowel disease patients (Bernard *et al*, 2012). Selective activation with the ERBB4 ligand, neuregulin-4 (NRG-4) is said to represent a survival pathway in colon epithelial cells and thus ERBB4 activation could be protective in the colon. Although data in the literature may suggest that ERBB4 inhibition could potentially contribute to the observed diarrhoea, the exact mechanism is yet to be elucidated. The contribution of ERBB4 inhibition to neratinib-induced diarrhoea is still unknown. 'Gastrointestinal toxicity' has been included as an important identified risk in the RMP.

Studies investigating secondary pharmacology have shown that at the highest dose tested (10 µM), significant inhibition was detected in the receptor-binding assays. Neratinib has a range of activity (IC50's) from 0.83 µM to 31 µM (100023347). The Applicant claimed that these calculated IC50 values do not indicate a cause of concern based on a Cmax in humans at a dose of 240 mg (73.5 ng/mL or 0.14 µM). However, this assumption does not apply to the intestinal lumen, where the estimated drug concentration is about 1.7 mM at the clinical dose of 240 mg. Considering the importance of diarrhoea in the dosing scheme and maintenance of neratinib therapy and the potential attenuation or elimination of this adverse effect through pharmacological approaches, further pharmacological evaluation, probing the contribution of the following receptors -NK1, NK2, NK3, M1, M2, M3 and EGFR, to neratinib-induced diarrhoea is recommended. Any agonistic effect besides EGFR is a potential contributor to the observed diarrhoea effect in all animals tested and should be duly evaluated. The potential for neratinib to exert effects at the central nervous and respiratory systems was evaluated in the rat and the potential to affect the cardiovascular system was evaluated in the dog. New study reports were provided examining the hERG channel inhibition due to metabolites M3, M6 and M7. These indicate similar IC_{50} values to the parent compound and are present to sufficiently high safety margins to be of limited concern. In order to fully evaluate safety pharmacology endpoints for the metabolite M3, a new set of studies has been conducted to examine effects of this metabolite on the CNS, respiratory and cardiovascular systems. Results and final study reports are presented for the CNS and respiratory parameters, their findings do not demonstrate the metabolite to have additional concerns for safety.

The cardiovascular safety study in dogs is currently ongoing (study 20130869). Preliminary data and conclusions were provided which shown a reduction in heart rate following treatment with M3 over controls immediately after dosing, however this effect is reversed by 30 minutes. There were no distinct changes in QTc interval, or for blood pressure. Relative exposures to humans cannot be calculated as no PK measurements were taken during this study. The Applicant has supplied some approximation based on approximate blood volumes and estimated values of Cmax. The cardiovascular safety study in dogs is currently ongoing and the final results are expected in Q1 2018.

On the basis of the data presented, the methods used for neratinib and its metabolites appear to be precise, accurate, and sufficiently reproducible for analysis of study samples. The Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) states that the validation of bioanalytical methods used in pivotal non-clinical safety studies should be performed according to the Principles of GLP. Although deficiencies were highlighted during the validation of some of the analytical methods by the Applicant during the assessment, the CHMP concluded that the overall conclusions were not affected.

The mean oral bioavailability (F%) of neratinib was low to moderate, ranging from 11% to 39% in the studied animal species. The Applicant discussed the reasons for the observed low oral bioavailability of neratinib, and presented data clearly suggesting a strong contribution of neratinib's profound pH-dependent solubility and modest-poor intrinsic permeability.

Exposure to metabolites M6 and M7 at the no-effect levels within the pivotal toxicology studies in the rat and dog were either similar to or greater than exposure in humans (exposure ratios of 1.3 to 3.4-fold). The metabolite M3 was not observed at appreciable levels in rats and dogs; therefore, additional studies were conducted with M3 including a 2-week study in the rat. The potential toxicity of these metabolites has been thoroughly investigated. However, further clarifications with respect to the qualification of these metabolites was sought with respect to the safety pharmacology (see section 2.3.2 Pharmacology above) and genotoxicity aspects (see section 2.3.4 Toxicology below). The human metabolites have not been yet defined in the provided ADME study.

Neratinib was highly bound to plasma proteins and this binding was independent of concentration in male mouse, rat, rabbit, and dog plasma. Based on the binding of neratinib to human serum albumin, the major plasma protein, the *in vitro* binding of neratinib in human plasma was estimated to be greater than 99%. The distribution of [14C]neratinib-derived radioactivity to tissues was evaluated in the rat and monitored after a single oral administration of [14C]neratinib (10 mg/kg). Distribution was extensive; tissue-to-plasma AUC ratios were greater than 10 for the small intestine and large intestine (indicative of elimination route and possibly toxicity profile) along with the adrenal gland, renal cortex, liver (identified target organ) and pituitary gland. Pituitary adenoma (one 1 mg/kg/day male) or carcinoma (1 vehicle control female, two 3 mg/kg/day females, and one 10 mg/kg/day female) has been noted in the completed 2-year carcinogenicity study in the rat. The pituitary and adrenal glands appear to be a target following extended exposure to neratinib, however there is no clear differentiation between treated and control animals to signify a potential signal for carcinogenicity. Overall it can be determined that the changes observed between treatment and control population were of limited significance for increased carcinogenic potential. Brain to plasma exposure ratios were low indicating poor penetration of neratinib to the brain. Data was provided indicating that neratinib may have clinically meaningful activity in the treatment of brain metastases when used in the extended adjuvant setting. In the rat, following single oral administration of ^{14}C-neratinib, high affinity for the skin and uveal tract was noted. The Applicant has indicated that in the 28-day and 39-week toxicity studies with neratinib in pigmented (beagle) dogs, ophthalmoscopic examination (including the uveal tract) and microscopic examination of the eyes revealed no neratinib-related changes in the eye. Similarly, results of a phototoxicity study in rats revealed no findings indicative of skin or ocular phototoxicity. Covalent binding most likely contributes to the observed retention by the skin and uveal tract and it is evident that that the extent of covalent binding is more pronounced in the monkey and human than it is for the rat and dog, the primary toxicological species used.

The toxicology package consisted of oral acute and chronic general toxicity studies in mice, rats and dogs. Given the applied indication (i.e. treatment of cancer) and the absence of any safety margin for toxicity from the dog studies, this arbitrary NOAEL can be agreed. The choice of the dog as the non-rodent species in the toxicology studies has been satisfactorily justified.

Treatment with neratinib has drawn up a number of toxicological findings ranging from increased mortality associated with hepatotoxicity and gastrointestinal changes, to findings of weight loss, skin toxicity, faecal changes, reproductive organ atrophy and changes in haematology and biochemical chemistry parameters. High sensitivity to neratinib in dogs and rabbits resulted in low safety margins of less than 1, in rats this was greater than 20.

A number of adverse effects detected in the dose-range finding rat toxicity studies showed evidence of reproductive organ toxicity, prostatic and uterine atrophy leading to reduced prostate and uterus weights. In addition, male rats experienced mammary gland atrophy (neratinib doses of ≥15 mg/kg/day). Reassuringly these findings were absent in the definitive chronic rat studies and absent from the reproductive toxicity studies. Exposure to neratinib in male rats was consistently below that seen with females, and this is not reflected in the increased adverse findings in males. The Applicant

explained the observed differences in exposure as potentially due to increased sensitivity in male rats over females or that these effects were mediated more at a local level than through simply exposure levels. A statement has been proposed to section 4.6 of the SmPC to reflect that no significant changes in fertility parameters in male and female rats were detected in dosing up to 12 mg/kg/day.

Neratinib has been confirmed to be non-genotoxic and carcinogenicity and was investigated in a six-month transgenic mouse model, and in a two-year study in the rat. Evidence suggests that neratinib is unlikely to pose an increased risk of carcinogenicity. Neratinib has been shown to be embryo-toxic and potentially teratogenic in rabbits, with minimal margin of safety to the clinical dose. The significantly different toxicological response between rats and rabbits regarding the embryo-foetal development studies is considered adequately reflected in sections 4.6 and 5.3 of the proposed SmPC. Neratinib is embryotoxic and potentially teratogenic to pregnant rabbits and there is minimal margin for safety to the proposed human dose. A strong restrictive warning for use during pregnancy and breastfeeding is currently proposed in section 4.6 of the SmPC. A paragraph on breast-feeding has been proposed in section 4.6 of the SmPC covering the unknown excretion in milk as well as the risk to breast-fed infants which cannot be excluded and 'Reproductive and developmental toxicity' has been included as an important potential risk in the RMP.

A number of studies have sought to determine the safety of the five identified human metabolites, however further clarification of the approach has been requested. The Applicant should submit the final results of the ongoing IV 14 day rat repeat dose toxicity study for metabolite M11 once available. Local tolerance suggests that neratinib is not a dermal irritant, but is mildly irritating to eyes. An *in vivo* phototoxicity study in rats was negative with neratinib. Potential effects of neratinib on the gastrointestinal tract and consequences of gene expression have been explored, although these findings require confirmation. Gastrointestinal toxicity has been observed with neratinib treatment and may be a result of an effect on epidermal cell growth. Gastrointestinal adverse effects have been observed in treated patients, diarrhoea, nausea and vomiting. 'Gastrointestinal toxicity' has been included as an important identified risk in the RMP. Hepatotoxicity' has also been included as an important identified risk in the RMP.

Neratinib is considered to be a non-irritant to skin, but a mild irritant to eyes.

The environmental risk assessment provided with this application is considered incomplete by the CHMP as the following studies should have been conducted: OECD study 106, 307, 2016, 208, 207, 123 and 218, and study ISO 11267.Conclusion on the non-clinical aspects

The overall non-clinical development programme of neratinib was considered adequate to support the recommendation for a marketing authorisation for Nerlynx even if a few studies should have been provided as part of this application (cardiovascular safety study in dogs, rat repeat dose toxicity for metabolite M11 as well as several ERA studies).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the

community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

The clinical pharmacology and pharmacokinetics of neratinib, an irreversible, covalent inhibitor of receptor tyrosine kinases ERBB1, ERBB2, and ERBB4, were determined in a comprehensive program of *in vitro* studies using human cells, subcellular fractions, recombinant enzymes and transporters, and after studies of single and multiple oral doses given to healthy volunteers and patients with cancer. These studies utilised sensitive and specific HPLC-MS/MS analysis for parent and metabolite quantitation or radiochemical analysis after incubation in vitro or dosing with ^{14}C-neratinib.

Table 7 List of clinical pharmacology studies

Study Number	Title
3144A1-102-US/B1891028 (Study 102)	An Ascending Single and Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HKI-272 Administered Orally to Subjects with HER-2/neu or HER-1/EGFR-Positive Tumors
3144A1-104-JA/B1891030 (Study 104)	An Ascending Single and Multiple Dose Study of the Safety, Tolerability, and Pharmacokinetics of HKI-272 Administered Orally to Japanese Subjects with Advanced Solid Tumors
3144A1-105-US/B1891031 (Study 105)	A Single Dose, Crossover, Placebo-and-Moxifloxcin-Controlled Study of the Effects of Neratinib (HKI-272) on Cardiac Repolarization in Healthy Adult Subjects
3144A1-106-US/B1891025 (Study 106)	An Open-label, Randomized, 2-Period Crossover, Drug Interaction Study to Evaluate the Potential Pharmacokinetic Interaction Between Multiple Doses of Ketoconazole and a Single Dose of HKI-272 Administered Orally to Healthy Subjects
3144A1-107-US/B1891032 (Study 107)	Ascending Single Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HKI-272 Administered Orally to Healthy Subjects
3144A1-1108-US/B1891033 (Study 1108)	An Open-Label, Single-Dose Study of the Mass Balance and Metabolic Disposition of Orally Administered [^{14}C]-Labeled HKI-272 in Healthy Male Subjects
3144A1-1109-US/B1891034 (Study 1109)	A Single Dose Bioavailability Study of 2 New Formulations of HKI-272 (240 mg) Compared With a Reference Capsule and an Oral Solution in Healthy Adult Subjects
3144A1-1110-US/B1891008 (Study 1110)	A Study to Examine the Potential Effect of Rifampin on the Pharmacokinetics of Neratinib When Administered Concomitantly to Healthy Subjects
3144A2-1115-JA/B18911001 (Study 1115)	A Phase 1 Study of Neratinib (HKI-272) in Combination With Paclitaxel in Subjects With Solid Tumors
3144A1-1116-US/B1891010 (Study 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 to Healthy Subjects
3144A1-1117-US/B1891036	A Single Dose Relative Bioavailability Study of a New Formulation

Study Number	Title
(Study 1117)	(2 Dose Strengths) and a Reference Capsule of Neratinib (HKI-272) in Healthy Adult Subjects
3144A2-1118-JA/B1891002 (Study 1118)	A Phase 1 Study of Neratinib (HKI-272) in Combination with Vinorelbine in Japanese Subjects with Advanced or Metastatic Solid Tumors
3144A1-1119-US/B1891011 (Study 1119)	An Open-Label, Nonrandomized, Crossover Study to Evaluate The Potential Effect of Multiple Doses of Neratinib on the Pharmacokinetics of a Single Dose of Digoxin When Administered Orally to Healthy Adult Subjects

Absorption

Neratinib is a BCS Class 4 and shows low solubility at pH above 5. Intravenous data is not available therefore absolute bioavailability cannot be determined. Drugs that effect gastric pH may be expected to affect the absorption of neratinib. The proposed commercial drug product is an immediate release, film-coated 40-mg tablet. Relative bioavailability and bioequivalence were determined in 3 studies (study 1109, study 1117, and study 1127) with healthy volunteers given single 240-mg oral doses of neratinib solution, capsule, or tablet formulations in the fed and fasted state.

Study 3144A1-1117-US formally tested the bioequivalence and relative bioavailability of 6x Phase 3, 40-mg tablets; a 1x Phase 3, 240-mg tablet; and 3x 80-mg capsules in fed healthy volunteers. The study was a single-dose, randomized, 3-period crossover with a 14-day washout between doses, and initially enrolled 24 subjects. Plasma concentrations of neratinib were measured by a validated, sensitive and specific HPLC/MS/MS assay and PK parameters were calculated using a non-compartmental approach. The plasma pharmacokinetics of neratinib were indistinguishable after identical dosages of all formulations. In this study, the Phase 3, 40-mg tablet was bioequivalent to the Phase 3, 240-mg tablet and reference 80-mg capsule formulation ($p<0.001$) at a common 240 mg dosage.

Results from study 3144A1-1109-US also demonstrated that statistically equivalent plasma concentrations were produced by the Phase 2, 240-mg tablet formulation and the reference 80-mg capsule formulation, and were indistinguishable from those produced by an aqueous solution in citric acid ($p<0.001$). These two clinical studies demonstrate that the drug substance physicochemical form, tablet and capsule formulations, and dosage strengths used in the early development program and the 40-mg tablet used in Phase 3 Study 3144A2-3004-WW (proposed commercial formulation) are bioequivalent. Moreover, these studies demonstrate that 3x 80-mg capsules are equivalent to 6x Phase 3, 40-mg tablets as well as a 1x 240-mg tablet, and are bioequivalent to a 240-mg neratinib oral solution. While not evaluated formally in either study, the median time to peak concentration (t_{max}) was similar for all solid dosage forms, although the range was large. These data (similar C_{max} and t_{max}) suggest that the rate of absorption among dosage forms was similar. These bioequivalence studies therefore demonstrate similar exposure following dosing of the different dose forms and strengths.

Study 3144A1-1127-US was a single-dose, randomized, open-label, 4-period, 4-treatment, 4-sequence crossover study assessing the safety, tolerability, and bioequivalence of 2 dose strengths of neratinib tablet formulations in healthy volunteers in fed and fasted state. Two tablet formulations: 240-mg and 40-mg were studied. Twenty-eight (28) male subjects ranging from 18 to 64 years old with a mean body mass index (BMI) of 25.5 kg/m2 (80.1 kg) were enrolled. Plasma concentrations of neratinib were measured by a validated, sensitive and specific HPLC/MS/MS assay and PK parameters were calculated using a non-compartmental approach.

Plasma exposure to neratinib was slightly higher after a standard breakfast; the geometric mean C_{max} and area under the concentration-versus-time curve from time zero extrapolated to infinity (AUC_{inf}) increased by approximately 23% and 16%, respectively, after a single 240-mg tablet, and by approximately 17% and 13%, respectively, after 6x 40-mg tablets (study 1127). Statistically, the upper limits of the 90% confidence intervals (CIs) for the fed and fasted groups were close to or greater than the 125% boundary, indicating a slight effect of food. Bioequivalence of the single 240-mg tablet and the 6x 240-mg tablet doses could not be established under fed or fasted conditions since the upper limits of the 90% CIs for the ratios of the adjusted mean Cmax and AUC_{last} were outside the acceptance range of 80 to 125%. Mean C_{max} and AUC values for study 3144A1-1127-US were somewhat lower than those observed in other clinical studies of single 240-mg oral doses (study 3144A1-1117-US and study 3144A1-1109-US); 39-53 ng/mL and 597-869 ng•h/mL versus 61-72 ng/mL and 81-84 ng/mL and 1090-1140 and 1302-1462 ng•h/mL. The reasons for this apparent difference are unknown.

A more pronounced food effect was observed after a high-fat meal, with a statistically significant (p=0.021) increase in the mean AUC and AUCT of approximately 2-fold after a single 240-mg oral dose of neratinib (study 3144A1-107-US). While mean Cmax was also increased from 45 ng/mL to 74 ng/mL, this increase was not statistically significant (p=0.057).

Distribution

Ex vivo protein binding of neratinib in human plasma samples from clinical protocol 3144A1-1111-EU as determined using ultracentrifugation

The plasma protein binding of neratinib was determined by ultracentrifugation and a validated HPLC-MS/MS assay with plasma samples collected at 3, 6, and 24 h post-dose from patients with Child-Pugh class A, B, or C degrees of chronic hepatic impairment (n=6 for each group) and matched healthy adults (n=9) given a single 120 mg oral dose of neratinib in study 3144A1-1111-EU. Ultracentrifugate concentrations of neratinib from each subject at each time point were measured in triplicate and the % free and % bound in each sample was calculated using the neratinib plasma (total) concentration, determined once. Group mean and SD (% free) were calculated using all available individual replicates. The free fraction for neratinib in healthy subjects was similar at 3, 6, and 24 h post-dose: 11.8 ± 5.61%, 12.1 ± 5.45%, and 12.4 ± 3.36%, respectively. The free fraction for neratinib was relatively higher in healthy subjects compared with patients with hepatic impairment; although, no formal statistical analysis was done and significant variability at each time point was observed.

Characterisation of Covalent Binding to Human Serum Albumin

The mass balance and recovery of total [14C] in plasma from subjects dosed orally with [14C]-neratinib was incomplete, and *in vitro* experiments demonstrated that extraction recovery of neratinib was species-dependent, ranging from approximately 100% from rodent and rabbit plasma to approximately 27 and 40% from *Cynomolgus* monkey and human plasma, respectively. [14C]-neratinib (500 µM, 1.0 µCi/mL) was incubated with human plasma for 6 h at 37°C and the protein-associated radioactivity was characterised to identify the plasma protein and residue to which neratinib was bound, and which is likely responsible for the incomplete recovery. Structural influences on the covalent binding were explored using structural analogues and metabolites of neratinib incubated with human plasma. After incubation *in vitro*, plasma was injected directly onto the HPLC-MS with radiochemical detection for molecular weight analysis, subjected to SDS-PAGE with subsequent tryptic digestion of the harvested radioactive band and LC/MS analysis, or digested with 2N HCl for 2 h at 90°C prior to neutralisation and LC-MS analysis. Based on the results of these studies, a lysine-neratinib (lysine-HKI-272) adduct was synthesised, purified, and characterised by 1H and 13C NMR.

Two radioactive peaks, intact [14C]-neratinib and a peak co-eluting with HSA were resolved after injection of plasma. The molecular weight of the intact neratinib protein adduct, determined by LC-MS, was 66,999 Da and is consistent with one molecule of neratinib (556 Da) covalently bound to HSA (66,443 Da).

Extensive peptide mapping experiments using high resolution MS and accurate mass measurement of samples from SDS-PAGE and acid digestion identified LYS190 of HSA as the most likely site of adduct formation. Incubations with purified HSA and neratinib followed by digestion and LC-MS analysis confirmed the binding to residue 182-195 of HSA was the same residue bound in HSA isolated from human plasma. Species differences in the amino acid sequences of albumin could explain the species-dependent binding and recovery of neratinib. Nuclear magnetic resonance (NMR) analysis unambiguously identified the structure of the neratinib-lysine adduct, and this adduct co-eluted in two different chromatographic systems with adduct recovered from plasma after acid digestion. Additional studies with structural analogues demonstrated that the α, β unsaturated amide is critical for covalent binding to the ε amino group of Lysine190 via a protein-enhanced Michael addition, the basicity of the N, N-dimethylamine affects the Michael reactivity, and the aromaticity of the pyridinyl moiety contributes to the binding. This binding is slowly reversible, with approximately 43% of unextractable (T0) radioactivity recovered 18 h after resuspension of the plasma protein pellet in phosphate buffer. This slow release of covalently bound neratinib is consistent with the retro-Michael addition, although the exact mechanism was not defined. These studies have localised the covalent binding of neratinib to a specific residue on HSA in plasma, and proposed a biochemical hypothesis for this covalent binding that is consistent with the known peptide sequence, potential binding geometry, and chemical reactivity of neratinib.

Recovery was similar after incubation with fresh or frozen plasma. The tight binding of neratinib was species-dependent, with greatest binding in human and *Cynomolgus* monkey plasma and negligible binding in dog, rat, or mouse plasma. This binding is consistent with the species- dependent amino acid sequence differences in albumins at the neratinib binding region, peptide 182-195. Covalent binding to human plasma and HSA was observed for the metabolites M3 and M6, but not for M7 or the structurally related compounds WAY-191544 and lapatinib. Neratinib, M3, M6, and M7 but not WAY-191544 or lapatinib possess an α,β-unsaturated amide, a Michael acceptor that reacts with nucleophilic lysine. The N-oxide adjacent to the α,β-unsaturated amide of M7 likely decreases the reactivity of this molecule, and hence the covalent binding. Binding was reversible by acidification of the albumin-bound neratinib.

Neratinib In Vitro Assessment of Hepatic Uptake in Human Hepatocyte Suspensions

The purpose of this study was to determine the uptake of neratinib into cryopreserved human hepatocytes (CHH). Neratinib (1 and 25 µM) and the positive control for active uptake rosuvastatin (1 µM), with or without the active transport inhibitor rifamycin SV, were added to warmed cell suspensions and mixed. Aliquots were removed after 0.5, 1, and 1.5 minutes of incubation and the cells were separated by centrifugation through mineral/silicone oil, and collected. The concentrations of neratinib or rosuvastatin measured by HPLC-MS/MS. The rate of uptake from 0.5 to 1 min was calculated and normalized per min per 106 cells. The uptake of neratinib appeared to be by passive diffusion and was not inhibited by rifamycin SV (Table 7). Rifamycin SV inhibited rosuvastatin uptake by 85.5%.

Transport of Neratinib across Caco-2 cell monolayers in the presence of ketoconazole, a cytochrome P-450 inhibitor, and other selective inhibitors

The ability of the P-gp inhibitors verapamil and ketoconazole, the BCRP inhibitor Ko-143, and the multi-drug resistant proteins (MRPs) inhibitor MK-571 to decrease the flux of neratinib was determined

using Caco-2 cell cultures and 14C-neratinib. Apparent permeability (A→B) of 1 µM neratinib was moderate, 1.71 ± 0.35 × 10-6 cm/sec with an efflux ratio of 6.0. Neratinib efflux was decreased by the P-gp inhibitors verapamil and, in a concentration-dependent fashion, ketoconazole, and was modestly diminished by Ko-143. Inhibition by the MRP inhibitor MK-571 was 6%. Verapamil (100 µM) inhibited the efflux of the positive control digoxin by 95%, while MK-571 and Ko-143 inhibited efflux by 22% and 17%, respectively.

Plasma protein binding of metabolite M6 (study 20138521)

The objective of this study was to determine the *in vitro* plasma protein binding of neratinib metabolite M6 in plasma from a female Wistar Han rat and a female human. The concentration of M6 in buffer and plasma compartments was measured using UPLC-MS analysis. The stability of M6 at the concentration of 1 µM when incubated for 6 hours at 37°C in plasma from rat and human was determined. The remaining percentage of M6 after 6 hours of incubation at 37°C was 93% in rat plasma indicating that M6 (1 µM) was slightly instable in rat plasma. The remaining percentage of M6 after 6 hours of incubation at 37°C was 3% in human plasma indicating that M6 (1 µM) was not stable in human plasma.

The non-specific binding of M6 was determined in buffer samples at the concentration of 1 µM at different dialysis time periods of 0.5, 2, 4 and 6 hours. The non-specific binding after 6 hours of dialysis was 60% indicating non-specific binding or instability of M6 in buffer samples incubated for 6 hours at 37°C. The equilibrium conditions of M6 were determined in plasma of each species (rat and human) at 37°C and a M6 concentration of 1 µM. In rat and human plasma equilibrium was not reached within 6 hours of dialysis. The recovery was 71% for rat plasma and 16.5% for human plasma after 6 hours of dialysis. As M6 was slightly instable in rat plasma and was not stable in human plasma and the equilibrium was not reached within 6 hours of dialysis, rapid equilibrium dialysis is not a suitable method to determine the plasma protein binding for these species. Therefore the plasma protein binding was determined by using ultrafiltration which is the preferred method for unstable compounds. The mean non-specific binding of M6 to the ultrafiltration device was 68.6%. As a consequence the recovery for the ultrafiltration experiment was 31.4%. The high non-specific binding observed in these samples could not be explained. However, since M6 is highly bound to plasma proteins, it is expected that the non-specific binding did not influence the plasma protein binding.

Protein binding of M6 in female Wistar Han rat plasma was 99.6% at a 0.3 µM concentration, 99.6% at a 1 µM concentration and 99.5% at a 3 µM concentration. The protein binding of M6 in female human plasma was 99.5% at a 0.3 µM concentration, 99.7% at a 1 µM concentration and 99.5% at a 3 µM concentration. These data indicate that the protein binding in both rat and human plasma is independent of the M6 concentration. In conclusion, based on the ultrafiltration experiment M6 is highly bound (≥ 99.5%) to plasma proteins in plasma from female Wistar Han rat and female human. The extent of protein binding was 99.5%-99.6% in female rat plasma and 99.5%-99.7% in female human plasma. The plasma protein binding in both rat and human was independent of the M6 concentration.

Metabolism

Metabolism of 14C- Neratinib in Nude Mouse, Rat, Dog, and Human Liver Microsomes and LC-MS/MS Characterization of Metabolites (RPT-49166)

14C-neratinib (10 µM, labeled in the chlorophenyl ring) was incubated for 30 min at 37°C with hepatic microsomes from female nude mice, male rats, male dogs, and humans (pooled from males and females, n=16) supplemented with the cofactors NADPH, UDPGA or GSH. After protein precipitation

and resolution by HPLC, metabolite structures were proposed based on MS/MS fragmentation patterns (RPT-49166). Recovery was high, ranging from 85 to 99%, and only metabolites representing >5% of the radiochemical profile were noted. Seven metabolites were produced by human microsomes, and profiles were generally similar for all species (except that microsomes from dog). The predominant metabolites were M6 and M7, the N-desmethyl and N,N-dimethyl N-oxide of neratinib (HKI-272), respectively. After incubation with only GSH as the cofactor, the only metabolite observed was M5, the glutathione conjugate of HKI-272. No glucuronide conjugates were found after incubation with NADPH and UDPGA. The predominant metabolites produced by incubations containing NADPH, UDPGA and GSH were M4 and M5, GSH conjugates of N-desmethyl neratinib and intact neratinib, respectively. M3 and M1 were produced by addition of oxygen to HKI-272 and GSH conjugation of an oxygenated neratinib, respectively while M2 was formed by oxidative dealkylation of the methylpyridine ether.

Neratinib (HKI-272) Cytochrome P450 Isozyme Identification Study in Human Liver Microsomes (RPT-49793)

This study was designed to identify the CYP isozymes involved in the metabolism of neratinib by human liver microsomes (HLM) or microsomes recombinantly enriched (cDNA expressed) with specific isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 (rCYP) (RPT-49793). Neratinib (1 and 20 µM) was incubated with and without NADPH and HLM or CYP for 60 min at 37°C. Metabolites were monitored by HPLC-MS/MS after precipitation of reaction protein with acetonitrile, followed by evaporation of solvent and reconstitution for injection. 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). These metabolites were formed by CYP3A4 but not by other isozymes. Formation of M2, M3, and M6 a by HLM was inhibited by the CYP3A4-selective inhibitor ketoconazole. However, formation of M7 was unaffected by ketoconazole. Formation of M7 was markedly reduced by pre-treatment of HLM at elevated temperature (50°C for 1 min), a condition known to inactivate flavin-dependent monooxygenases (FMO) metabolism. These studies demonstrate that CYP3A4 is responsible for the HLM metabolism of neratinib to M3 and M6 and to a small degree M7, but that M7 is also formed by FMO.

During the evaluation, the Applicant was requested to provide further information on the elimination and metabolism of neratinib so that at least 80% of the total drug related components in faeces has been accounted for.

Elimination

An Open-label, Single-dose Study of the Mass Balance and Metabolic Disposition of Orally Administered [^{14}C]- Neratinib in Healthy Male Subjects (study 1108)

This was a phase 1, open-label, single dose, inpatient study conducted at a single centre. The primary objective of the study was to characterise the mass balance, metabolic disposition, and to identify the metabolites and general metabolic pathways after administration of a single oral dose of [14C]-neratinib to six healthy men.

Six male subjects (4 White, 1 Black, and 1 Other) ranging from 22 to 44 years old with a mean BMI of 24.3 kg/m2 (73.2 kg) were enrolled. Blood samples for the determination of total radioactivity in whole blood, total radioactivity and potential metabolite analysis in plasma, and for measurement of plasma concentrations of neratinib and its metabolites were collected up to 2 hours before, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, and 216 hours following neratinib dosing. Urine was collected for determination of total radioactivity and potential metabolite analysis from up to 2 hours before and at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours (Day 1), and then daily at 24-hour intervals through Day 10, or 216 hours and faeces were collected daily. The dosing solution was prepared from [14C]-neratinib powder, a mixture of [14C]-neratinib (mean specific activity of

4.08×10-4 µCi/mg, mean chemical purity of 98.9%) and unlabeled neratinib. Subjects received neratinib 200 mg containing 0.099 µCi 14C- neratinib. A 50-mL oral solution was mixed with 240 mL of Sprite and given to the subjects with a standard meal. 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 (studies RPT-72542, RPT-73428). 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 data acquisition software developed by NEC provides 14C counts, 13C and 12C currents, as well as the isotopic ratios 14C/13C and 13C/12C. Further calculations including normalisation, corrections for fractionation, and machine and chemical background were performed using in-house developed and validated software. The LLOQ in plasma and blood was estimated to be approximately 0.04 and 0.01 dpm/mL, respectively. Plasma radioactivity was too low to profile or quantitate parent or metabolites, and plasma PK parameters are reported for the analysis of unlabeled compounds. The AUC of neratinib was 1190 ng•h/mL, the Cmax was 53.7 ng/mL, and the CL/F was 204 L/h. The t½ was 16.2 hours. The mean recovery of radioactivity was 98.2% of the total dose. Faecal excretion accounted for approximately 97.1% and urine accounted for 1.13% of the total dose.

The recovery of total radioactivity after a single 200 mg oral dose of [^{14}C]-neratinib was 98.2% (0-216 h). The excretion of total radioactivity was primarily via the faeces (97.1%) and urinary excretion was minor (1.1%). Due to the low sensitivity of the assay and low radioactivity level in the body, the metabolic profiling and disposition of neratinib was not characterised in study 3144A1-1108-US.

Dose proportionality and time dependencies

Dose proportionality

Ascending Single Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Neratinib Administered Orally to Healthy Subjects (Study 107)

This was a randomized, double-blind, placebo-controlled, inpatient, sequential group study conducted at a single site. The study was designed to assess the safety and tolerability of single ascending oral doses of neratinib administered in capsules to healthy volunteers. Fifty-six subjects (52 men and 4 women; 40 White, 13 Black, 1 Asian, 2 Native American or native Alaskan) ranging from 19 to 49 years old with a mean BMI of 25.6 kg/m2 (79.34 kg) were enrolled. Pharmacokinetic parameters and exploratory pharmacodynamic responses (p-ERK) were determined after subjects were given neratinib after an overnight fast of at least 10 h, or a standard FDA high-fat meal. Seven cohorts of 6 neratinib and 2 placebo-dosed subjects received single oral doses of 120 to 800 mg, including one crossover food effect (240 mg under fast or with high fat meal) and two parallel treatment food effect cohorts (400 and 640 mg under fast or with standard breakfast). There was no apparent trend in p-Erk expression 6 or 24 h after treatment with neratinib, and staining was similar in samples collected from placebo or neratinib treated subjects. Sixteen (16) plasma samples were collected from 0 to 96 h post-dose and pharmacokinetic analysis was done with WinNonlin v.4.1 (Pharsight Corporation, Mountain View, CA), were available (n=42).

Absorption of neratinib after single oral doses of 120 mg to 800 mg in the fasted state was slow, with median tmax ranging from 4 to 7 h and a median t_{lag} ranging from 0.5 to 1.5 h. Exposure (C_{max} and AUC) increased with increasing dosage from 120 to 400 mg, but did not increase further above a 640 mg dose. Mean C_{max} ranged from 27 to 121 ng/mL, and mean AUC ranged from 453 to 2624 ng•h/mL, after 120 to 800 mg, respectively. Plasma concentrations declined from Cmax in an apparent mono-phasic decay; the mean apparent elimination half-life ranged from 10 to 17 h and was independent of dosage and fed/fasted status. Apparent volume of distribution (Vz) was large, ranged from 63 to 95

L/kg, and the mean CL/F ranged from 2.6 to 6.3 L/h/kg. Urinary excretion of neratinib was low, with 0.29% and 0.41% of the dose excreted after single 640 or 800 mg oral doses, respectively.

Time dependency

Mean Cmax, t_{max} and AUC_T are similar in healthy volunteers given a single or once-daily 240 mg oral dose of neratinib with food in different studies (Table 45). Accumulation (AUC) after 7, 14, or 21 once-daily, 240 mg oral doses given to healthy volunteers or cancer patients is negligible; mean R= 1.2, 1.2, and 1.18, respectively. The degree of accumulation observed after multiple doses is consistent with a mean half-life of approximately 14 h. Visual inspection of Ctrough concentrations suggests steady-state for neratinib is reached by Day 4.

An Ascending Single and Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Neratinib Administered Orally to Patients with HER-2/neu or HER-1/EGFR-positive Tumors (study 102)

This was an open-label, ascending single and multiple dose study conducted at 6 US sites, to assess the safety, tolerability, and define the maximum tolerated dose of neratinib in patients with advanced-stage tumor types expressing HER-2/neu (ERBB-2) or HER-1/EGFR (ERBB-1) refractory to prior therapy. Seventy two (72) patients (52 female and 20 male; 66 White, 2 Black, 2 Hispanic, 1 Asian, and 1 other) ranging from 34 to 90 years old with a mean weight of 74.71 kg and with immunohistochemical confirmation of ERBB-2 or ERBB1 tumors were treated. The most common primary diagnoses were breast (29 subjects or 40%), non-small cell lung cancer (NSCLC) (15 subjects, 21%), colorectal (5 subjects, 7%), and ovarian (6 subjects, 8%) and all subjects had received prior cancer therapy including chemotherapy, immunotherapy, or hormonal therapy. All patients received concomitant therapy (including 33 [45.8%] taking drugs for the treatment of peptic ulcers).

Oral doses of neratinib ranging from 40 to 400 mg and including the MTD (as 10 mg or 40 mg capsules) were given once daily in the morning with food. After one week, once-daily oral doses were given to 3-6 subjects per cohort for 28 days/cycle, for up to 6 cycles (6 months). Blood samples (n=10) were taken from 0 to 48 h post- dose on Day 1, pre-dose through 24 h on Day 21, and immediately pre-dose at scheduled visits through 6 cycles (C_{trough}). PK parameters were calculated by WinNonlin v.4.1 (Pharsight Corporation, Mountain View, CA) using noncompartmental analysis (NCA) methods. Individual percent differences between original and updated t1/2 values ranged between 0 and 22.4%. The reanalysis resulted in mean differences between original and updated mean $t_{1/2}$ values by treatment group ranged between 0 and 45%.

PK parameters were calculated from all subjects randomized and treated who received at least 1 dose. PK were available from 72 patients. Absorption of single doses of neratinib was slow with a median t_{max} of 3-6.5 h. Exposure increased with increasing dose; however, the relationship between C_{max} or AUC and single or multiple doses was not linear. While the 95% CIs for the exponents bracketed 1.0, the lack-of-fitness tests were significant.

Mean Cmax after single doses of 40 to 400 mg ranged from 5.0 to 76.5 ng/mL, and from 5.8 to 105 ng/mL after multiple doses (Day 21). Mean AUC0-24 or AUCss after single doses of 40 to 320 mg ranged from 43 to 1582 ng•h/mL and ranged from 76 to 1704 ng•h/mL on Day 21 (40-400 mg/day). Accumulation on Day 21 was 1.2 to 2.7-fold greater at doses of 40 to 400 mg/day, and was 1.2 and 1.5 at doses of 240 and 320 mg/day, respectively. Mean C_{trough} concentrations of neratinib were similar on Days 21 through Day 147 of intermittent daily dosing, although a limited number of patients were sampled at Days 63 and longer.

Phase 2 Study of Neratinib in Patients with Advanced Breast Cancer (study 201)

This was a phase 2, open-label, multi-center, multi-regional study conducted in the USA, Belgium, Brazil, China, France, India, Mexico, the Netherlands, and Russia. The purpose of this study was to evaluate the efficacy of neratinib given as a continual oral 240 mg dose daily to women with ERBB2 positive advanced breast cancer in two-arms, described subsequently. The primary objective of the study was to determine the 16 week PFS rate for neratinib in women with advanced breast cancer. Patients enrolled were assigned to a treatment arm based on baseline disease characteristics and prior cancer therapy:

- Arm A: Women with ERBB2-positive breast cancer and ERBB2 gene amplification confirmed in tumor tissue; and disease progression during or after trastuzumab-containing adjuvant therapy, or following at least 6 weeks of standard doses of trastuzumab in a metastatic or locally advanced setting.
- Arm B: Women with ERBB2-positive breast cancer and ERBB2 gene amplification confirmed in tumor tissue and no prior trastuzumab or other ERBB2-targeted treatment.

One hundred thirty-six (136) women (66 subjects in arm A and 70 subjects in arm B; 70 subjects, 51.5%) were white, 30 subjects (22.1%) were Asian, 28 subjects (20.6%) were Indian, 2 subjects were black (1.5%), and 6 subjects were Hispanic (4.4%)) with a median age of 49 years (range, 32 to 83 years) for treatment arm A and 51 years (range, 31 to 79 years) for treatment arm B. One hundred thirty-one (131) subjects (96%) had stage IV breast cancer at screening; 65 subjects (98%) were in arm A and 66 subjects (94%) were in arm B. Sixty-nine (69) subjects (54%; 25 subjects in arm A and 44 subjects in arm B) had an ECOG performance status of 0 and 53 subjects (41%; 32 subjects in arm A and 21 subjects in arm B) had an ECOG performance status of 1 at screening. All subjects had prior cancer-related surgical procedures and 92 subjects (68%) had prior radiotherapy. A total of 135 subjects, 66 subjects in arm A and 69 subjects in arm B, received at least 1 concomitant therapy during the study (including 21 (15.4%) taking drugs for the treatment of peptic ulcers). Single 240 mg oral doses of neratinib (3, 80 mg capsules [formulation 0932256V]) were to be taken once daily in the morning preferably with food. Blood samples were taken pre-dose on Month 1 Day 1 and pre-dose at scheduled visits on Months 2, 3, 4, 5, and 6 Day to determine Ctrough. Plasma concentrations of neratinib were measured with a validated HPLC-MS/MS assay (LLOQ 3 ng/mL). The sparse sampling results were used in the construction of the population PK model. C_{trough} measured through cycle 6 did not show any significant changes with protracted treatment.

Special populations

Population pharmacokinetic (POPPK)

A population pharmacokinetic (POPPK) model was developed and fitted to patient pharmacokinetic data collected from four phase 1/2 clinical studies (studies 3144A1-104-JA, 3144A1- 201-WW, 3144A1-2206-WW, and 3144A2-3003-WW). Additionally, an exploratory analysis of exposure-response (E-R) and biomarkers was completed.

The objectives of the analysis was to characterise the population pharmacokinetics of neratinib in patients with solid tumours, assess sources of variability in exposure to neratinib, and explore the relationship between exposure metrics and efficacy/safety endpoints (exposure-response, E-R). Study 3004, sparse pharmacokinetic (PK) samples were collected as soon as possible but no later than 96 hours from the last dose of investigational product for determination of plasma concentrations of neratinib/its metabolites for patients who experienced any of the following: Grade 4 ALT increase, or Grade 4 total bilirubin increase that were potentially related to investigational product, or any events of ALT >3x upper limit of normal (ULN) associated with total bilirubin >2 x ULN and ALP <2 x ULN. The

plasma concentration of neratinib/its metabolites were evaluated to assess whether the elevation in liver function tests (LFTs) was associated with the plasma concentrations of investigational product. With amendment 11, unscheduled PK samples were no longer required to be collected. Sampling occurred in 5 patients during the study period. Since there were so few patients in this study, the data were not included in the population pharmacokinetic analysis as any conclusions with regards to modelling, safety, efficacy or exposure-response could not be made. All patients from studies 3144A1-104-JA, 3144A1-201-WW, 3144A1-2206-WW, and 3144A2- 3003-WW who received at least one dose of study drug and had at least one efficacy or safety endpoint collection were included in the E-R analysis.

A total of 372 patients were included in the PK population dataset contributing 2749 PK observations for compartmental modeling. A total of 171 observations had associated time-afterdose greater than 100 h, and were therefore ignored. Prespecified covariates included age, body size (e.g., weight), liver enzymes ALT and AST, total bilirubin, and concomitant administration of capecitabine, trastuzumab, or ketoconazole.

Concentration-time data of neratinib was modeled using first-order compartmental models (e.g. 1- , 2- , and 3-compartmental model). 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. The evaluation of the between subject variability (BSV) models included addition of BSV terms (ETAs) to the model parameters, evaluation of the most appropriate form of the ETAs, and evaluation of pair-wise plots of the ETAs for any correlations. Models with shared ETA were evaluated where separate ETAs were not supported. 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 by evaluation of pertinent graphical representations of goodness-of-fit (GOF). Covariate analysis was performed using a full model approach to identify sources of variability in PK parameters of neratinib. No hypothesis testing was conducted. Rather, parameter estimation was emphasised. Candidate covariates were pre-specified based on scientific or clinical interest, mechanistic plausibility, or *a priori* knowledge about covariate effects of clinical relevance. Weight effects were included on clearance and volume terms during base model development. Other pre-specified covariates that were supported by delivered study data were screened as described below for simultaneous inclusion in the full model on relevant parameters. Effects of age (years), total bilirubin (mg/dL), ALT (U/L), concomitant trastuzumab exposure (yes/no) and concomitant capecitabine exposure (yes/no) were included on CL/F; an age effect was also included on apparent central volume of distribution (Vc/F). The final model was validated using two methods. First model parameter estimates and 95% confidence intervals (CI) were obtained via non-parametric bootstrap with 1000 resampled datasets (stratified on study). Point estimates and 95% CI were used to assess clinical relevance of covariate effects as well as the precision of covariate effect estimates. Second, the ability of the model to simulate data like the observed data was assessed using a posterior predictive check. Five hundred data sets were simulated and systematically compared to the observed data using quantile-quantile plots of subject-level exposure measures (minimum, median, and maximum concentration).

The data was described by a two compartment model with absorption lag and proportional error. Absorption was adequately characterised by first-order kinetics. Weight was included allometrically on clearance and volume terms; alternative measures of body size (IBW, LBW, BMI) did not perform better than weight. Body surface area (BSA) was highly correlated with weight (r = 0.98) and was not evaluated. Weight effects were shared between apparent systemic clearance and intercompartmental clearance, as well as between central volume and peripheral volume. AST was highly correlated with ALT (r = 0.763), and therefore was excluded as a covariate. Estimated creatinine clearance (CrCl) was explored retrospectively by plotting vs random effects and did not show a relationship with conditional

individual weighted residuals (PUMA-PCS-101), or with random effects for CL/F, Vc/F, or Ka (ETA1, ETA2, ETA3: PUMA-PCS-101).

For the final model, the bootstrap median apparent clearance of neratinib (95% CI) was 183 (171, 195) L/h, and apparent central volume of distribution was 4270 (3450 , 5000) L. These values compare favorably with 204 ±94.3 L/h and 4530 ±2480 L, respectively, per analysis of 200 mg neratinib in healthy men (N= 4, prot. 3144A1-1108-US, [18]). Effects of age, weight, ALT, and total bilirubin on apparent clearance, as well as effects of age and weight on apparent central volume, were well-estimated but not clinically important. Proportional residual error was ~ 35% CV. CV for random effects on CL/F, Vc/F, and Ka are ~ 47%, 71%, and 115% respectively.

Impaired renal function

No study was performed in patients with renal impairment. A retrospective analysis in the POPK did not show any effect of renal impairment. However it is noted that age is a covariate in the model used and this would be expected to be correlated with renal clearance.

Impaired hepatic function

An Open-label, Single Dose, Parallel-group Study of the Pharmacokinetics and Safety of Neratinib in Patients with Chronic Hepatic Impairment and in Matched Healthy (study 3144A1-1111-EU)

This was single-centered, open-label, single-dose, parallel-group, inpatient, nonrandomized phase 1 study in patients with chronic hepatic impairment and in matched healthy subjects. A single 120 mg oral dose of neratinib was administered with a standard breakfast. Twenty seven (27) subjects (20 men and 7 women; 27 White) ranging from 31 to 65 years old with a mean BMI of 25.14 kg/m2 (76.63 kg) were enrolled; 9 healthy subjects and 6 each in Child-Pugh Class A, B, and C. The etiology of hepatic impairment was alcoholism, hepatitis C, or both. The effect of hepatic impairment on neratinib PK was tested with log-transformed PK parameters and a 1-factor ANOVA, with group as a fixed effect. Confidence intervals (90%) for the geometric mean differences (healthy vs. impaired) were also compared. Blood samples were taken from extensible predose to 72 h post-dose, and plasma concentrations of neratinib and metabolites M3, M6, and M7 were measured by a validated HPLC-MS/MS assay. Plasma protein binding was determined ex vivo by ultracentrifugation on samples taken 3, 6, and 24 h after dosing, and the free fraction was used to convert and express PK parameters in terms of free drug. Neratinib exposure in the Child-Pugh Class A and B patients was similar to that in normal healthy volunteers. Exposure to neratinib was increased approximately 3-fold in patients with severe hepatic impairment (Child- Pugh Class C). The apparent elimination half-life for neratinib was also increased 3-fold in Child-Pugh Class C patients.

Gender

Statistical analysis of the relationship between sexes suggests no difference in C_{max} or AUC for male and female patients given single or multiple oral doses of 320 mg of neratinib.

Race

An Ascending Single and Multiple Dose Study of the safety, Tolerability, and Pharmacokinetics of Neratinib Administered Orally to Japanese Patients with Advanced Solid Tumors (study 104)

This was a phase 1, open-label, ascending single and multiple dose study conducted at multiple sites in Japan, designed to assess the safety and tolerability and pharmacokinetics (PK) of neratinib in patients with advanced solid tumors. This trial was a modification of a standard phase 1 oncology study design based on a modified Fibonacci dose escalation scheme, incorporating a single dose phase before beginning the standard continual dose design. Twenty one patients (8 female and 13 male), mean age

58.48, ranging from 39 to 78 years old, with a mean weight of 59.49 kg were treated. The primary diagnoses were breast (3 patients or 14%), colorectal (17 patients, 81%), and gastric (1 subject, 5%) and all patients had received prior cancer therapy including chemotherapy, immunotherapy, or hormonal therapy. All patients received concomitant therapy (including 14 (66.7%) taking drugs for the treatment of peptic ulcers). Oral doses of neratinib ranging from mg and including the MTD (as 40 mg or 80 mg capsules) were given once daily in the morning with food. After one week, once-daily oral doses were given to 3-6 patients per cohort for 28 days/cycle, for up to 6 cycles (6 months). Blood samples (n=10) were taken from 0 to 48 h post-dose on Day 1, pre-dose through 24 h on Day 21, and immediately pre-dose at scheduled visits through 6 cycles (C_{trough}).

Neratinib absorption was slow, and the C_{max} was generally attained within 4 to 6 hours. After single or multiple daily oral doses of neratinib, C_{max} 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). The apparent steady-state volume of distribution of neratinib was large, indicating extensive tissue distribution of neratinib. 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.

The C_{max} and AUC_{ss} in combination trials with Japanese patients were similar to those found in world-wide (including US) patients treated with similar dosages and regimens.

Weight

Weight was incorporated in the POPK as an allometric relationship however the exponents on clearance and volume, 0.31 and 0.5, are lower than those that would be physiologically expected. Plots (above) appear to show a good fit to the data. The Applicant provided further plots that show that there is no correlation with creatinine clearance when age is not a covariate in the model. In addition fitting exponents to those expected for weight on clearance and volume did not have a significant impact on the model.

Elderly

Age was a covariate in the POPPK however an analysis was only performed for the difference between 36 and 75 years.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	35/372 (9.4%)	13/372 (3.5%)	1/372 (0.3%)

Pharmacokinetic interaction studies

In vitro

Neratinib (HKI-272) IC50 Determination For the Inhibition of Cytochrome P450 Isozymes in Human Liver Microsomes (RPT-48255)

The objective of this study was to determine the potential for neratinib (HKI-272) to inhibit the catalytic activity of CYP 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4 in pooled HLM (study RPT-48255). CYP activity was determined by measuring ethoxyresorufin O-deethylation, coumarin 7-hydroxylation, paclitaxel 6α-hydroxylation, diclofenac 4'-hydroxylation, S-mephenytoin 4'-hydroxylation, bufuralol 1'-hydroxylation, and midazolam 1'-hydroxylation at their respective Km values in the presence of

neratinib (0.1 to 100 µM). Probe substrates were added as a cocktail and metabolites were quantitated by HPLC-MS/MS as described by Dierks et al (Dierks et al, 2001). There was negligible inhibition of CYP1A2, 2C8, 2C9, 2D6, or 3A4 by neratinib at 100 µM, with 80 to 103% of control activity remaining. The extrapolated IC50 for the inhibition of CYP2A6 was 460 µM. The IC50 for the inhibition of CYP2C19 was reported as 21 µM; however, the mean (n=3) % of control activity was 53% and 31% at 2.5 and 10 µM neratinib, respectively.

HKI-272: Initial Assessment Of Mechanism-Based Inhibition Of Cytochrome P450 Enzymes In Human Liver Microsomes (RPT-79460)

The potential for mechanism-based inhibition of CYP2C9, 2C19, 2D6, or 3A4 by neratinib was determined using pooled (n=200) human liver microsomes (HLM) preincubated for 30 min at 37°C with or without a NADPH generating system and neratinib (1, 10, or 100 µM) prior to the addition of a cocktail of the CYP-selective substrates diclofenac, S-mephenytoin, bufuralol or midazolam (RPT-79460). After quenching the reactions with acetonitrile, the CYP-selective metabolites 4'-hydroxy diclofenac, 4'hydroxy S-mephenytoin, 1'-hydroxy bufuralol and 1'-hydroxy midazolam were quantitated by HPLC-MS/MS using standard curves constructed with authentic metabolite standards. The positive control mechanism-based inhibitors tienilic acid (2C9), ticlopidine (2C19), paroxetine (2D6), and troleandmycin (3A4) were used to confirm the appropriateness of the test system. Neratinib was not a mechanism-based inhibitor of CYP2C9, 2C19, 2D6, or 3A4, with no increased inhibition observed after preincubation in the presence of NADPH.

Potential Induction of Cytochrome P450 Genes by Neratinib in Human Hepatocytes (RPT-72053)

The potential for neratinib to induce CYP1A2, 2B6, and 3A4 enzyme activity and mRNA levels, and CYP2C9 mRNA levels was determined after incubation of neratinib (0.056, 0.1, and 1.0 µM, added every 24 h) with (2) lots of cryopreserved hepatocytes (1 male, 1 female) and (1) lot of primary hepatocytes (female) for 48 h at 37°C (RPT-72053). Neratinib did not change mRNA or enzyme activity at concentrations up to 10-fold the total Cmax of neratinib produced by a single 240 mg oral dose of neratinib (44.6 ng/mL or 0.081 µM). The positive control inducer rifampin induced CYP2B6, 2C9, and 3A4 mRNA 6.0, 3.3, and 26.3-fold, respectively. The increase in CYP2B6 and 3A4 mRNA was accompanied by a 2.1 and 6.6-fold increase in enzyme activity. CYP1A2 mRNA and enzyme activity were induced 8.9 and 10.9-fold respectively after treatment with β-naphthoflavone. These data suggest neratinib is unlikely to induce CYP1A2, 2B6, 2C9, or 3A4 *in vivo*.

Evaluating the Potential for Induction of CYP3A4 by Neratinib Using a CYP3A4 Reporter Gene Assay (RPT-71420)

The objective of this study was to determine if neratinib increased the luciferase response in HepG2 cells transfected with a CYP3A4 promoter/enhancer and PXR plasmid DNA (RPT-71420). Briefly, HepG2 cells were cultured to 75% confluence, harvested, transfected, and allowed to recover for 16 h before the addition of DMSO vehicle, neratinib (0.05, 0.1, and 1.0 µM) or rifampin (10 µM), added every 24 h for 2 days. There was no increase in response produced by neratinib even at concentrations of up to 12.5× the mean Cmax observed for subjects given a single 240 mg oral dose of neratinib (44.6 ng/mL or 0.08 µM). Rifampin reliably increased the response 41-fold above vehicle control. These data demonstrate that neratinib is unlikely to induce CYP3A4.

Pgp inhibition

The absorptive permeability and potential for neratinib to be a substrate for or inhibitor of P-glycoprotein (P-gp) mediated transport were determined in Caco-2 cell cultures using 14C- neratinib and the prototypical P-gp inhibitor and substrate verapamil and digoxin, respectively (RPT-71571). Near confluent Caco-2 cell cultures (grown in-house, passage number not reported) were harvested

and seeded on semi-permeable filter inserts at approximately 140,000 cells/cm2 and cultured for 21 days. After rinsing with DMEM, incubations (triplicate) of drug in DMEM were conducted for 2h at 37° C with concentrations of 14C- neratinib or 3H-digoxin added to the apical or basolateral chamber. Concentrations were measured by LSC and apparent permeability (Papp), and efflux ratios (B→A/A→B) values calculated. Mean passive permeability (A→B) of neratinib was moderate, 0.79 to 1.18 X 10-6 cm/sec, and independent of concentrations ranging from 1 to 30 µM. Efflux was inhibited by 100 µM verapamil, decreasing from 4.89 to 2.54, and was markedly concentration-dependent, ranging from 12.3 to 2.49 at 1 to 30 µM neratinib. Neratinib inhibited the P-gp mediated transport of digoxin with an IC50 of 1 µM, with 96% inhibition produced by 50 µM neratinib. Both systemic and lumenal drug interactions between neratinib and P-gp substrates are suggested by R values calculated with the mean total plasma Cmax concentrations produced after oral doses of 240 mg and the intestinal concentrations produced by 240 mg/250 mL (0.14 and 1.7 µM, respectively).

Neratinib and M6 substrate of OATP1B1 and OATP1B3 (study 6502)

The aim of this study was to evaluate if neratinib and M6 are substrates of the human drug uptake transporters OATP1B1*1a and OATP1B3 using HEK293 cells expressing the relevant transporter. Sample analysis was by liquid chromatography-mass spectrometry (LC-MS/MS) using methods selective for neratinib, M6 or the probe substrate for each transporter. Neratinib and M6, at 10 µM, did not appear to be substrates of OATP1B1 or OATP1B3. Studies compared the uptake of test compound in HEK293 cells transfected with the transporter gene to uptake of the test compounds in control HEK293 cells. In all cases, uptake ratios <2 were observed. Both compounds were highly permeable suggesting that transport into the cells was driven more by passive rather than active mechanisms.

Neratinib as an inhibitor of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, OCT1, BCRP and BSEP (study PMA/REP/01 CRD/5551/2017)

The aim of this study was to evaluate any inhibitory effect of neratinib on human drug uptake transporters OATP1B1*1a, OATP1B3, OAT1, OAT3, OCT1 and OCT2 using suspensions of HEK293 cells expressing the relevant transporter. Sample analysis was done by liquid scintillation counting. Neratinib produced no inhibitory activity towards the uptake transporters, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2, with reported IC50 values were >10 µM. Neratinib produced inhibitory activity in OCT1 uptake transporter, reporting an IC50 value of 2.9 µM. An *in vitro* investigation to assess if neratinib is an inhibitor of the human Bile Salt Export Pump (BSEP) and Breast Cancer Resistance Protein (BCRP) efflux transporters was conducted. The study was performed using commercially available inside-out vesicles prepared from insect cells (Sf9) infected a recombinant baculovirus encoding the cDNA for BSEP. Sample analysis was done by liquid scintillation counting. Neratinib was not a potent inhibitor of human BSEP efflux transporter activity *in vitro*, at the concentration range tested with reported IC50 values of >10 µM. Neratinib was evaluated as an inhibitor of the human BCRP efflux with human BCRP gene. Sample analysis was by liquid chromatography mass spectrometry (LC-MS/MS). Neratinib at 10 µM appeared to inhibit the BCRP efflux transporter as an increase in prazosin A> B permeability and reduction in prazosin efflux was observed. A 78% reduction in prazosin efflux was observed. When prazosin was incubated on its own, poor apparent permeability was reported (mean A>B Papp 3.4 x 10·-6 cm/s with an efflux ratio of 25) compared to moderate apparent permeability observed in the presence of Neratinib (mean A>B Papp 14 X 10-6 cm/s with an efflux ratio of 5.7).

M6 as an inhibitor of cytochrome P450s isoenzymes (study 517193)

The objective of this study was to determine *in vitro* whether M6 inhibits the activity of the human cytochrome P450 isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 towards model substrates, using human liver microsomes.

Reversible (direct), time- and metabolism-dependent inhibition mechanisms were evaluated. Batch ga4021050aa of M6 was a yellow solid with a purity of 98.77%. M6 was soluble in acetonitrile (ACN): Milli-Q water (MQ) 1:1 (v/v) at a concentration of 10 mM. The following substrate/metabolite combinations were used: phenacetin/acetaminophen for CYP1A2, bupropion/hydroxybupropion for CYP2B6, paclitaxel/6α-hydroxypaclitaxel for CYP2C8, diclofenac/4'-hydroxydiclofenac for CYP2C9, (S)-mephenytoin/(S)-4'-hydroxymephenytoin for CYP2C19, bufuralol/1'-hydroxybufuralol for CYP2D6, midazolam/1'-hydroxymidazolam and testosterone/6β-hydroxytestosterone for CYP3A4.

Incubations to determine reversible (direct) inhibition were performed at 37°C for 5 minutes (CYP3A4 midazolam), 10 minutes (CYPs 2C8, 2C9, 2D6 and 3A4 testosterone), 20 minutes (CYP2B6) or 30 minutes (CYPs 1A2 and 2C19), in the presence or absence of inhibitor.

M6 was tested in duplicate at concentrations ranging from 0.03 to 100 µM. M6 working solutions to prepare incubations were made in ACN: MQ 1:7 (v: v). Positive control inhibitors were used (in duplicate) to confirm the validity of the data; fluvoxamine for CYP1A2, ticlopidine for CYP2B6, ketoconazole for CYP2C8, sulfaphenazole for CYP2C9, tranylcypromine for CYP2C19, quinidine for CYP2D6 and ketoconazole for CYP3A4. For all results the IC50 values of the control inhibitors were within 30% to 300% of the historical control data range determined at Charles River Den Bosch from 2005–2016. Incubations to determine possible time-dependent inhibition (TDI) were performed using the same conditions as for the reversible (direct) inhibition, with the only difference that an additional pre-incubation of M6 with the microsomal mixture was performed in absence of NADPH for 30 minutes. After pre-incubation the reaction was started by the addition of substrate and NADPH.

Incubations to determine possible metabolism-dependent inhibition (MDI) were performed using the same conditions as for the reversible (direct) inhibition, with the only difference that an additional pre-incubation of M6 with the microsomal mixture was performed in presence of NADPH for 30 minutes. After pre-incubation the reaction was started by the addition of substrate and NADPH. Positive control metabolism-dependent inhibitors were used (in duplicate) to confirm the validity of the data; furafylline for CYP1A2, ThioTEPA for CYP2B6, isoniazid for CYP2C8, tienilic acid for CYP2C9, S-fluoxetine for CYP2C19, paroxetine for CYP2D6 and mifepristone for CYP3A4. For all CYP isoforms the positive control inhibitors showed a metabolism-dependent IC50-shift of at least 1.5-fold. Probe substrate metabolite formation in incubation samples was analyzed by UPLC-MS/MS. IC50 values were calculated for each of the positive control inhibitors and for M6 if inhibition of metabolite formation was observed. Calculation of the IC50 shift comparing the IC50 after pre-incubation with NADPH (MDI) to the IC50 after pre-incubation without NADPH (TDI) was used to indicate possible metabolism-dependent inhibition mechanisms.

M6 displayed reversible (direct) inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (using both midazolam and testosterone as substrates). For CYP1A2, CYP2D6 and CYP3A4 (using both midazolam and testosterone as substrate) IC50 values for reversible (direct) inhibition could not be calculated and were therefore determined to be ≥ 100 µM (the highest concentration tested). M6 inhibited CYP2B6, CYP2C8, CYP2C9 and CYP2C19 with IC50 values of 39 µM, 19 µM, 3.1 µM and 11 µM, respectively. For reference, the highest mean total (bound plus unbound) Cmax values of M6 observed after multiple, once-daily 240 mg oral doses of neratinib, were 28.3 ng/mL which equals to 52 nM (Day 7, healthy volunteers: Puma Biotechnology Study 3144A1-1116-US) and 42.8 ng/mL which equals to 79 nM (Day 15, Japanese cancer patients treated with paclitaxel: Puma Biotechnology Study 3144A2-1115-JA). These data suggest that the likelihood of clinically relevant direct inhibition of CYP isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 by M6 is remote when using the most conservative Cmax value of 79 nM.

M6 was not a time-dependent inhibitor (pre-incubation for 30 minutes in the absence of NADPH) of CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. M6 inhibited CYP2B6 in a time-dependent manner,

with a 4-fold RI/TDI shift. The TDI of CYP3A4 was substrate-dependent, with no inhibition observed using testosterone as the substrate but with a 2.6-fold RI/TDI shift for the metabolism of midazolam. This time dependence may be rationalized based on the Michael acceptor moiety present in M6 and potential interactions with nucleophilic residues in the active site of CYP2B6 and CYP3A4.

M6 was not a metabolism-dependent inhibitor (pre-incubation for 30 minutes in the presence of NADPH) of CYP2B6, CYP2C19 and CYP2D6. Based on the inhibition results obtained at the highest test item concentration (100 µM) it might be possible that M6 is a metabolism-dependent inhibitor of CYP1A2 at this concentration. M6 produced a marginal IC50-fold shift (1.7-fold) for CYP2C8 and CYP2C9 which indicates that a metabolism-dependent inhibition mechanism may be involved. For CYP3A4, M6 produced an IC50-fold shift of 3.8 and 5.7 when using midazolam and testosterone as substrate, respectively, which indicates that M6 is a metabolism-dependent inhibitor of CYP3A4.

Neratinib as an inhibitor of cytochrome P450 isoenzyme 3A4 (study 517194)

The objective of this study was to determine *in vitro* whether neratinib inhibits the activity of the human cytochrome P450 isoenzyme 3A4 reversibly (directly), or in a time- or metabolism-dependent fashion using the model substrates midazolam and testosterone and human liver microsomes (HLM). CYP3A4-selective 1'-hydroxymidazolam and 6β-hydroxytestosterone formation were monitored.

Incubations to determine reversible (direct) inhibition were performed at 37°C for 5 minutes (CYP3A4 midazolam) and 10 minutes (CYP3A4 testosterone). Neratinib was tested in duplicate at concentrations ranging from 0.03 to 100 µM. Neratinib working solutions to prepare incubations were made in ACN: MQ 1:7 (v: v). Ketoconazole was used as a positive control inhibitor (in duplicate) to confirm the validity of the data. The IC50 valuesof the control inhibitor ketoconazole were within 30% to 300% of the historical control data range determined at Charles River Den Bosch from 2005–2016. Incubations to determine possible TDI were performed using the same conditions as for the reversible inhibition, with the only difference that an additional pre-incubation of neratinib with the microsomal mixture was performed in absence of NADPH for 30 minutes. After pre-incubation the reaction was started by the addition of substrate and NADPH.

Incubations to determine possible MDI were performed using the same conditions as for the reversible inhibition, with the only difference that an additional pre-incubation of neratinib with the microsomal mixture was performed in presence of NADPH for 30 minutes. After pre-incubation the reaction was started by the addition of substrate and NADPH. Mifepristone was used as a positive control for the MDI (in duplicate) to confirm the validity of the data. The positive control inhibitor showed a metabolism-dependent IC50-shift of at least 1.5-fold using both midazolam and testosterone as substrates.

Metabolite formation in incubation samples was analysed by UPLC-MS/MS. IC50 values were calculated for each of the positive control inhibitors and for neratinib if inhibition of metabolite formation was observed. Calculation of the IC50 shift by comparison of the IC50 after pre-incubation with NADPH (MDI) to the IC50 after pre-incubation without NADPH (TDI) provided characterisation of possible metabolism-dependent inhibition mechanisms.

In conclusion, the reversible (direct), time- and metabolism-dependent inhibition mechanisms of neratinib were evaluated.

Neratinib displayed reversible (direct) inhibition of CYP3A4 using both midazolam and testosterone as substrates with IC50 values of 13 µM and 56 µM, respectively. For reference the highest mean total (bound plus unbound) Cmax values of neratinib, observed after multiple, once-daily 240 mg oral doses of neratinib, were 73.1 ng/mL which equals to 109 nM (Day 7, healthy volunteers: Puma Biotechnology Study 3144A1-1116-US) and 81.5 ng/mL which equals to 121 nM (Day 15, Japanese cancer patient

treated with paclitaxel: Puma Biotechnology Study 3144A2-1115). These data suggest that the likelihood of clinically relevant direct inhibition of CYP3A4 by neratinib is remote when using the most conservative Cmax value of 121 nM.

Neratinib was not a time-dependent inhibitor of CYP3A4 using both midazolam and testosterone as substrates.

Neratinib produced marginal IC50-fold shifts (1.5-fold when using midazolam as substrate; 1.8-fold when using testosterone as substrate) for CYP3A4 which indicates that a metabolism-dependent inhibition mechanism may be involved.

Effect of neratinib as an inhibitor of CYP 2B6 (study 517195)

The objective of this study was to determine *in vitro* whether neratinib inhibited the metabolism of efavirenz using human liver microsomes (HLM). Reversible, time- and metabolism-dependent inhibitions were evaluated.

An UPLC-PDA-MS method for detection of efavirenz and its major metabolite 8-Hydroxyefavirenz was developed. A protein time dependency experiment and determination of the Michaelis-Menten parameters (Km and Vmax) were performed to establish the optimal incubation conditions in order to study efavirenz metabolism in pooled HLM.

Selection of the optimal incubation conditions was based on the formation of the major metabolite 8-Hydroxyefavirenz. The optimal incubation conditions were determined to be an incubation time of 30 minutes, a final protein concentration 0.15 mg/mL and a final efavirenz concentration of 5 µM.

After the method development part, the assay was validated by performing incubations in which the inhibiting effect of the control inhibitor ticlopidine at different concentrations (0, 0.03, 0.1, 0.3, 1, 3 and 10 µM) on the HLM-mediated efavirenz metabolism was investigated.

Since a concentration-dependent inhibiting effect was observed for HLM-mediated formation of 8-Hydroxyefavirenz by the control inhibitor ticlopidine, it was concluded that the metabolic conditions were successfully validated and could be used to perform the main study.

Incubations to determine reversible (direct) inhibition were performed at 37°C for 30 minutes. Neratinib was tested in triplicate at concentrations ranging from 0.03 to 100 µM. Neratinib working solutions to prepare incubations were made in ACN: MQ 1:7 (v:v). Ticlopidine was used as a positive control inhibitor (in triplicate) to confirm the validity of the data.

Incubations to determine possible TDI were performed using the same conditions as for the reversible inhibition with the only difference that an additional pre-incubation of neratinib with the microsomal mixture was performed in absence of NADPH for 30 minutes. After pre-incubation the reaction was started by the addition of substrate and NADPH.

Incubations to determine possible MDI were performed using the same conditions as for the reversible inhibition with the only difference that an additional pre-incubation of neratinib with the microsomal mixture was performed in presence of NADPH for 30 minutes. After pre-incubation the reaction was started by the addition of substrate and NADPH. ThioTEPA was used as a positive control for the MDI (in triplicate) to confirm the validity of the data.

Metabolite formation in incubation samples was analyzed by UPLC-MS/MS. IC50 values were calculated for each of the positive control inhibitors and for Neratinib if inhibition of metabolite formation was observed. Calculation of the IC50 shift by comparison of the IC50 after pre-incubation with NADPH (MDI) to the IC50 after pre-incubation without NADPH (TDI) provided characterization of possible metabolism-dependent inhibition mechanisms.

The reversible (direct), time- and metabolism-dependent inhibition mechanisms of neratinib on efavirenz metabolism were evaluated. Neratinib displayed reversible (direct) inhibition of HLM-mediated efavirenz metabolism. Since no IC50 values for reversible (direct) inhibition could be calculated, the IC_{50} value was determined to be >100 µM (the highest neratinib concentration tested). The IC50 values that were determined based on the averaged time- and metabolism-dependent curves were 38 µM and 57 µM, respectively. It was therefore concluded that neratinib is a time-dependent inhibitor (pre-incubation for 30 minutes in the absence of NADPH). The calculated IC50-fold shift (TDI/MDI) was 0.7 which indicates that neratinib is not a metabolism-dependent inhibitor of HLM-mediated efavirenz metabolism.

In vivo

An Open-label, Randomized, 2-period Crossover Drug Interaction Study to Evaluate the Potential Pharmacokinetic Interaction Between Multiple Doses of Ketoconazole and a Single Dose of Neratinib Administered Orally to Healthy Subjects (study 106)

This was a single centre, open label, randomized, 2-period, 2-sequence crossover, inpatient/outpatient study designed to assess the pharmacokinetics (PK) of a single 240 mg oral dose of Neratinib administered with or without multiple (5 days) 400 mg daily oral doses of ketoconazole. Each neratinib dose was separated by at least 13 days. Twenty four (24) healthy subjects (12 per treatment sequence; 23 male and 1 female; 16 White, 7 Black, 1 Asian) ranging from 19 to 48 years old with a mean BMI of 25.1 kg/m2 (77.06 kg) were enrolled. Twenty-one subjects completed the study. PK assessments were conducted following an overnight fast. Blood samples (15) were taken from 0 to 72 h post-dose and plasma concentrations of neratinib were measured by a validated HPLC-MS/MS assay. The geometric mean (log transformed) relative bioavailability of neratinib, C_{max}, AUC, and AUC_T and their 90% CIs were calculated to determine the magnitude of the effect of ketoconazole treatment on neratinib PK (with neratinib alone as the reference). Whole blood samples were available from 22 patients in periods 1 and 2.

Analyses showed that neratinib alone and neratinib administered with ketoconazole had mean peak drug concentrations (C_{max}) of 55 ng/mL and 201 ng/mL, respectively, and mean values for area under the concentration-time curve (AUC) were 903 ng•hr/mL and 4660 ng•hr/mL, respectively. Exposure within treatment was associated with a modest degree of intersubject variability, with CV values of 36 to 58% for Cmax and 45 to 53% for AUC. Time to reach peak plasma concentration (tmax) was consistent (median tmax = 6) between the two treatments. When neratinib was administered with ketoconazole, the mean apparent oral clearance of neratinib decreased approximately 4- fold, from 346 L/hr to 87 L/hr. Elimination half-life of neratinib increased from 12 to 18 h when neratinib was administered with concomitant ketoconazole. Neratinib PK parameters following a single 240 mg dose of neratinib alone and in combination with ketoconazole are summarized in Table 30. Findings from statistical comparison indicated that the least squares geometric mean (LSGM) ratios (and 90% confidence interval) for Cmax, AUCT, and AUC of neratinib were 321% (241 to 428%; p-value <0.001), 494% (365-669%; p-value <0.001), and 481% (359-645%; p value <0.0001), respectively.

Collectively, data indicated that exposure to neratinib was increased by 3.2-fold for Cmax and 4.8-fold for AUC when coadministered with ketoconazole compared with neratinib administration alone. This indicates that neratinib is a sensitive substrate of CYP3A and is susceptible to interaction with potent CYP3A inhibitors.

Metabolite PK were also determined after single 240 mg oral doses of neratinib with the CYP3A4/5 inhibitor ketoconazole (study 105) or the inducer rifampin (study 1110). After multiple doses of ketoconazole, mean (SD for M3 (n=6) and M7 (n=55), respectively) C_{max} was 3.93 ± 0.41 and 41.62 ± 26.28 ng/mL, respectively. Mean AUCT was 24 ± 19 and 419 ± 331 (n=54) ng•h/mL, respectively.

Median (range) tmax was 12 (5.0-24), and 4.0 (1.5-6.0), respectively. Mean t½ was 11.4 (n=1) for M3 and 7.73 ± 3.08 (n=54) for M7.

A Study to Examine the Potential Effect of Rifampin on the Pharmacokinetics of Neratinib when Administered Concomitantly to Healthy Subjects (study 1110)

This was an open label, single center, nonrandomized, crossover, sequential dose, inpatient/outpatient study designed to assess the effects of multiple doses of rifampin on the pharmacokinetics (PK) of a single 240 mg oral dose of neratinib. Twenty four (24) subjects (all men; 21 White, 3 Black) ranging from 21 to 50 years old with a mean BMI of 26.91 kg/m2 (81.39 kg) were enrolled. Twenty three (23) subjects completed the study (1 subject withdrew consent). Neratinib was given on Day 1 with a meal, and blood samples (10) were taken from 0 to 48 h post-dose on study Days 1 and 14). Rifampin (600 mg) was administered under fasted conditions on Days 8-15. On Day 14 neratinib 240 mg was administered with a standard breakfast one hour after rifampin. Plasma concentrations of neratinib and metabolites M3, M6, and M7 were measured by a validated HPLC-MS/MS assay with a LLOQ of 3 ng/mL (neratinib, M3, M7) and 1.5 ng/mL (M6). PK, calculated with WinNonlin v. 4.1 (Pharsight Corporation, Mountain View, CA), was available from 21 patients. PK parameters were compared statistically using separate ANOVA models for a nonrandomized crossover design. The geometric mean (log transformed) relative bioavailability of neratinib, Cmax, AUC, and AUCT and their 90% CIs were calculated to determine the magnitude of the effect of rifampin treatment on neratinib PK (with neratinib alone as the reference). There was no carryover of neratinib or metabolites between treatment periods.

Mean (SD) Cmax and AUC for neratinib were 47.68 (24.7) ng/mL and 928 ng•h/mL, and were decreased to 11 ng/mL and 113 ng•h/mL after multiple oral doses of rifampin. The apparent oral clearance of neratinib was increased approximately 7.5-fold by rifampin, from 321 to 2410 L/h. Mean Vz/F was also increased after rifampin, from 6200 L to 18200 L; however this parameter was highly variable. Mean elimination half-life was decreased from 13 to 5.7 h. Exposure to neratinib (Cmax, AUCT, AUC) was significantly ($p<0.001$) decreased to 24.05%, 6.87%, and 12.69%, respectively when 240 mg of neratinib was given with the CYP3A4 inducer rifampin. Mean Cmax and AUCT for M3 were increased by 235% and 310% relative to neratinib administered alone, and were 153% and 62% for M6 and 143% and 88% for M7.

An Open-label, 2-period, Fixed-sequence Study to Evaluate the Effects of Lansoprazole on the Pharmacokinetics of Neratinib in Healthy Subjects (study 0101)

This was an open label, 2-period, fixed sequence study conducted at a single site, designed to assess the effects of multiple doses of lansoprazole on the PK of a single 240 mg oral dose of neratinib. Fifteen (15) subjects (6 men, 9 woman; 14 White, and 1 Black) ranging from 28 to54 years old with a mean BMI of 27.85 kg/m^2 (75.08 kg) were enrolled and all subjects completed the study. Neratinib was given on Day 1 with a standard meal, and blood samples (19) were collected extensively from 0 to 72 h post-dose on study Days 1 and 5. 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 geometric mean (log transformed) relative bioavailability of neratinib, Cmax, AUC, and AUC0-t and their 90% CIs were calculated to determine the magnitude of the effect of lansoprazole treatment on neratinib PK (with neratinib alone as the reference). Evaluation of a drug interaction was based on whether the 90% CIs for the geometric mean ratios of neratinib PK (C_{max}, AUC_{0-t}, AUC_{0-inf}) for neratinib+lansoprazole vs neratinib alone lay entirely within the interval 80% to 125%.

There was no carryover of neratinib between treatment periods. Mean Cmax and AUC for neratinib alone were 84 ng/mL and 1478 ng•h/mL, and were significantly decreased to 24 ng/mL and 426 ng•h/mL after multiple oral doses of lansoprazole. The 90% CI ranged from 22.17-37.87 to 28.68-

42.18. Median tmax was delayed from 5.75 to 7.25 h. The apparent oral clearance of neratinib was increased approximately 3-fold by dosing with coadministration of lansoprazole, from 167 to 483 L/h. Mean apparent volume of distribution was also increased in combination with lansoprazole, from 3333 L to 9960 L. Mean elimination half-life was 14 h in both treatment groups. Exposure to neratinib (C_{max}, AUC_{0-t}, AUC) was lower by approximately 70% when 240 mg of neratinib was given with the proton pump inhibitor lansoprazole.

Raising gastric pH with the administration of lansoprazole decreases mean Cmax and AUC of neratinib, consistent with the in vitro pH-dependent solubility of neratinib.

Effect of paclitaxel, capacitabine, vinorelbine, temsirolimus and trastuzumab on the PK of neratinib

A number of phase 1/ 2 clinical studies were performed where neratinib was dosed in combination with other agents: paclitaxel, capacitabine, vinorelbine, or temsirolimus. In addition trastuzumab was dosed in the phase 2 study.

Reports show that the exposure to neratinib in cancer patients given multiple doses in combination with trastuzumab, paclitaxel, vinorelbine, or temsirolimus was very similar to exposure in cancer patients dosed solely with neratinib.

2.4.3. Pharmacodynamics

Neratinib is an irreversible covalent inhibitor of receptor tyrosine kinases ERBB1, ERBB2 and ERBB4. The applicant has investigated the primary pharmacodynamics by means of non-clinical *in vitro* and *in vivo* studies. In addition, exploratory pharmacodynamics biomarkers have been investigated in some clinical studies. Regarding secondary pharmacology, a thorough QT/QTc study has been conducted, and the effect of the dosing regimen on severity of diarrhoea has been evaluated. A PK/PD model has been constructed to investigate exposure-response relationships.

Mechanism of action

Neratinib is an orally bioavailable small molecule that irreversibly binds at the intracellular tyrosine kinase domain of the ERBB1 (HER-1 or EGFR), ERBB2 (HER-2), and ERBB4 (HER-4) receptors. All 3 receptors are tyrosine-protein kinases and consist of an extracellular ligand-binding domain, a single membrane-spanning region, and a cytoplasmic kinase domain. Ligand binding results in receptor oligomerisation (homo- or heterodimerisation), autophosphorylation, and intracellular signal transduction, ultimately leading to cell proliferation. Neratinib binding reduces ERBB1 and ERBB2 autophosphorylation, downstream signaling, and growth of ERBB1- and ERBB2-dependent cell lines, with cellular half-maximal inhibitory concentration (IC_{50}) <100 nM. *In vivo*, neratinib is active in ERBB2- and ERBB1-dependent tumor xenograft models when administered orally once-daily.

Neratinib's mechanism of action differs from that of trastuzumab, which binds to the juxtamembrane portion of the extracellular domain of the ERBB2 receptor to prevent activation of its intracellular tyrosine kinase.

Primary and Secondary pharmacology

Primary pharmacology

Study 3144A1-107-US (107)

Ascending Single Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HKI-272 Administered Orally to Healthy Subjects

This was a randomized, double-blind, placebo-controlled, sequential-group study of ascending single oral doses of neratinib (HKI-272) administered to healthy subjects after an overnight fast or with a high fat meal. Eight subjects (6 receiving active drug, 2 receiving placebo) were assigned to each of 7 sequential dose groups: 120 mg (fasted), 240 mg (fasted and fed), 400 mg (fasted), 640 mg (fasted), 800 mg (fasted), 400 mg (fed) and 640 mg (fed). Each subject participated in 1 period and received only 1 dose of neratinib except for those subjects who participated in the preliminary food-effect cohort (240 mg) who received the same single dose in period 1 and period 2 to assess preliminary food effects. Fifty-five subjects completed the study.

There were 118 pre- and post-dose (6 hours and 24 hours) 4 mm skin biopsy samples available from 40 subjects who received 120 to 800 mg doses of neratinib or placebo under fasted conditions. These skin biopsy samples were examined by an immunohistochemistry assay for activation of Erk, measured by phosphorylated Erk (p-Erk). There were no clear trends in the inhibition of p-Erk expression in skin.

Study 3144A1-102-US/B1891028 (102)

An Ascending Single and Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HKI-272 Administered Orally to Patients with HER-2/neu or HER-1/EGFR-positive Tumours

This was an open-label, ascending single and multiple dose study to assess the safety, tolerability, and define the maximum tolerated dose of neratinib in patients with advanced-stage tumour types expressing HER-2/neu (ERBB-2) or HER-1/EGFR (ERBB-1) refractory to prior therapy. Seventy two patients were dosed: cohorts of 3-6 patients received daily doses of 40 mg, 80 mg, 120 mg, 180 mg, 240 mg, 320 mg and 400 mg. In addition, there was an expanded MTD cohort. At baseline and day 21 (14 days of continual dosing) a skin biopsy and optional tumour biopsy were obtained. An analysis by immunohistochemistry was conducted for expression of the following markers: activated erbB-2 (perbB-2), activated erbB-1 (perbB-1), activated MAPK (pMAPK, pERK), activated AKT (pAKT), and p27Kip1.

Evaluable tumour samples were available for analyses from 3 subjects at 40 mg, 3 subjects at 80 mg, 4 subjects at 120 mg, 5 subjects at 180 mg, and 1 subject at 240 mg doses. Evaluable skin samples were available from 3 subjects at 40 mg, 4 subjects at 80 mg, 5 subjects at 120 mg, 4 subjects at 180 mg, 3 subjects at 240 mg, 5 subjects at 320 mg, 4 subjects at 400 mg, and 29 subjects at 320 mg (MTD cohort).

Expression of total erbB-1 in skin specimens was commonly observed. However p-ErbB-1 was less reliably observed due to insufficient numbers of sebaceous glands. Overall, there was not an appreciable difference in overall distribution in skin between pre-dose and post-dose expression of p-erbB-1 and pERK. Markers of erbB-2 activation status (total erbB-2, p-erbB-2, and pAKT) were not reproducibly observed in baseline and on treatment skin samples, prohibiting this PD evaluation. Trends for increase or decrease in p27 and pAKT expression were mixed across all cohorts, with slight changes up or down.

Regarding baseline and on-treatment tumour specimens, p-erbB-1 expression was typically lower post-dose than pre-dose. There was a trend towards a decrease in pERK expression post-dose compared to pre-dose.

Secondary pharmacology

Study 3144A1-1116-US/ B1891010 (1116)

A Double-blind, Sponsor-unblinded, Randomized, Multiple-dose, Parallel Group Study to Characterize the Occurrence of Mild to Moderate Diarrhoea After Administration of Neratinib Either 240 mg Once Daily or 120 mg Twice Daily for 14 Days to Healthy Subjects

The purpose of this study was to examine whether neratinib 120 mg, administered as a continual oral twice daily (BID) dose for 14 days could reduce the occurrence of diarrhoea, relative to neratinib 240 mg as a continual oral once daily (QD) dose over the same period of 14 days. Fifty healthy subjects (48 male, 2 female) were randomised to neratinib 240 mg QD or 120 mg BID with a standard meal and 240 mL of water. Dosage administration was discontinued for subjects with moderate or greater diarrhoea (NCI CTCAE version 3.0). Subjects were confined to the study site for 14 days and reported stool form each day according to the Bristol Stool Chart. The applicant was un-blinded to each subject's treatment throughout the study to evaluate subject safety data on an ongoing basis, while the investigator and subjects remained blinded to subject treatment throughout the study, by means of matching placebo capsules. The primary endpoint was the proportion of subjects with moderate diarrhoea. Subjects who had moderate diarrhoea or completed 14 days of dose administration were considered evaluable for the primary endpoint of the study. Plasma samples for PK analysis were also collected.

Five subjects discontinued dosage administration before 14 days because of moderate TEAEs other than diarrhoea: three subjects in 240 mg QD group (two subjects with dermatitis acneiform; one subject with abdominal pain) and two subjects in the 120 mg BID group (one subject with dermatitis acneiform and one subject with moderate increase in transaminase levels).

Eleven of 22 evaluable subjects (50%) reported moderate diarrhoea following administration of neratinib 240 mg QD, and 17 of 23 evaluable subjects (74%) reported moderate diarrhoea following administration of neratinib 120 mg BID. All fifty study subjects reported diarrhoea of mild or greater severity. Kaplan-Meier curves demonstrated that the onset of mild diarrhoea (median around 2 days) was not affected by dosing frequency. The onset of moderate diarrhoea was delayed for the 240 mg QD group compared to the 120 mg BID group (median onset approximately 9 days and 6 days respectively). The mean ratio (BID to QD at steady-state) of neratinib exposure (Cmax and AUC) following multiple oral doses of neratinib 120 mg BID to 240 mg QD on day 7, was 0.68 for Cmax and 0.82 for AUC0-24h.

Study 3144A1-105-US/B1891031 (105)

A Single Dose, Crossover, Placebo-and-Moxifloxcin-Controlled Study of the Effects of Neratinib (HKI-272) on Cardiac Repolarization in Healthy Adult Subjects

This was a randomized, single-dose, double-blind (with respect to neratinib), crossover, placebo- and open-label moxifloxacin-controlled thorough QT/QTc study in healthy men or women, conducted at a single site. Part A consisted of 3 periods in which subjects were administered a single dose of neratinib 240 mg, placebo, or moxifloxacin 400 mg in a fed state (high-fat meal). Part B consisted of 2 periods in which subjects were administered a single dose of neratinib 240 mg or placebo concomitantly with ketoconazole 400 mg daily (days -1 to 3) in a fasting state. Subjects were randomly assigned to 1 of 12 dosage administration sequences, which consisted of a combination of each of the 5 treatment arms. Each period was separated by a 5-day washout. Each neratinib dose was separated by a minimum 14-day washout. Triplicate electrocardiogram (ECG) recordings were obtained on day 1 at -1, -0.5 and 0 hours (pre-dose), and at 1.5, 3, 4, 5, 6, 8, 12, 24 and 48 hours post-dose. Blood samples were collected to measure concentrations of neratinib and metabolites within 2 hours pre-dose and at 1.5, 3, 4, 5, 6, 8, 12, 24, and 48 hours post-dose.

Statistical analysis of QTc, QT interval, and heart rate data was conducted on baseline adjusted data, on the average of the triplicate ECG readings at each time-point. Four different heart rate correction

formulas were applied to the data: QTcN (QTc based on a population-specific correction formula), QTcI (QTc based on an individual-specific correction), QTcF (QTc based on Fridericia's correction) and QTcB (QTc based on Bazett's correction).

Sixty subjects were enrolled in this study, 47 men and 13 women, age range 18 to 57 years. Eight subjects discontinued, one due to an AE following moxifloxacin administration (ventricular extrasystoles). With concomitant administration of ketoconazole, the mean Cmax and mean AUC0-t of neratinib were increased 2.4-fold and 3-fold respectively. For the M3 metabolite, the mean Cmax and mean AUC0-t were both decreased 3-fold with concomitant ketoconazole. For the M7 metabolite, the mean Cmax and mean AUC0-t were increased 3.7-fold and 4.3-fold respectively with concomitant ketoconazole.

The 90% upper bound of the mean difference in baseline adjusted QTcF for neratinib 240 mg (with and without ketoconazole) vs placebo did not exceed 5 msec. The results for QT, QTcN, QTcI and QTcB were in line with QTcF for neratinib vs placebo and neratinib + ketoconazole vs placebo + ketoconazole. For moxifloxacin vs placebo, the greatest baseline adjusted mean difference in QTcF was 9.18 msec (90% CI: 7.12, 11.25) at 4.0 hours post-dose. There were no increases from baseline of QTcF of > 30 msec for placebo, neratinib or neratinib + ketoconazole. There were no QTc intervals >450 msec (men) or 370 msec (women).

The PK/PD relationships between QTcN and neratinib (with and without ketoconazole), and between QTcN and moxifloxacin, were examined graphically and statistically. A slight positive relationship was identified for moxifloxacin (slope coefficient 1.04; p=0.0016) but not neratinib (slope coefficient –0.48).

Relationship between plasma concentrations and effect

The Applicant has conducted a population PK/PD analysis (study PUMA-PCS-101) to explore the relationship between exposure metrics derived from the population PK model and efficacy/safety endpoints. The PK/PD analysis included all patients from studies 104, 201, 2206 and 3003 who received at least one dose of study drug and had at least one efficacy or safety endpoint collection (n=378). Safety endpoints included grade 3 or greater diarrhoea or fatigue, and elevated liver enzymes ALT or AST. The efficacy endpoint evaluated was objective response (partial response + complete response). For each efficacy and safety endpoint, individual responses were plotted versus exposure (AUCss). A generalized linear model for a binomial distribution with a logistic link function was used to characterize the relationship. Binomial CIs (95%) were computed and displayed on the plot. The linear fit and CI bounds were back-transformed from the log-odds domain to give probability of the response conditional on exposure.

The objective response rate for the PK/PD population was 40.4% (non-evaluable patients considered non-responders). The linear relationship between objective response and AUCss is statistically significant at the 0.95 confidence level for monotherapy but not for combination therapy:

For incidence of diarrhoea, fatigue and elevated liver enzymes, none of the linear relationships with AUCss for either combination therapy or monotherapy were significant at the 0.95 confidence level.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Following oral administration of 240 mg neratinib, absorption was slow and peak plasma concentrations of neratinib occurred around 7 hours after administration. A single dose of 240 mg neratinib taken with food increased C_{max} and AUC by approximately 17% and 23%, respectively,

compared with administration in the fasting state. A single oral dose of 240 mg neratinib taken with a meal high in fat increased both C_{max} and AUC by approximately 100%.

Binding of neratinib to human plasma proteins, including covalent binding to human serum albumin (HSA), was greater than 98% and independent of concentration. Neratinib bound predominantly to HSA and human alpha-1 acid glycoprotein (AAG). *In vitro* studies demonstrated that neratinib is a substrate for {-glycoprotein (P-gp). Neratinib was not a potent inhibitor of human BSEP efflux transporter activity in vitro, with a reported IC50 value of > 10µM. Neratinib at 10 µM appeared to inhibit the BCRP efflux transporter. Neratinib produced no inhibitory activity towards the uptake transporters, OATP1B1*1a, OATP1B3, OAT1, OAT3 and OCT2, with reported IC50 values were > 10µM. Neratinib produced inhibitory activity in OCT1 uptake transporter, with an IC50 of 2.9 µM.

Neratinib is metabolised primarily in liver microsomes by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).

Preliminary metabolite profiling in human plasma indicates that after oral administration, neratinib undergoes oxidative metabolism through CYP3A4. Circulating metabolites include neratinib pyridine N-oxide (M3), N-desmethyl neratinib (M6), neratinib dimethylamine N-oxide (M7) and traces of hydroxyl neratinib N-oxide and neratinib bis-N-oxide (M11). Neratinib represents the most prominent component in plasma and systemic exposure to the metabolites (M3, M6, M7 and M11) after oral administration of neratinib is between 10% and 33% lower than parent in healthy subjects. The neratinib metabolites M3, M6, M7 and M11 were shown to have similar potencies to neratinib in either in vitro enzyme (binding assays) or cell based assays against cells expressing ERBB1, ERBB2 (HER2) and ERBB4.

The Applicant is conducting another mass balance study (study PUMA-NER-0105) which is expected to be finalised by end of 2018. The primary objectives of this study are to determine the recovery of radioactivity, the whole blood to plasma concentration of total radioactivity, the urinary and faecal recovery of total radioactivity, and provide plasma urine and faecal samples for metabolite profiling and metabolite identification. In the event that additional major metabolites are identified the Applicant will consider the evaluation of plasma protein binding and pharmacokinetic characterisation. Profiling of neratinib and metabolites to isolate and quantify the peaks of interest will be conducted. M11 is only 4% of the total serum concentrations of neratinib and therefore as a minor metabolite has a limited role in comparison to parent and major metabolites (M3, M6, and M7). The Applicant committed to continue bioanalytical assay development in order to characterise M11. In addition, M10 is <1% of parent and is considered a minor metabolite and has not been characterised.

Following single doses of neratinib, the mean apparent plasma half-life of neratinib was 17 hours in patients. Excretion of neratinib is primary via the faeces. Following the administration of a single radiolabelled dose of 200 mg neratinib oral solution, 97.1% and 1.1% of the administered dose was recovered in the faeces and urine, respectively. The excretion was rapid and complete, with the majority of the radioactivity (61%) recovered within 96 hours and 98% recovered after 10 days. It is not known if elimination is as unchanged drug or metabolites. As mentioned above the Applicant is conducting another mass balance study (study PUMA-NER-0105) which is expected to be finalised by end of 2018.

Neratinib exposure increases linearly with dose in healthy volunteers up to doses of 640 mg above this the exposure increases less than proportionally to dose. In patients, with food, the results are broadly similar. The non-linearity is more marked at lower doses in the fasted state. This is non-linearity is probably due to solubility limited absorption. Following multiple, once a day, dosing in patients the accumulation ratio is 1.2 to 1.7 fold, consistent with the half-life. Steady state is reported to be reached by Day 4.

A population PK model (POPPK) was used to investigate the effects of covariates and to estimate exposure for the exposure response modelling. In the POPPK model inter-individual variability on clearance was 47%, intra-individual variability was not measured but the residual error was 35%. Gender and race do not appear to affect the pharmacokinetics of neratinib. Weight and age were included as covariate in the POPPK model. A statement that no dose adjustment is required in elderly patients and that no data is available in patients above 85 years of age was proposed to be included in section 4.4 of the SmPC.

Pharmacokinetic studies in patients with renal impairment or undergoing dialysis have not been carried out. Population pharmacokinetic modelling revealed that creatinine clearance did not explain the variability between patients, hence, no dose modifications are recommended for patients with mild to moderate renal impairment. A warning was proposed in section 4.4 of the SmPC: "Patients with renal impairment are at a higher risk of complications of dehydration if they develop diarrhoea, and these patients should be carefully monitored (see section 4.2)". In addition, use in patients with severe renal impairment was considered to be included as missing information in the RMP.

Neratinib is extensively metabolised in the liver. In subjects with severe pre-existing hepatic impairment (Child Pugh Class C) without cancer, the clearance of neratinib was decreased by 36% and exposure to neratinib increased by about 3-fold as compared to healthy volunteers. Use in patients with significantly impaired hepatic function (Child-Pugh class C) was considered to be included as missing information in the RMP.

Co-administration of a single oral dose of 240 mg of neratinib in the presence of ketoconazole (400 mg once daily for 5 days), a strong CYP3A4/Pgp inhibitor, increased neratinib systemic exposure. The Cmax of neratinib increased by 3.2 fold and AUC increased by 4.8 fold when co-administered with ketoconazole, compared with neratinib administered alone.

Concomitant use of strong CYP3A4/Pgp inhibitors (e.g. atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, clarithromycin, telithromycin, and voriconazole) should be avoided. Grapefruit or grapefruit juice may also increase neratinib plasma concentrations and should be avoided. This was considered to be addressed in section 4.4 and 4.5 of the SmPC.

The solubility of neratinib is pH-dependent. Concomitant treatment with substances that increase gastric pH should be avoided, as neratinib solubility and absorption may decrease. A single 240 mg dose of neratinib combined with lansoprazole decreased AUC by up to 70%. Co-administration with proton pump inhibitors (PPIs) and H2-receptor antagonists is not recommended. Separate dosing of Nerlynx and antacids by at least 3 hours.

Following concomitant administration with repeated doses of 600 mg rifampin, a strong CYP3A4/Pgp inducer, neratinib exposures were significantly decreased with mean values that were 24% and 13% of reference values (neratinib administered alone) for Cmax and AUC, respectively.

Concurrent use of neratinib with potent CYP3A4/Pgp inducers (e.g. phenytoin, carbamazepine, rifampin, phenobarbital or herbal preparations containing St John's Wort/Hypericum perforatum) should be avoided. This was considered to be addressed as a contraindication in section 4.3 of the SmPC.

It is currently unknown whether Nerlynx reduces the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method. The Applicant committed to conduct a clinical study to investigate the possible interaction with oral contraceptives and to provide the final results post-approval.

Neratinib may inhibit breast cancer resistance protein (BCRP) moderately as suggested by *in vitro* studies. Clinical studies with BCRP substrates have not been conducted. Patients who are treated with BCRP inhibitors (e.g., rosuvastatin and sulfasalazine) should be monitored carefully.

In *in-vitro* studies, neratinib is an inhibitor of P-glycoprotein (P-gp) substrates. In healthy subjects, digoxin increased Cmax by 54% and AUC increased by 32% when co-administered with multiple oral doses of neratinib 240 mg compared with exposures of digoxin alone. The clearance values of digoxin were equivalent following digoxin and digoxin plus neratinib. It appeared that the inhibitory effect of neratinib was primarily on P-gp activity in the gastrointestinal tract as a result of pre-systemic inhibition. This pre-systemic interaction of neratinib with digoxin might be clinically relevant for P-gp substrates with a narrow therapeutic window (e.g. dabigatran, digoxin, and fexofenadine). Patients who are treated concomitantly with therapeutic agents whose metabolism involves P-gp substrates in the gastrointestinal tract should be monitored carefully.

Drug-drug interaction (inhibitors and inducers of CYP3A4, PPIs, H2-receptor antagonists, antacids, and P-gp transporters), this was proposed to be reflected in section 4.5 of the SmPC and was added as an important identified risk in the RMP.

Pharmacodynamics

Neratinib is an orally bioavailable small molecule that irreversibly binds at the intracellular tyrosine kinase domain of the ERBB1 (HER-1 or EGFR), ERBB2 (HER-2), and ERBB4 (HER-4) receptors. All 3 receptors are tyrosine-protein kinases and consist of an extracellular ligand-binding domain, a single membrane-spanning region, and a cytoplasmic kinase domain. Ligand binding results in receptor oligomerisation (homo- or heterodimerisation), autophosphorylation, and intracellular signal transduction, ultimately leading to cell proliferation. Neratinib binding reduces ERBB1 and ERBB2 autophosphorylation, downstream signalling, and growth of ERBB1- and ERBB2-dependent cell lines, with cellular half-maximal inhibitory concentration (IC50) <100 nM. In vivo, neratinib is active in ERBB2- and ERBB1-dependent tumour xenograft models when administered orally once-daily.

The Applicant explored the effect of neratinib on pharmacodynamics (PD) biomarkers in healthy volunteers and patients.

Study 3144A1-1116-US/ B1891010 was conducted to characterise the occurrence of mild to moderate diarrhoea after administration of neratinib either 240 mg once daily or 120 mg twice daily for 14 days to 50 healthy subjects. Eleven of 22 evaluable subjects (50%) reported moderate diarrhoea following administration of neratinib 240 mg QD, and 17 of 23 evaluable subjects (74%) reported moderate diarrhoea following administration of neratinib 120 mg BID. All fifty study subjects reported diarrhoea of mild or greater severity. Based on this result, a twice daily regimen does not reduce the frequency of moderate diarrhoea or delay its onset compared to a once daily regimen.

Study 3144A1-105-US/B1891031 was a randomized, single-dose, double-blind (with respect to neratinib), crossover, placebo- and open-label moxifloxacin-controlled thorough QT/QTc study in healthy volunteers. With concomitant administration of ketoconazole, the mean C_{max} and mean AUC_{0-t} of neratinib were increased 2.4-fold and 3-fold respectively. For the M3 metabolite, the mean C_{max} and mean AU_{C0-t} were both decreased 3-fold with concomitant ketoconazole. For the M7 metabolite, the mean C_{max} and mean AU_{C0-t} were increased 3.7-fold and 4.3-fold respectively with concomitant ketoconazole.

The 90% upper bound of the mean difference in baseline adjusted QTcF for neratinib 240 mg (with and without ketoconazole) versus placebo did not exceed 5 msec. The results for QT, QTcN, QTcI and QTcB were in line with QTcF for neratinib vs placebo and neratinib + ketoconazole vs placebo + ketoconazole. For moxifloxacin vs placebo, the greatest baseline adjusted mean difference in QTcF was

9.18 msec (90% CI: 7.12, 11.25) at 4.0 hours post-dose. There were no increases from baseline of QTcF of > 30 msec for placebo, neratinib or neratinib + ketoconazole. There were no QTc intervals >450 msec (men) or 370 msec (women).

The PK/PD relationships between QTcN and neratinib (with and without ketoconazole), and between QTcN and moxifloxacin, were examined graphically and statistically. A slight positive relationship was identified for moxifloxacin (slope coefficient 1.04; p=0.0016) but not neratinib (slope coefficient –0.48).

This thorough QT/QTc study demonstrated that the parent drug neratinib does not prolong the QT/QTc interval. The Applicant has provided non-clinical study reports examining the hERG channel inhibition due to metabolites M3, M6 and M7. These indicate similar IC50 values to the parent compound and are present to sufficiently high safety margins to be of limited concern.

The Applicant has conducted a population PK/PD analysis (study PUMA-PCS-101) to explore the relationship between exposure metrics derived from the population PK model and efficacy/safety endpoints. The PK/PD analysis included all patients from studies 104, 201, 2206 and 3003 who received at least one dose of study drug and had at least one efficacy or safety endpoint collection (n=378). Safety endpoints included grade 3 or greater diarrhoea or fatigue, and elevated liver enzymes ALT or AST. The efficacy endpoint evaluated was objective response (partial response + complete response). The objective response rate for the PK/PD population was 40.4% (non-evaluable patients considered non-responders). The linear relationship between objective response and AUCss was statistically significant at the 0.95 confidence level for monotherapy but not for combination therapy. This provides some justification for the dose selection of 240 mg daily which was the maximum dose tolerated during Phase 1/2. For incidence of diarrhoea, fatigue and elevated liver enzymes, none of the linear relationships with AUCss for either combination therapy or monotherapy were significant at the 0.95 confidence level. A clear relationship between exposure and incidence of diarrhoea has not been observed. It has been suggested that gastrointestinal toxicity of TKIs is predominantly luminal origin, which would explain the lack of relationship.

2.4.5. Conclusions on clinical pharmacology

Overall the pharmacokinetics of neratinib is well characterised in healthy volunteers and patients with no significant difference observed between exposure in healthy volunteers and patients or for different gender and race. The results of a new mass balance study and of a clinical study investigating the possible interaction with oral contraceptives are missing to support the long term safety of neratinib. Neratinib is a substrate of Pgp and inhibits Pgp and BCRP. Neratinib and its major metabolite, M6, show time dependency of inhibition of CYP 3A4 and 2B6 but it is not currently known if this is physiologically relevant. A number of co-administered products were tested: paclitaxel, vinorelbine, capecitabine, temsirolimus and trastuzumab and show no significant effect on the exposure of neratinib.

The mechanism of action is adequately described. The applicant has evaluated exploratory primary pharmacodynamics biomarkers in some clinical studies. The thorough QT/QTc study demonstrated that the parent drug neratinib does not prolong the QT/QTc interval. The Applicant has provided non-clinical study reports examining the hERG channel inhibition due to metabolites M3, M6 and M7. These indicate similar IC50 values to the parent compound and are present to sufficiently high safety margins to be of limited concern.

The PK/PD model demonstrates a positive exposure response relationship, supporting the dose selection. However, only a slight positive trend in dose-response was observed for incidence of moderate diarrhoea.

2.5. Clinical efficacy

2.5.1. Dose response studies

Results from 3 studies led to the selection of 240 mg daily as the optimal dose: study 102 (first-in-human), study 200 (phase 2 in non-small cell lung cancer) and study 104 (phase 1 in Japan).

Study 3144A1-102-UK (102)

An Ascending Single and Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HKI-272 Administered Orally to Subjects with HER-2/Neu or HER-1/EGFR-Positive Tumours

This phase 1 open-label sequential group study was designed to assess the tolerability and safety, to define the maximum tolerated dose (MTD), and assess anti-tumour activity. Subjects were eligible if analysis of tumour biopsy by a central laboratory showed HER2 or EGFR positivity (+1, +2 or +3 levels) by immunohistochemistry (IHC). Each subject participated in only 1 dose group and received a single dose of neratinib, followed by a 1-week observation period, and then received the same dose administered once daily with food for up to 6 months (6 cycles) or until progression or unacceptable toxicity. Subjects were enrolled in cohorts of 3 to 6. Up to 40 subjects were enrolled in the MTD cohort. The following doses were planned: 40 mg, 80 mg, 120 mg, 180 mg, 240 mg, 320 mg and 400 mg. The starting dose was based on non-clinical data.

A dose-limiting toxicity (DLT) was defined as any neratinib-related non-haematologic grade 3 or any grade 4 adverse event (AE) except grade 3 nausea, vomiting, or diarrhoea, unless subject was receiving appropriate medical therapy. Additional DLTs included grade 2 diarrhoea lasting > 2 days on medical therapy or associated with fever or dehydration. If none of 3 to 6 subjects in a dose cohort had a neratinib-related grade 3 or 4 DLT by day 14 of continuous daily dose administration, then inclusion of 3 to 6 subjects at the next dose level continued. If 1 of 3 to 6 subjects at a dose level had a neratinib-related grade 3 or 4 DLT by day 14 of continuous daily dose administration, then 6 subjects were treated at the same dose level. The dose was escalated if only 1 of 6 subjects had a DLT. If 2 of 3 to 6 subjects at a dose level had a neratinib-related DLT by day 14 of continuous daily dose administration, dose escalation stopped and the prior dose level was considered the MTD. Up to 40 additional subjects were to be added at the MTD. The MTD cohort was expanded to include 10 subjects with NSCLC that had progressed after at least 8 weeks of treatment with either erlotinib or gefitinib, and 10 subjects with breast cancer. Disease assessments were performed at screening and at every 2 cycles.

A total of 73 subjects were enrolled, of which 72 were treated (20 men and 52 women). Median age was 57 years. The predominant tumour types were breast (n=29) and NSCLC (n=15). Thirteen subjects were excluded from the efficacy evaluation. All were excluded either because they had no follow-up tumour assessment or because they received <2 weeks of treatment without early progressive disease or death and had no follow-up tumour assessment. In the total evaluable population of 60, eight (13.3%) subjects had a best overall response of partial response. In the expanded MTD cohort (320 mg), six (16.2%) subjects had a best overall response of partial response. In the 25 evaluable patients with breast cancer, eight (32.0%) had a best overall response of partial

response. The median duration of response was 4.8 months in subjects with breast cancer. There were no subjects with partial response for NSCLC or other tumour types.

The primary DLT was diarrhoea. DLT was not reported among subjects who received neratinib at doses of 40 mg to 120 mg and 1 subject had grade 3 diarrhoea at the 180-mg dose level. Four subjects at the 400-mg dose level had grade 3 diarrhoea, and per protocol, the MTD was determined to be 320 mg. The 320-mg dose level was expanded to include an additional 39 subjects to confirm the safety and tolerability of the MTD. The most common AEs in the expanded MTD cohort were diarrhoea in 36 (92.3%) subjects, nausea in 21 (53.8%) subjects, fatigue in 19 (48.7%) subjects, and vomiting in 19 (48.7%) subjects. The most common grade 3 or higher AE in the expanded MTD cohort were diarrhoea in 16 (41.0%) subjects and dehydration in 3 (7.7%) subjects. In the 240 mg cohort (n=3), all subjects reported diarrhoea, but there were no grade 3 or higher AEs.

Study 3144A1-200-WW/B1891037 (200)

A Phase 2 Study of Neratinib in Subjects with Advanced Non-Small Cell Lung Cancer

This open-label non-randomized study was designed to evaluate the efficacy of neratinib in subjects with advanced non-small cell lung cancer (NSCLC). Oral neratinib was evaluated at doses of 240 mg daily and 320 mg daily with food for one year. A total of 172 patients were enrolled, of which 167 were treated. Median age was 60 years and 118 (71%) subjects were women. There were 4 (2.4%) subjects with a best response of partial response. A total of 128 subjects were started on 240 mg daily and 39 subjects were started on 320 mg daily.

The proportion reporting a Grade 3 or higher AE was 71.8% for the 320 mg cohort vs 53.9% for the 240 mg cohort. AEs led to dose reduction in 48.7% and 21.1% of the 320 mg and 240 mg cohorts respectively. AEs led to discontinuation in 10.3% and 5.5% of the 320 mg and 240 mg cohorts respectively. AEs of diarrhoea were reported for 92.3 and 90.6% of the 320 mg and 240 mg cohorts respectively. Regarding Grade 3 or higher AEs, blood and lymphatic system disorder AEs were reported in 12.8% and 3.1% of the 320 mg and 240 mg cohorts respectively. Diarrhoea ≥ grade 3 was reported in 46.2% and 22.7% of the 320 mg and 240 mg cohorts respectively. Diarrhoea led to dose reduction in 33.3% and 14.8% of the 320 mg and 240 mg cohorts respectively, and to discontinuation in 5.1% and 1.6% respectively.

Study 3144A1-104-JA (104)

An Ascending Single and Multiple Dose Study of the Safety, Tolerability, and Pharmacokinetics of Neratinib Administered Orally to Japanese Subjects with Advanced Solid Tumours

This open-label, phase 1, ascending single and multiple oral dose study was designed to assess the safety and tolerability and to define the MTD of orally administered neratinib in subjects with advanced solid tumours. The preliminary anti-tumour activity was also evaluated. Each subject participated in only 1 dose group and received a single dose of neratinib. This was followed by a 1-week observation period, and the subject then received neratinib administered as a continual oral daily dose with food for up to 6 months (6 cycles). Subjects were enrolled in cohorts consisting of 3 to 6: 40 mg, 80 mg 160 mg, 240 mg and 320 mg. DLT was defined as any drug-related non-hematologic grade 3 or any grade 4 AE except grade 3 nausea, vomiting, diarrhoea, or rash, unless the subject was receiving appropriate medical therapy. Additional DLTs included the following: grade 2 or 3 diarrhoea lasting >2 days for which the subject was receiving medical therapy or that was associated with fever or dehydration.

Twenty-one subjects were enrolled (8 women and 13 men), 3 subjects in the neratinib 80-mg cohort, 3 subjects in the 160-mg cohort, 10 subjects in the 240-mg cohort, and 5 subjects in the 320-mg cohort. Median age was 61 years. Seventeen subjects had a primary cancer diagnosis of colorectal

cancer, 3 subjects had a diagnosis of breast cancer, and 1 subject had a diagnosis of gastric cancer. All patients reported diarrhoea except for one patient in the 40 mg-cohort. DLTs were reported for 2 subjects in the 320 mg cohort, one with grade 3 diarrhoea and grade 3 anorexia, and one with grade 2 diarrhoea and grade 3 anorexia. Neratinib 240 mg was determined to be the MTD. Two subjects (9.5%) had a best overall response of partial response.

Based on the data from these 3 studies, the recommended dose for the pivotal phase 3 study was 240 mg daily with food..

2.5.2. Main study

Study 3144A2-3004-WW

The Applicant has submitted the data from a single phase 3 pivotal study in support of this application. This was a multicentre, randomized, double-blind, placebo-controlled trial of neratinib in women with early stage HER2 over-expressed (+) breast cancer. The primary objective of this study was to compare invasive disease-free survival (iDFS) of women with early-stage HER2+ breast cancer who received neratinib or placebo, following trastuzumab in the adjuvant setting. The study was initiated in 2009 and is on-going (the last patient completed 5-year follow-up in October 2016).

The original Sponsor was Wyeth. The Sponsor was changed to Pfizer under Amendment 3 (25/02/2010) following the acquisition of Wyeth by Pfizer. Sponsorship was transferred to Puma Biotechnology, Inc. under Amendment 11 (21/03/2012). There was a total of 13 protocol amendments of which 6 were global. All of them were initiated after recruitment had commenced. The amendments included changes to the eligibility criteria, sample size and study length.

Methods

Study 3144A2-3004-WW was a phase 3, multicentre, randomized, double-blind study of neratinib versus placebo in women with early-stage HER2-overexpressed/amplified breast cancer who have received adjuvant treatment with trastuzumab. Eligible patients were randomized in a 1:1 ratio to treatment with either neratinib daily or placebo daily for a period of 1 year. The study consisted of 3 parts:

- Part A: Follow-up period of 2 years post randomization to provide data for the primary analysis (iDFS)
- Part B: Extended follow-up for 2-5 years – recurrent disease events and deaths ascertained from medical records upon re-consent
- Part C: Long-term follow-up of overall survival (OS).

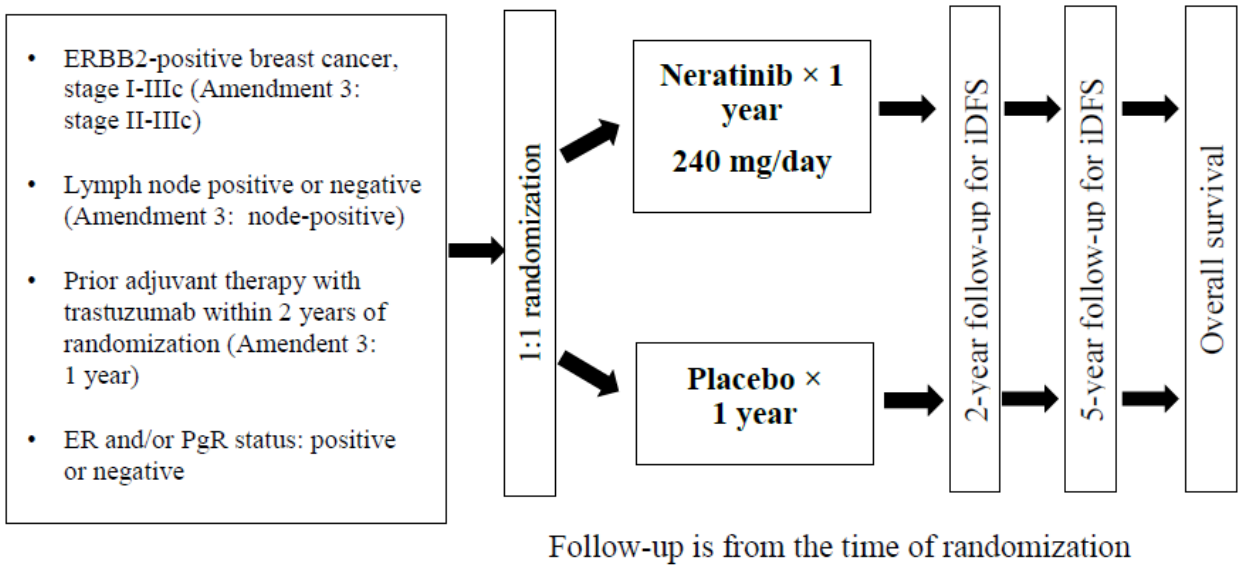


Figure 2 Design of study 3004

During first 2 years (Part A), study visits were scheduled at 1, 3, 6, 9, 12 months and 2 years. Brief, symptom-guided physical examinations were conducted at months 1, 3, 6 and 9. A full physical examination was conducted at month 12. Mammograms were conducted at baseline and every 12 months.

For patients who discontinued the treatment period due to distant recurrence:

- Survival information was collected every 6 months.
- The first new anti-cancer treatment after completion of the treatment period was to be collected.

For patients who discontinued the treatment period due to reasons other than distant recurrence, or patients who completed the entire 1-year treatment period:

- Targeted physical examinations (including, but not limited to, breast and loco-regional lymph node draining areas) was continued to be performed until documentation of distant recurrence every 4 months for 2 years post-randomization.
- Mammogram, when appropriate every 12 months
- Survival information was to be collected every 6 months
- The first new anti-cancer treatment after completion of the treatment period was to be collected.

As clinically indicated, and in case of any new symptoms or signs indicative of potential recurrence, bone scan, CT, ultrasound, or MRI scan of chest, abdomen, or pelvis were performed. Pathology was obtained to confirm local or regional recurrence, and pathology and/or radiology to confirm distant recurrence.

From 2-5 years post-randomization, recurrent disease events and deaths were ascertained from the patient's medical records upon re-consent of the patient. Survival follow-up will continue for patients who re-consented for long-term follow-up and will start from 5 years post-randomization.

Study Participants

Inclusion criteria

For inclusion into the trial, patients were required to fulfil all of the following criteria:

1. Histologically-confirmed primary adenocarcinoma of the breast that was ERBB2-positive by one of the following assays, performed locally:
    - Fluorescence in situ hybridization or silver in situ hybridization (SISH) showing gene amplification (defined as >2.2), OR
    - Chromogenic in situ hybridization (CISH) showing gene amplification according to the manufacturer's kit instructions, OR
    - Immunohistochemistry assay showing strong positive (i.e. 3+ in ≥30% of invasive tumour cells) staining score.
2. Archived diagnostic tumour sample had to be available, and patient had to agree to submission of sample for central ERBB2 testing. (For confirmation of eligibility, results from local ERBB2 testing were acceptable.)
3. Primary tumour ER/PR status had to be known before study entry. [Patients were ER and/or PR+ve or ER and PR–ve. There was no pre-specified quantitative requirement for HRc status]
4. Patients must have had completed a course of prior adjuvant trastuzumab. If less than 12 months of trastuzumab had been given, at least 8 prior doses of weekly trastuzumab, or at least 3 prior doses of trastuzumab given every 3 weeks must have been administered. Also, it had to be specified that the patient was either not eligible or unable to receive further adjuvant trastuzumab, since the patient either 1) completed the intended treatment course of adjuvant trastuzumab-based on published data (FinHER regimen), or 2) experienced side effects that resulted in early discontinuation of trastuzumab that have since resolved.
5. If patients had prior neoadjuvant therapy (chemotherapy with or without neoadjuvant trastuzumab, regardless of nodal status at initial diagnosis), they were eligible provided they had residual invasive cancer in the breast and/or axilla after completing neoadjuvant therapy. Patients were excluded if they achieved a pathologic complete response (pCR) in breast and axilla (if axillary status was known), or if they have only residual in situ disease in breast (DCIS) and pCR in axilla (if axillary status was known).
6. The last dose of trastuzumab must have been given >2 weeks and <2 year from randomization. [Revised in Amendment 3 to >2 weeks and ≤1 year from randomization]
7. Had a diagnosis of Stage 1 through Stage 3c primary breast cancer with node negative or axillary node-positive disease according to the American Joint Committee on Cancer (sixth edition) staging criteria for breast cancer. (For clarification, isolated tumour cells are considered pN0 and micrometastases are considered pN1.) Note that patients who completed neoadjuvant therapy and had residual invasive disease only in the breast, with negative or unknown nodal status, were eligible. [Revised in Amendment 3 to include only Stage 2 through 3c and axillary node-positive disease]
8. Adequately treated primary breast cancer with surgery, as defined by prior mastectomy OR lumpectomy, with margins clear of invasive carcinoma and ductal carcinoma in situ. Patients with positive sentinel node biopsies had to have subsequent axillary dissection to be eligible.

9. Completed treatment with a neoadjuvant or adjuvant chemotherapy regimen containing an anthracycline and/or a taxane or any cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen.
10. Clinical and radiologic assessments that were negative for local or regional recurrence of disease or metastatic disease at the time of study entry, including:
    - Bone scan; required only if alkaline phosphatase (ALP) is ≥2 x upper limit of normal (ULN) and/or there are symptoms of metastatic bone disease. A confirmatory imaging study was required if the results from the bone scan were questionable.
    - Computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound of the abdomen and chest; required only if aspartate transaminase (AST)/alanine transaminase (ALT) or ALP is ≥2 x ULN.
    - Chest radiograph.
11. Negative bilateral mammogram (or unilateral mammogram of the remaining breast if unilateral total mastectomy was performed) within 12 months (≤365 days) before randomization. Mammogram was not indicated in case of bilateral total mastectomy.
12. Patients with bilateral breast cancers were eligible only if their cancers were synchronous (i.e. diagnosed at the same time [occurring within 6 months of each other]). One or both tumors needed to be ERBB2-positive. One could be negative.
13. Female patients aged 18 years or older. (For Japan: 20 years or older).
14. Subjects must have had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
15. QTc interval had to be ≤0.450 seconds.
16. Adequate organ function as defined by:
    - Absolute neutrophil count: ≥1.5 × 109/L (1500/mm3).
    - Platelet count: ≥100 × 109/L (100,000/mm3).
    - Hemoglobin: ≥9.0 g/dL (90 g/L).
    - Serum creatinine: ≤1.5 x ULN.
    - Total bilirubin: ≤1.5 × ULN (in case of known Gilbert's syndrome, <2 x ULN is allowed).
    - AST and ALT: ≤2.5 × ULN.
    - ALP: ≤2.5 x ULN.
17. Left ventricular ejection fraction (LVEF) within institutional range of normal; performed by multigated acquisition (MUGA) or echocardiogram (ECHO).
18. Negative β-HCG pregnancy test (serum) for premenopausal women of reproductive capacity (those who were biologically capable of having children) and for women less than 12 months after the menopause. All female patients who were biologically capable of having children had to agree and commit to the use of a reliable method of birth control from 2 weeks before administration of the first dose of investigational product until 28 days after the last dose of investigational product.

19. Recovery (i.e. to Grade 1 or baseline) from all clinically significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).

Exclusion criteria

A patient was excluded from the study if any of the following criteria were met:

1. Clinical or radiologic evidence of local or regional recurrence of disease or metastatic disease prior to or at the time of study entry.
2. Was receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer.
3. Any prior mediastinal irradiation except internal mammary node irradiation for the present breast cancer.
4. Metachronous invasive or metachronous DCIS breast cancer (ie, primary breast cancers diagnosed at different times [diagnosed greater than 6 months apart from each other]).
5. Prior therapy with an ERBB1 and/or ERBB2 inhibitor other than trastuzumab.
6. Received any investigational agent within 14 days or 5 half-lives, whichever was longer, before administration of the first dose of investigational product.
7. Pregnant or breastfeeding women.
8. Patients with a second malignancy, other than adequately treated non-melanoma skin cancers, in situ melanoma or in situ cervical cancer. Patients with other non-mammary malignancies must have been disease-free for at least 5 years.
9. Patients with unstable angina, congestive heart failure (New York Heart Association class II, III, or IV) (including individuals who used digitalis, beta-blockers, or calcium channel blockers specifically for congestive heart failure), ventricular arrhythmia requiring medical therapy, or with a history of myocardial infarction within 12 months.
10. Patients with active, unresolved infections.
11. Inability or unwillingness to swallow tablets.
12. Significant chronic gastrointestinal disorder with diarrhoea as a major symptom (e.g. Crohn's disease, ulcerative colitis, malabsorption, or Grade ≥2 diarrhoea of any etiology at baseline).
13. QTc interval >0.450 seconds or known history of QTc prolongation or Torsades de Pointes.
14. History of idiopathic ventricular tachycardia or ventricular fibrillation.
15. Patients with a psychiatric illness that would prevent them from understanding the nature of the investigational therapy and complying with protocol requirements.
16. Any major concurrent illness or medical condition that, in the investigator's judgment, substantially increased the risk associated with the patient's participation in and completion of the study.
17. On treatment or in follow-up of any other neoadjuvant or adjuvant breast cancer trial with DFS as an endpoint.

Patients could have discontinued from the study treatment if any of the following circumstances occurred:

- Treatment Phase Complete (i.e. completed 12 months of protocol-specified treatment)

- Clinically documented disease recurrence as determined by the investigator
- Adverse event
- Patient request
- Investigator request
- Protocol violation
- Lost to follow-up (defined as after 3 attempts by phone followed by 1 attempt of sending a certified letter)
- Discontinuation of the study by the Sponsor
- Death

When a patient discontinued or was withdrawn from treatment, the investigator notified the Sponsor and every effort was made to perform the procedures indicated for collection of efficacy and survival data. The enrolment system was updated as outlined in the Randomization section. Every effort was made to determine why a patient was lost to follow-up or withdrew consent. Also, a specific reason was documented when a patient was withdrawn for any of the following: noncompliance, protocol violation or per investigator's request. If a patient withdrew from treatment, it was expected that she would continue the study safety follow-up. Unless a subject specifically requested to withdraw from the entire study (i.e. withdrawal of consent), every effort was made to continue collecting long-term efficacy and survival data from her.

Treatments

Subjects were randomized to neratinib or placebo in a 1:1 ratio. Neratinib 240 mg (6 x 40 mg tablets) or placebo (6 x 40 mg tablets) was self-administered by mouth with food. Study treatment was administered for 12 months, or until disease recurrence as determined by the investigator, or toxicity requiring discontinuation.

Dose reductions to 200 mg, 160 mg and 120 mg daily were permitted for toxicity. Re-escalation to the previous dose level was permitted under certain circumstances prior to Amendment 9.

For each AE, the start date, stop date, and indication for concomitant therapies and medications given were recorded on the eCRF from the signing of the ICF until the end of treatment. Any use of excluded medication was a violation of the protocol and was documented.

The following treatments were prohibited throughout the duration of the treatment phase of the study:

- Any chemotherapy, radiation therapy, immunotherapy, biotherapy, or surgery for breast cancer.
- Any other investigational agent.

Other medications that were cautioned against during the treatment phase of the study are noted in the study protocol; these included inducers or inhibitors of CYP3A4, grapefruit juice, and St John's Wort.

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

- Standard therapies for pre-existing medical conditions and for medical and/or surgical complications.

- Adjuvant endocrine therapy for HRc-positive disease.
- Bisphosphonates, regardless of the indication.

Raloxifene or other selective ER modulators were not prohibited for use in approved indications (i.e. prevention or treatment of osteoporosis or osteopenia in postmenopausal women). Bone mineral density was documented in the source documents confirming osteoporosis/osteopenia. Raloxifene is not approved for the adjuvant treatment of breast cancer and was not to be used for this purpose during a patient's participation in this trial.

Investigational product 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. In order for patients to be considered compliant, they were expected to have taken the prescribed investigational product dose 75% of the days in the treatment period. If a dose adjustment was required, the 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 Sponsor's drug accountability forms.

Objectives

The primary objective of this study was to compare invasive disease-free survival (iDFS) of women with early-stage HER2-overexpressed/amplified breast cancer who received neratinib versus placebo, following trastuzumab in the adjuvant setting.

The secondary objectives of this study were to compare additional endpoints of patients receiving neratinib with those of patients receiving placebo. Secondary endpoints included DFS including ductal carcinoma in-situ (DFS-DCIS), time to distant recurrence (TTDR), distant disease-free survival (DDFS), incidence of central nervous system (CNS) recurrence, and OS, as well as safety endpoints. Exploratory analyses included biomarker analyses and patient-reported quality of life (QoL).

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint was iDFS. This was defined as the time from randomization to the first occurrence of one of the following iDFS events:

- Invasive ipsilateral breast tumour recurrence
- Invasive contralateral breast cancer
- Local/regional invasive recurrence
- Distant recurrence
- Death from any cause

The date of recurrence was based on a definitive radiology or pathology procedure, or the date of suspected recurrence that was confirmed by a subsequent radiology or pathology procedure.

The primary analysis was based upon the ITT population. A sensitivity analysis was conducted on the amended ITT (aITT) population, that excluded patients with stage I disease, or who were node

negative, or who received the last dose of trastuzumab more than one year prior to randomization (i.e. those that were excluded following Amendment 3).

Secondary endpoints

- DFS including ductal carcinoma in situ (DFS-DCIS)
- Distant disease-free survival (DDFS) - time from randomization to the first distant tumour recurrence or death from any cause
- Time to distant recurrence (TTDR) - time between randomization and the date of the first distant tumour recurrence, or death from breast cancer
- Incidence of CNS recurrence – cumulative incidence of CNS recurrence as a site of distant recurrence
- Overall survival (OS) - time from the date of randomization until the date of death, censored at the last date known alive.

In the final version of the statistical analysis plan (SAP), following FDA comments, an interim analysis on OS was included. In Part C of the study, long-term follow-up of OS will continue for patients who re-consented and will start from 5 years post randomization.

Exploratory endpoints

Patient-reported outcomes (PROs) were collected using validated questionnaires: (i) FACT-B (version 4) for breast cancer-specific quality of life; (ii) EQ-5D for generic quality of life.

Optional testing of tumour sample was conducted at baseline and at recurrence for biomarkers to define a patient population that would benefit from treatment with neratinib (e.g. ERBB1, 3 and 4; PI3K signalling pathway activation, PTEN loss).

Sample size

The original protocol of the study (dated 29 April 2009) was designed to provide approximately 90% power to detect a difference in DFS between the 2 treatment arms assuming a hazard ratio of 0.70, based on a 1-sided log-rank test controlling the type 1 error at 0.025. The planned sample size was 3850. The sample size was established by assuming a placebo arm hazard rate of 0.056 events per year per patient, assuming a peak accrual rate of 240 patients per month and 1 year time for accrual ramp-up, and assuming a 15% dropout rate in the first year and a 5% annual dropout rate thereafter. Accrual was projected to last for approximately 2 years, and the study was projected to reach the planned number of DFS events in 3.6 years from the randomization of the first patient.

As more mature data from the pivotal adjuvant trastuzumab trials emerged, the study protocol was amended (Amendment 3, dated 25 February 2010) to only include subjects with a higher risk of recurrence (node positive subjects only, within one year from completion of prior trastuzumab therapy). Under Amendment 3, this study was designed to provide approximately 90% power to detect a difference in DFS between the 2 treatment arms in terms of a hazard ratio of 0.713, based on a 1-sided log-rank test controlling the type 1 error at 0.025. It was a group sequential trial with 2 interim analyses planned at information fractions of approximately 40% and 70%, respectively, for the primary endpoint. The primary efficacy analysis would be conducted on the amended intent to treat (aITT) population, consisting of all subjects randomized under Amendment 3, and all subjects randomized prior to implementation of Amendment 3 if they met the key eligibility criteria of Amendment 3. The planned sample size for the aITT population was 3300.

Due to changes in organisational strategy (Amendment 9, dated 14 October 2011), the sponsor chose to stop enrollment of new subjects immediately, to limit the follow-up period to 2 years after randomization, and to limit the scope of the exploratory objectives. The planned sample size for the study was approximately 1700 subjects for the aITT population. If the hazard rates of DFS events for the placebo arm are the same as assumed in Amendment 3 of the protocol, i.e. 0.079 and 0.049 per person per year for the 1st year and 2nd year, respectively, hazard ratio (neratinib versus placebo) for DFS is 0.667, and the hazard rates for dropout are the same as assumed in Amendment 3, i.e. 0.0513 and 0.0160 per person per year for the 1st year and 2nd year, respectively, then the study was expected to have 165 DFS events and provide approximately 83% power to detect a difference in DFS between the 2 treatment arms based on a 1-sided log-rank test with Type 1 error of 0.05. There was no pre-specified total number of DFS events. If the actual hazard rate for DFS events was lower than expected, then the expected number of DFS events would be smaller and the power of the study will be lower.

In amendment 13 the primary population was changed to be the ITT population, including all randomised patients.

There were 2842 patient randomizations to the study. Excluding 2 doubly-randomized patients, 2840 patients comprised the ITT population and there were 173 iDFS events that occurred within 2 years + 28 days of randomisation.

Randomisation

At screening, the patient number was obtained from the e-clinical and enrolment system (IVRS or IWRS), and entered into the ICON ICOPhone /IWRS the same day. On Day 1 of treatment (month 0), the ICON ICOPhone IWRS again accessed to randomize the patient.

Patients were randomized to neratinib or placebo, in a 1:1 ratio. The randomization was stratified by HRc status (positive or negative), prior trastuzumab (concurrent with chemotherapy or sequential) and nodal status (1-3 positive nodes or ≥4 positive nodes). Note that subjects with residual invasive disease in the breast but node-negative or unknown nodal status in the axilla after neoadjuvant therapy were included under “1-3” positive nodes.

Blinding (masking)

This was a double-blind study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. All investigational products used were identical in size, colour, and shape.

Unblinding for analysis did not occur until after the database snapshot was taken for the primary analysis. Unblinding occurred on 07 July 2014 according to the Sponsor Standard Operating Procedure.

OS remains blinded until the requisite 248 death events are reported.

The statistical analysis plan was approved prior to the un-blinding.

Statistical methods

General considerations

All statistical tests for efficacy endpoints were 1-sided at a significance level of 0.025.

To control the study-wide false-positive error rate for efficacy, the statistical significance of OS would be declared only if the statistical assessments for iDFS and OS are both significant at the nominal level of 0.025 (1-sided). All other secondary efficacy endpoints, i.e. DFS-DCIS, TTDR, DDFS, and the cumulative incidence of CNS recurrence, were used to provide supportive evidence of iDFS only. Therefore, no adjustments were made for multiplicity.

Analysis populations

Four analysis populations were used for this study: the ITT population, amended ITT population (aITT), centrally-confirmed ERBB2-positive population, and the Safety population.

Statistical analysis of the primary and secondary efficacy endpoints were performed on the ITT, aITT, and centrally-confirmed ERBB2-positive populations. Statistical analyses of the exploratory endpoints were performed only on the ITT population. All safety analyses were performed using the Safety population.

The analyses based upon the ITT population were considered the primary analyses.

The ITT population was defined as all patients who were randomized into the study. Patients were analysed in the treatment arm to which they were randomly assigned, regardless of which treatment they received.

The aITT population was defined as all patients who met all of the following criteria:

1. Randomized under Amendment 3 or subsequent amendments

2. Randomized prior to implementation of Amendment 3 if they met the following key eligibility criteria: Had node-positive disease AND Randomization within 1 year from completion of prior trastuzumab therapy.

The centrally-confirmed ERBB2 (HER2)-positive population is defined as all patients randomized who were confirmed by central testing using PathVysion HER2/CEP17 DNA dual probe to be ERBB2-positive. ERBB2-positive was defined as an ERBB2 gene amplification documented by a FISH score of ≥2.2. This population was used for a sensitivity analysis of the primary efficacy endpoint.

The Safety population was defined as all patients who received at least 1 dose of IP. Patients were analyzed based upon the treatment they received, regardless of the treatment to which they were randomized, with the exception of the following 5 patients.

Five patients were dispensed IP in error. Patient 2530 and 3676 were randomized to the neratinib arm and were dispensed 1 and 2 bottles (210, 40 mg pills) of placebo, correspondingly. Both of them returned 0 pills from these bottles, per the accountability log. One placebo patient (2535) was dispensed 1 bottle of neratinib but returned all the pills. Another placebo patient (3678) was dispensed 1 bottle of neratinib and returned 0 pills. The last placebo patient (10336) was dispensed 3 bottles of neratinib, but returned 2 full bottles of pills and 1 bottle with 95 pills remaining. For analysis purposes, the actual arms for these 5 patients remained the same as the randomization arm in the Safety population, because the patients took relatively small amount of the wrong drug relative to the treatment duration.

Analysis of the primary endpoint

Time-to-event methods were used for the primary analysis of iDFS. The primary analysis was the stratified log-rank test (1-sided with 2.5% significance level). The Cox proportional hazards model (stratified) was used to estimate the treatment hazard ratio and accompanying 95% confidence interval. A Kaplan Meier plot was drawn. The stratification factors are: ER/PR status, nodal status dichotomized ≤ 3 nodes versus ≥ 4 nodes, and trastuzumab given sequentially versus concurrently

with chemotherapy. These stratification variables are the same variables that were used to stratify the randomization.

All iDFS events up to the cutoff date (2 year + 28 days from randomization) were included in the analysis unless the events occurred after 2 or more missing physical exams. For the primary analyses of all efficacy endpoints, a gap of at least 8 months was used to indicate 2 or more missing physical exams. For any patient for whom an iDFS event was not observed by the cutoff date of the analysis, iDFS was censored at the date of the last PE (including targeted PE), either scheduled or unscheduled that occurred within 2 years, 4 months and 28 days from randomization. If an event occurred after 2 or more missing physical exams, the patient was censored at the last available physical exam prior to the event.

Sensitivity analyses were conducted in Part A to determine whether the analyses of the primary endpoints were robust. The sensitivity analyses include the following:

- All recurrent disease events and deaths occurring within 2 years and 28 days post randomization were regarded as events in the sensitivity analysis.
- The interval between 2 missing PEs was determined by a 6-month window instead of the 8-month window, i.e., if an event occurred ≥ 6 months from a prior PE, the patient was censored at the last available PE prior to the event.
- If a new anti-cancer treatment was started with no claim of recurrent disease, the patient was censored at the last PE prior to the commencement of a new anti-cancer treatment.
- Trimming all the patients in a site if ≥10% of patients had less than 3 month follow-up, and trimming all the patients in a site if ≤90% of the patients had ≥20 months follow-up.

Also, iDFS data collected in Part B, ie, from 2 years post randomization to 5 years post randomization, will be considered a sensitivity analysis of the primary endpoint.

Interim analyses

No interim analyses were conducted for this study prior to the primary iDFS analysis in Part A. An interim analysis for OS is planned.

Results

A total of 3278 patients were screened for eligibility. After exclusions, mainly for ineligibility (n=355) and withdrawal of consent (n=63), 2840 patients were randomized, 1420 to each treatment arm, of which 1408 received study drug in each arm. Patients who prematurely discontinued the study treatment were planned in the protocol to still continue to be followed-up in the trial. While there was a large imbalance in terms of the number of patients who prematurely discontinued from treatment (307 patients) due to adverse event or patient request, the imbalance was smaller in terms of those who prematurely discontinued from follow-up (88 patients). The protocol deviations were well-balanced between treatment groups.

The study population was generally representative of an early breast cancer population. The baseline demographics and disease characteristics are similar to those for the ALTTO trial (lapatinib ± trastuzumab as adjuvant treatment of early breast cancer); except for a lower proportion of node negative patients, due to Amendment 3. Median age was 52 years; 81% were Caucasian. At baseline, 57% had HRc+ positive disease, 47% were pre-menopausal, 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. Approximately 10% of patients had

Stage I tumours, 40% had Stage II tumours and 30% had Stage III tumours, of which 1.8% were stage IIIB. The baseline and disease characteristics are well-balanced between treatment groups.

At baseline, 68% of the study population had received an anthracycline and a taxane. The distribution of choices and duration of adjuvant chemotherapy between arms do not seem to be a source of bias in study 3004. However, in contrast with the usually recommended 6-months duration of (neo)adjuvant treatment, the patients in this trial seem to have received a median of only around four months of anthracycline + taxane (considering the two types of drugs being administered sequentially), and 3, 5 months of taxane in case of combined taxane + carboplatin or taxane-only. However, the effect of neratinib in the iDFS rates at 2 years was consistent for patients with < 4 months (neo)-adjuvant therapy or ≥4 months (neo)-adjuvant therapy. 97% of the HR+ population had received prior endocrine therapy, which was well balanced between arms and overall apparently adequate. The median time from last trastuzumab to randomisation was 4.5 months. 19% of the study population had received last trastuzumab > 1 year before randomisation. The duration of adjuvant trastuzumab between arms does not seem to be a source of bias, neither a reason for concern regarding its external validity

Participant flow

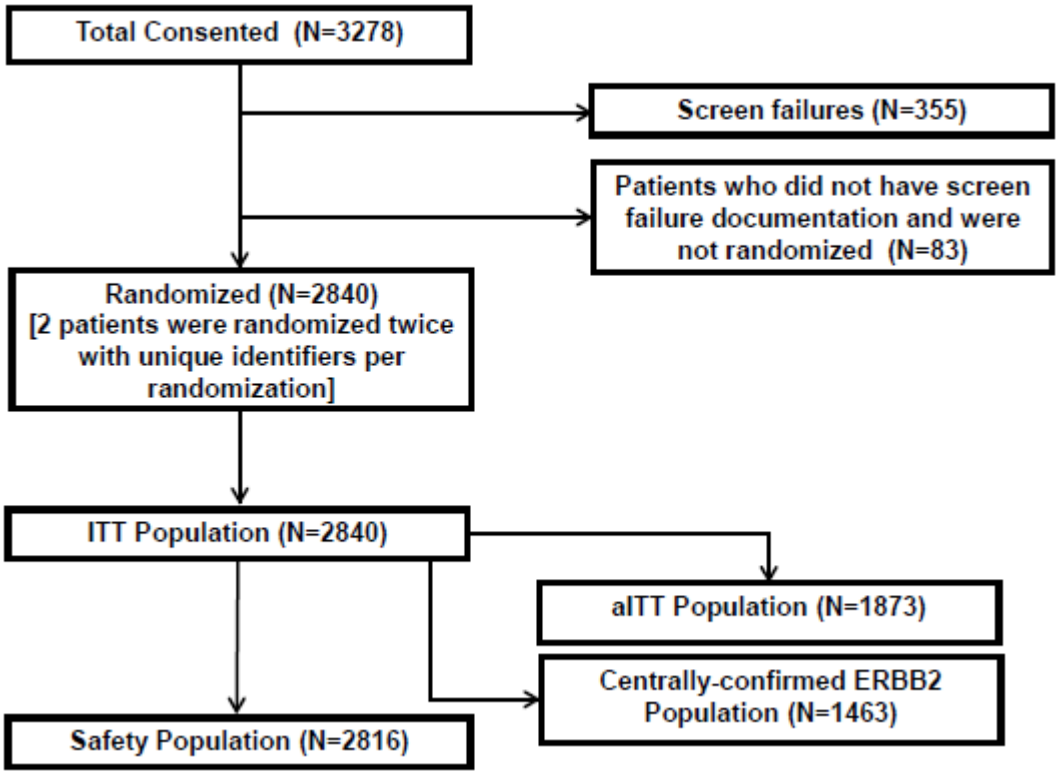


Figure 3 Patient enrolment flow diagram

Recruitment

A total of 571 centres with 680 investigators in 40 countries participated in this multicentre study and among them 476 centres (in North America, South America, Europe, Australia, South Africa and Asia Pacific) with 580 investigators randomized patients.

Conduct of the study

The original protocol for this study was approved on 29/04/2009. The study started on 09/07/2009. There were 6 global amendments over the course of the study. In addition, there were 7 Japan-specific amendments and 1 site-specific amendment.

Table 8 Description of Key Protocol Amendments in study 3004

Original Protocol (June 2009)	• Enrolled women with locally-confirmed, invasive ERBB2-positive breast cancer, stage I to III, node-positive or node-negative (tumor size ≥ 10 mm), without evidence of recurrence. • Completion of adjuvant trastuzumab within 2 years of randomization. • Target patient population = 3850. • Primary efficacy endpoint iDFS (defined in Section 2.4.7). • Primary analysis population ITT.
Amendment	**Key Changes to Original Protocol**
Amendment 3 (February 2010)	• Restricted recruitment to higher risk patients (ie, Stage II–III, node-positive, completion of trastuzumab within one year of randomization). • Target patient enrollment reduced from 3850 to 3300. • Primary analysis population changed to aITT.
Amendment 9 (October 2011)	• Recruitment ceased immediately. • Follow-up was truncated from 5 years to 2 years, for reasons unrelated to data. • Target patient enrollment reduced to 2850. • Primary iDFS analysis changed from event-driven to time-driven (last patient randomized, last visit). • Tumor samples for pharmacogenetics and data for patient-reported health outcomes no longer collected.
Amendment 13 (January 2014)	• Primary analysis restored to iDFS at 2 years in the ITT population. • Patients re-consented for long-term follow-up for 5-year analysis of iDFS and long-term analysis of OS. • Blinding was maintained.

Abbreviations: aITT = amended ITT; iDFS = invasive disease-free survival; ITT = intent-to-treat; OS = overall survival

Table 9 Number randomised according to amendment

Amendment	Number
1-2	1580
3-4	355
5-6	353
7-8	540
Amendment information missing	12
Total	2840

Protocol violations/deviations

Important protocol deviations included: (i) patients who entered the study even though they did not strictly meet inclusion/exclusion criteria, (ii) patients who met withdrawal criteria during the study but were not withdrawn, and (iii) patients who received the wrong treatment or incorrect dose and patients who received an excluded concomitant treatment. There were 152 (5.4%) 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 10 Summary of important protocol deviations, ITT population

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Any Important Protocol Deviation – n (%)	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)

Important protocol deviations are those thought to potentially impact the safety or efficacy analysis.
Study drug includes patients who developed withdrawal criteria but were not withdrawn or received the wrong treatment or incorrect dose.

Baseline data

Table 11 Summary of patient demographics, ITT population

	Neratinib (n=1420)	Placebo (n=1420)
Region – n (%)		
N. America	519 (36.5)	477 (33.6)
W. Europe, Australia, S. Africa	487 (34.3)	532 (37.5)
Asia Pacific, E. Europe and S. America	414 (29.2)	411 (28.9)
Race – n (%)		
Asian	188 (13.2)	197 (13.9)
Black or African American	27 (1.9)	47 (3.3)
White	1165 (82.0)	1135 (79.9)
Other	40 (2.8)	41 (2.9)
Age (year)		
Median (range)	52 (25 – 83)	52 (23-92)
Age group – n (%)		
< 50 years	569 (40.1)	570 (40.1)
50 to <65 years	678 (47.7)	675 (47.5)
≥ 65 years	173 (12.2)	175 (12.3)
Sex – n (%)		
Female	1420 (100.0)	1420 (100.0)
Body mass index (kg/m^2)		
n	1376	1361
Mean (SD)	27.43 (5.83)	27.45 (5.80)

Table 12 Baseline disease characteristics, ITT Population

	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)
Unknown	5 (0.4)	3 (0.2)	8 (0.3)
Nodal Status[a] - 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[a] - n (%)			
Positive	816 (57.5)	815 (57.4)	1631 (57.4)
Negative	604 (42.5)	605 (42.6)	1209 (42.6)
Prior Trastuzumab[a] - 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)

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
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 (month)			
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
Q1, Q3	17.97, 27.83	18.17, 28.22	18.10, 28.06
Min, Max	7.7, 73.7	7.8, 103.0	7.7, 103.0

[a] From stratification factors.
One month is defined as 365.25/12 days.
Source: Table 69

HER2 positive status by local laboratory was an inclusion criterion. For 66% of patients, the method was IHC (3+), and for 30% the method was FISH >2.2, with no imbalance between groups. Central confirmation of HER2 status was conducted for 1704 (60%) of patients. Of those tested centrally, 241 (14%) were non-amplified, 110 (12.9%) in the neratinib population and 131 (15.4%) in the placebo group. Oestrogen receptor (ER) status was positive for 54%, progesterone receptor (PR) status was positive for 44%, and ER/PR status was positive for 40%, with no imbalance between groups.

Table 13 Prior anti-cancer therapy, ITT population

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Prior Radiotherapy - n (%)			
No	290 (20.4)	270 (19.0)	560 (19.7)
Yes	1130 (79.6)	1150 (81.0)	2280 (80.3)
Prior Surgery - n (%)			
Lumpectomy only	468 (33.0)	511 (36.0)	979 (34.5)
Mastectomy	951 (67.0)	908 (63.9)	1859 (65.5)
Prior Anti-cancer Medication - n (%)			
Yes	1420 (100.0)	1420 (100.0)	2840 (100.0)
Anti-cancer Medication Type - n (%)			
Trastuzumab	1420 (100.0)	1420 (100.0)	2840 (100.0)
Anthracycline only	136 (9.6)	135 (9.5)	271 (9.5)
Anthracycline + Taxane	962 (67.7)	965 (68.0)	1927 (67.9)
Taxane only	318 (22.4)	316 (22.3)	634 (22.3)
Neither Anthracycline or Taxane	4 (0.3)	4 (0.3)	8 (0.3)
Prior Neo-adjuvant Therapy - n (%)			
No	1078 (75.9)	1041 (73.3)	2119 (74.6)
Yes	342 (24.1)	379 (26.7)	721 (25.4)
Neo-adjuvant Therapy Type			
Trastuzumab	232 (16.3)	257 (18.1)	489 (17.2)
Anthracycline only	40 (2.8)	35 (2.5)	75 (2.6)
Anthracycline + Taxane	214 (15.1)	258 (18.2)	472 (16.6)
Taxane only	84 (5.9)	84 (5.9)	168 (5.9)
Neither Anthracycline or Taxane	4 (0.3)	2 (0.1)	6 (0.2)

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Pathological Complete Response Status			
Pathologic Complete Response	61 (4.3)	65 (4.6)	126 (4.4)
No Pathologic Complete Response	258 (18.2)	298 (21.0)	556 (19.6)
Unknown	23 (1.6)	16 (1.1)	39 (1.4)
Prior Adjuvant Therapy - n (%)			
No	5 (0.4)	1 (0.1)	6 (0.2)
Yes	1415 (99.6)	1419 (99.9)	2834 (99.8)
Adjuvant Therapy Type			
Trastuzumab	1414 (99.6)	1417 (99.8)	2831 (99.7)
Anthracycline only	146 (10.3)	147 (10.4)	293 (10.3)
Anthracycline + Taxane	723 (50.9)	677 (47.7)	1400 (49.3)
Taxane only	282 (19.9)	289 (20.4)	571 (20.1)
Neither Anthracycline or Taxane	264 (18.6)	306 (21.5)	570 (20.1)
Time from Last Trastuzumab to Randomization (month)			
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
Q1, Q3	1.64, 10.35	1.54, 10.84	1.61, 10.61
Min, Max	0.2, 30.9	0.3, 40.6	0.2, 40.6
Duration of Prior Adjuvant Trastuzumab (month)			
n	1413	1416	2829
Mean (SD)	11.01 (3.08)	10.91 (2.61)	10.96 (2.85)
Median	11.50	11.40	11.43
Q1, Q3	10.87, 11.93	10.81, 11.91	10.84, 11.93
Min, Max	0.7, 56.9	1.4, 38.0	0.7, 56.9
Time from Last Trastuzumab to Randomization			
<= 1 year	1152 (81.1)	1145 (80.6)	2297 (80.9)
> 1 year	268 (18.9)	275 (19.4)	543 (19.1)
Prior Endocrine Therapy Use for Hormone Positive[a] Patients - n (%)			
No	44 (3.1)	41 (2.9)	85 (3.0)
Yes	772 (54.4)	774 (54.5)	1546 (54.4)
Anti-estrogen only	392 (27.6)	371 (26.1)	763 (26.9)
Anti-estrogen & aromatase inhibitor	47 (3.3)	40 (2.8)	87 (3.1)
Aromatase inhibitor only	328 (23.1)	357 (25.1)	685 (24.1)
Non anti-estrogen & aromatase inhibitor	5 (0.4)	6 (0.4)	11 (0.4)
Prior Endocrine Therapy Use for Hormone Negative Patients - n (%)			
No	590 (41.5)	580 (40.8)	1170 (41.2)
Yes	14 (1.0)	25 (1.8)	39 (1.4)

[a] from stratification factors. One month is defined as 365.25/12 days, and one year is defined as 365.25 days.

Concomitant adjuvant breast cancer treatment

Table 14 Summary of concomitant adjuvant breast cancer treatment*

	Neratinib (n=1408) N (%)	**Placebo (n=1408)** N (%)
Anti-oestrogens	402 (28.6)	392 (27.8)
Tamoxifen	338 (24.0)	318 (22.6)
Tamoxifen citrate	62 (4.4)	72 (5.1)
Toremifene	1 (0.1)	4 (0.3)
Toremifene citrate	1 (0.1)	0
Aromatase inhibitors	388 (27.6)	421 (29.9)
Anastrozole	198 (14.1)	183 (13.0)
Aromatase inhibitors	0	1 (0.1)
Exemestane	32 (2.3)	57 (4.0)
Letrozole	165 (11.7)	197 (14.0)
Bisphosphonates	131 (9.3)	115 (8.2)
Bisphosphonates, Combinations	3 (0.2)	5 (0.4)
Gonadotrophin Releasing Hormone Analogues	81 (5.8)	79 (5.6)
Trastuzumab	1 (0.1)	0
Other Antineoplastic Agents	0	3 (0.2)
Indole-3-carbinol	0	3 (0.2)
Other antineoplastic agents	0	1 (0.1)
Protein kinase inhibitors	0	1 (0.1)
Lapatinib	0	1 (0.1)
Pyrimidine Analogues	1 (0.1)	1 (0.1)
Capecitabine	1 (0.1)	1 (0.1)
Selective Estrogen Receptor Modulators	1 (0.1)	5 (0.4)
Raloxifene	0	2 (0.1)
Raloxifene hydrochloride	1 (0.1)	3 (0.2)
Taxanes	0	2 (0.1)
Paclitaxel	0	2 (0.1)

* The indication for use is not provided. Therefore, it is not known e.g. whether bisphosphonates were prescribed as adjuvant treatment of breast cancer or to treat osteoporosis.

The Applicant has provided summary of concomitant endocrine therapy according to hormone receptor status:

Table 15 Summary of Concomitant Endocrine Therapy, ITT Population

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Hormone Receptor Positive Patients	816 (57.5)	815 (57.4)	1631 (57.4)
Concomitant Endocrine Therapy Use			
Yes	760 (93.1)	764 (93.7)	1524 (93.4)
No	56 (6.9)	51 (6.3)	107 (6.6)
Concomitant Endocrine Therapy - n (%)			
Anti-estrogen & aromatase inhibitor	20 (2.6)	34 (4.5)	54 (3.5)
Anti-estrogen only	375 (49.3)	347 (45.4)	722 (47.4)
Aromatase inhibitor only	362 (47.6)	379 (49.6)	741 (48.6)
Non anti-estrogen & aromatase inhibitor	3 (0.4)	4 (0.5)	7 (0.5)
Hormone Receptor Negative Patients	604 (42.5)	605 (42.6)	1209 (42.6)
Concomitant Endocrine Therapy Use			
Yes	12 (2.0)	20 (3.3)	32 (2.6)
No	592 (98.0)	585 (96.7)	1177 (97.4)

Page 1 of 1

Hormone Receptor Status using stratification factor.
The denominator for concomitant endocrine therapy use yes/no is based on patients with corresponding hormone receptor status.
The denominator for the type of endocrine therapy is based on patients who had concomitant endocrine therapy.
Program: Y:\stat\neratinib\breast\3004\primary\csr_adam\program\tables\t_conmed.sas
Output: t14-06-02-03-cm-endo.rtf (Date Generated: 24DEC2015:15:11) Source: adam.adsl

Numbers analysed

The table below presents the disposition of the 2840 patients in the ITT population. In all, 2816 (99.2%) patients received IP; 1408 (99.2%) patients in each arm. Among the randomized patients, 24 (12 in each arm) did not receive any IP.

All patients who received the IP ended treatment, 1408 in each arm. Among patients who received IP and ended treatment, 2027 (72.0%) completed the treatment phase: 860 (61.1%) in the neratinib arm and 1167 (82.9%) in the placebo arm. The most frequent reason for discontinuation of treatment other than completion of treatment phase was AEs. A total of 444 (15.8%) of the treated patients discontinued due to AEs: 372 (26.4%) in the neratinib arm and 72 (5.1%) in the placebo arm. More patients discontinued treatment due to subject request (121 [8.6%]) in the neratinib arm than in the placebo arm (69 [4.9%]); more patients discontinued treatment due to recurrence in the placebo arm (59 [4.2%]) than in the neratinib arm (15 [1.1%]).

All patients randomized concluded Part A of the study. Among them, 2278 (80.2%) completed Part A treatment and follow-up: 1095 (77.1%) in the neratinib arm and 1183 (83.3%) in the placebo arm. More patients in the neratinib arm (197 [13.9%]) discontinued the study due to subject request than in the placebo arm (120 [8.5%]).

Table 16 Disposition, ITT population

	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)
Patients Randomized - n (%)	1420 (100)	1420 (100)	2840 (100)
Did Not Receive Study Drug	12 (0.8)	12 (0.8)	24 (0.8)
Received Study Drug	1408 (99.2)	1408 (99.2)	2816 (99.2)
Patients Ended Treatment[a] - n (%)	1408 (100)	1408 (100)	2816 (100)
Phase Completed	860 (61.1)	1167 (82.9)	2027 (72.0)
Disease Recurrence	15 (1.1)	59 (4.2)	74 (2.6)
Adverse Event	372 (26.4)	72 (5.1)	444 (15.8)
Subject Request	121 (8.6)	69 (4.9)	190 (6.7)
Protocol Violation	12 (0.9)	20 (1.4)	32 (1.1)
Lost To Follow-Up	4 (0.3)	4 (0.3)	8 (0.3)
Other	23 (1.6)	17 (1.2)	40 (1.4)
Missing	1 (0.1)	0 (0.0)	1 (0.0)
Patients Ended Study[b] - n (%)	1420 (100)	1420 (100)	2840 (100)
Study Completed	1095 (77.1)	1183 (83.3)	2278 (80.2)
Subject Request	197 (13.9)	120 (8.5)	317 (11.2)
Investigator Decision	11 (0.8)	6 (0.4)	17 (0.6)
Discontinuation of Study by Sponsor	3 (0.2)	4 (0.3)	7 (0.2)
Lost To Follow-Up	35 (2.5)	33 (2.3)	68 (2.4)
Other	53 (3.7)	51 (3.6)	104 (3.7)
Screen Failure	0 (0.0)	1 (0.1)	1 (0.0)
Missing	1 (0.1)	0 (0.0)	1 (0.0)

[a] Denominator for EOT reason is based on patients who have received at least one dose of study drug.
[b] End of study due to death is not included in the disposition table.
EOT = end of treatment

Outcomes and estimation

- **Part A (cut-off date: 7 July 2014)**

Primary Analysis of iDFS, ITT Population

Table 16. Primary efficacy analyses – ITT population

Variable	Estimated 2 year event free rates[1] (%)		Stratified hazard ratio (95 percent confidence interval)[2]	Stratified log rank test two sided p value[3]
	Nerlynx (n = 1420)	Placebo (n = 1420)		
Invasive disease-free survival	94.2	91.9	0.66 (0.49, 0.90)	0.008

Variable	Estimated 2 year event free rates[1] (%)		Stratified hazard ratio (95 percent confidence interval)[2]	Stratified log rank test two sided p value[3]
	Nerlynx (n = 1420)	Placebo (n = 1420)		
Disease-free survival including ductal carcinoma *in situ*	94.2	91.3	0.61 (0.45, 0.83)	0.001
Distant disease-free survival	95.3	94.0	0.74 (0.52, 1.05)	0.094
Time to distant recurrence	95.5	94.2	0.73 (0.51, 1.04)	0.087
CNS recurrence	0.92	1.16	–	0.548

CNS = central nervous system.

[1] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

[2] Stratified Cox proportional hazards model

[3] Stratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

The most frequent site of disease recurrence for an iDFS event was distant recurrence, with 51 (3.6%) and 71 (5.0%) patients in the neratinib arm and the placebo arm, respectively, followed by local/regional invasive recurrence with 8 (0.6%) and 25 (1.8%) patients, respectively.

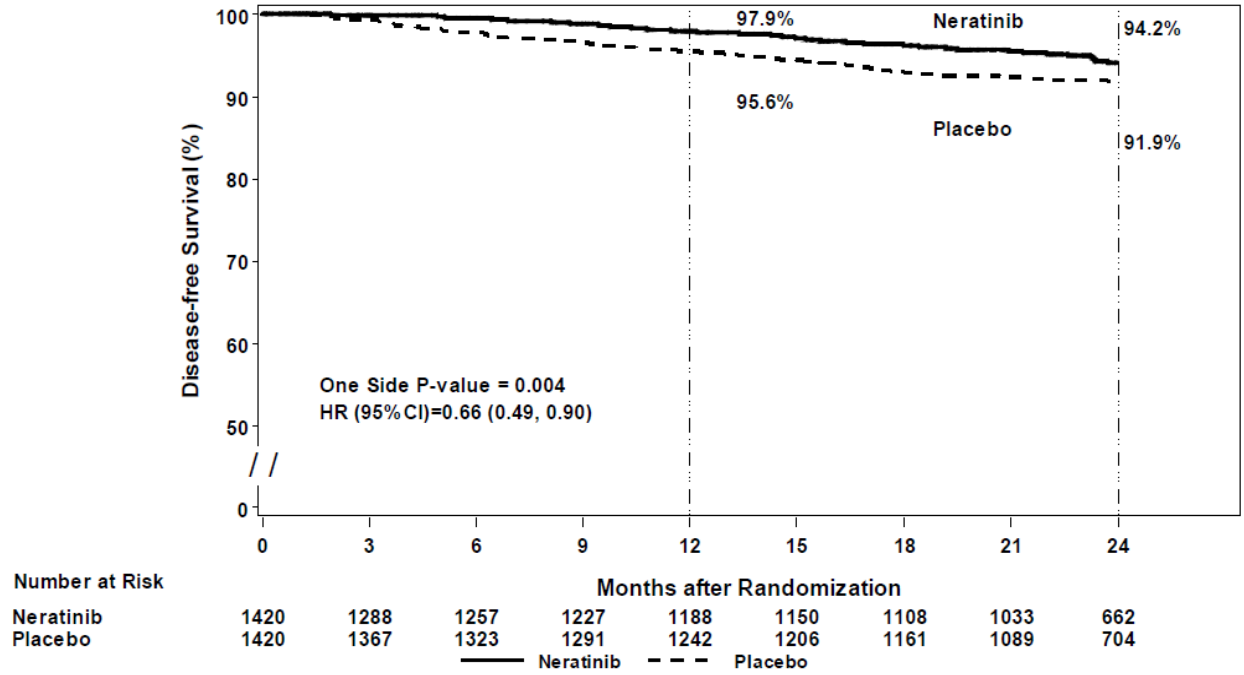


Figure 4 Kaplan-Meier Plot of Disease-free Survival – ITT Population

Following amendment 9, there was no prospective and systematic follow-up after 2 years and only the review of clinical notes of patients that have been re-consented could be provided..

Analyses were conducted on the aITT and centrally-confirmed ERBB2-positive analysis populations. In addition, other sensitivity analyses were conducted to assess the influence of other factors that could potentially affect the interpretation of the iDFS results. These include missed visits, use of other systemic anti-cancer therapy, and early drop-outs.

Analysis of iDFS, aITT Population

The aITT population consists of 1873 subjects randomized to the 2 treatment arms: 938 in the neratinib arm and 935 in the placebo arm. The number of patients with an iDFS event that occurred within 2 years + 28 days after randomization was 137: 53 (5.7%) in the neratinib arm and 84 (9.0%) in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than the placebo arm, 93.1% and 90.1%, respectively. The estimated stratified HR was 0.65 (95% CI, 0.46-0.92); the 1-sided p-value from the stratified log rank test was 0.007.

Analysis of iDFS: Effect of Censoring

The majority of patients (65%) had 8 or more physical examinations (PEs) during follow-up and 75.2% had a follow-up duration of >22 months. There are, however, 130 patients in the neratinib arm who dropped out within 3 months of treatment for reasons other than recurrent disease compared to 44 patients in the placebo arm. These include patients who did not have any post-randomization PE or patients whose last post-randomization PE was within 3 months of randomization (see table below).

Table 17 Sensitivity Analysis: Resampling Disease-free Survival for Early Drop-Out Patients, ITT Population

	Neratinib (N=1420)	Placebo (N=1420)
Early Drop-out Patients[a] – n (%)	130 (0.09)	44 (0.03)
Number of events after resampling[b]		
N	10000	
Mean (SD)	182 (2.9)	
Q1, Q3	180, 184	
Min, Max	174, 195	
Hazard ratio[c] from Stratified Cox proportional hazards model[d]		
N	10000	
Mean (SD)	0.69 (0.03)	
Q1, Q3	0.67, 0.71	
Min, Max	0.61, 0.81	

The demographic, baseline disease characteristics, and prior anti-cancer therapy were similar for patients who dropped out with ≤3 months of follow-up and patients who were followed up for >3 months in the 2 treatment arms.

To assess the potential impact of the early drop-outs (patients censored at <3 months) on the primary analysis, the following sensitivity analysis was performed. Patients who dropped out early in the neratinib group were assumed to have iDFS events following the distribution observed in the placebo group. Specifically, imputation of iDFS events for the neratinib early dropout patients was achieved via resampling from the placebo patients by matching HRc status, nodal status, and prior trastuzumab regimen (i.e. concurrent versus sequential). The resampling was done 10,000 times. On average, 9 additional iDFS events were observed in the resampled populations, ranging from 1 to 22 events. The average HR was 0.69 with standard deviation of 0.03. Among the 10,000 resampled populations, 98.08% of the time the stratified log-rank test yielded 1-sided p-value ≤0.025.

This analysis has been repeated, defining early drop-out patients as a) those with iDFS follow up time of < 6 months and censored b) iDFS follow up time of < 12 months and censored. These results suggest that the hazard ratios and the 95% CIs are consistent across the different scenarios. The analysis was then repeated for all three definitions of early drop-out with resampling restricted to the worst 50% of placebo patients, defined as patients who either had 4 or more positive nodes or who had between 1-3 positive nodes and T stage of 2 or above. The mean hazard ratios and the 95% CIs were little changed for all three definitions of early drop-out when the sampling population is restricted to the worst 50% of the placebo patients. Based on the additional sensitivity analyses, the results seem robust to the method of handling missing data.

Two sensitivity analyses of iDFS were performed, 1 excluding all patients from sites with a high rate of early dropout patients and 1 including only patients from sites that had a high rate of complete follow-up. Essentially, only patients from investigational sites that rigorously followed the protocol are included in these analyses. After excluding patients from sites with ≥10% patients censored at <3 months (early drop out patients), there were 145 patients with an iDFS event: 57 in the neratinib arm and 88 in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than the placebo arm, 94.1% and 91.6%, respectively. The estimated stratified HR was 0.66 (95% CI, 0.47-0.93), with a 1-sided p-value from the stratified log rank test of 0.008. Including only patients in sites with ≥90% patients with complete follow-up (follow-up was considered complete if a patient experienced an iDFS

event or was followed for at least 20 months), the estimated HR was 0.69 (95% CI, 0.47-1.01) with a 1-sided p-value from the stratified log rank test of 0.028. The majority of patients (65%) had 8 or more PEs during follow-up and 75.2% had a follow-up duration of >22 months. A summary of the primary iDFS analysis and the key sensitivity analyses thereto is shown in the below table.

Table 18 Analyses for iDFS in Defined Study Populations

Population	Number of Events by 24 Months		K-M Estimate 24-month Rate % (95% CI)		Stratified Hazard Ratio (95% CI)[a]	Stratified Rank Test p-value (1-sided)[a]
	Neratinib	Placebo	Neratinib	Placebo		
ITT	67	106	94.2 (92.6,95.4)	91.9 (90.2,93.2)	0.66 (0.49,0.90)	0.004
aITT	53	84	93.1 (91.1,94.7)	90.1 (87.9,92.0)	0.65 (0.46, 0.92)	0.007
Centrally-confirmed ERBB2-positive	32	61	94.9 (92.8,96.3)	90.9 (88.5,92.9)	0.51 (0.33,0.78)	<0.001

Subgroup Analysis

Population	Number of Events by 24 Months		K-M Estimate 24-month Rate % (95% CI)		Unstratified Hazard Ratio (95% CI)	Unstratified Rank Test p-value (1-sided)
	Neratinib	Placebo	Neratinib	Placebo		
HRc-positive	29	63	95.6 (93.8,96.9)	91.5 (89.2,93.3)	0.49 (0.31,0.75)	<0.001
HRc-negative	38	43	92.2 (89.4,94.3)	92.4 (89.8,94.3)	0.93 (0.60,1.43)	0.365
Centrally-confirmed ERBB2-positive and HRc-positive	9	39	97.3 (94.8,98.6)	89.0 (85.2,91.9)	0.23 (0.11,0.46)	<0.001
Centrally-confirmed ERBB2-positive and HRc-negative	23	22	92.3 (88.6,94.9)	93.1 (89.7,95.4)	1.02 (0.57,1.84)	0.523
Randomized ≤1 Year from Completion of Prior Trastuzumab	58	95	93.8 (92.0,95.2)	90.9 (89.0,92.5)	0.63 (0.45,0.88)	0.003
HRc-positive and ≤1 Year from Completion of Prior Trastuzumab	26	55	95.3 (93.1,96.7)	90.8 (88.2,92.9)	0.49 (0.30,0.78)	0.001
Centrally-confirmed ERBB2-positive and ≤1 Year from Completion of Prior Trastuzumab	25	58	95.0 (92.6,96.6)	89.1 (86.1,91.5)	0.42 (0.26,0.66)	<0.001

Population	Number of Events by 24 Months		K-M Estimate 24-month Rate % (95% CI)		Unstratified Hazard Ratio (95% CI)	Unstratified Log Rank Test p-value (1-sided)
	Neratinib	Placebo	Neratinib	Placebo		
Centrally-confirmed ERBB2-positive HRc-positive and ≤1 Year from Completion of Prior Trastuzumab	8	37	97.1 (94.2,98.5)	87.0 (82.5,90.4)	0.22 (0.09,0.44)	<0.001

Sensitivity Analyses of ITT

Population	Number of Events by 24 Months		K-M Estimate 24-month Rate % (95% CI)		Stratified Hazard Ratio (95% CI)[a]	Stratified Log Rank Test p-value (1-sided)[a]
	Neratinib	Placebo	Neratinib	Placebo		
All Events up to 2 Year + 28 Days	70	109	93.9 (92.4,95.2)	91.6 (90.0,93.0)	0.67 (0.50,0.91)	0.005
Patients Missing 2 Visits (6 Month Window)	65	105	94.4 (92.9,95.6)	91.9 (90.3,93.3)	0.65 (0.47,0.88)	0.003
Patients with Systemic Anti-cancer Therapy	66	104	94.2 (92.7,95.4)	92.0 (90.4,93.4)	0.67 (0.49,0.90)	0.005
Site Early Dropout Rate <10%	57	88	94.1 (92.4,95.4)	91.6 (89.7,93.1)	0.66 (0.47,0.93)	0.008
Site Completed Follow-up ≥90%	43	67	93.9 (91.8,95.4)	91.3 (89.1,93.1)	0.69 (0.47,1.01)	0.028

[a] Compared with placebo based upon a Cox proportional hazards model stratified by factors used in randomization.

Evaluation of Secondary Efficacy Endpoints

The secondary efficacy endpoints were DFS-DCIS, DDFS, TTDR, and the incidence of CNS recurrence. Analysis of DFS-DCIS was also performed for the centrally-confirmed ERBB2-positive population. In addition, DFS-DCIS and DDFS were evaluated in the HRc-positive and HRc-negative patient subgroups.

Table 19 Summary of Analyses for the Secondary Efficacy Endpoints

Population	Efficacy Endpoint	K-M Estimate 24-month Rate % (95% CI)		Stratified Hazard Ratio (95% CI)[a]	Stratified Log Rank Test p-value (1-sided)[a]
		Neratinib	Placebo		
ITT	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)	0.047
	TTDR	95.5 (94.1,96.6)	94.2 (92.8,95.3)	0.73 (0.51,1.04)	0.043
	CNS Recurrence Cumulative Incidence Estimate[b]	0.92 (0.49,1.59)	1.16 (0.68,1.87)	NA	0.274
aITT	DFS-DCIS	93.1 (91.1,94.7)	89.6 (87.3,91.4)	0.62 (0.44,0.86)	0.002
	DDFS	93.9 (92.0,95.4)	92.7 (90.8,94.3)	0.81 (0.55,1.18)	0.140
	TTDR	94.2 (92.3,95.6)	93.0 (91.0,94.5)	0.80 (0.54,1.18)	0.134
	CNS Recurrence Cumulative Incidence Estimate[b]	1.10 (0.55,2.02)	1.30 (0.69,2.26)	NA	0.383
Centrally-confirmed ERBB2	DFS-DCIS	94.9 (92.8,96.3)	90.5 (88.0,92.5)	0.48 (0.31,0.74)	<0.001
	DDFS	96.5 (94.8,97.7)	93.1 (90.8,94.8)	0.47 (0.28,0.77)	0.001
	TTDR	96.7 (95.0,97.8)	93.4 (91.2,95.0)	0.47 (0.27,0.77)	0.002
	CNS Recurrence Cumulative Incidence Estimate[b]	0.77 (0.30,1.73)	1.50 (0.77,2.67)	NA	0.114

Subgroup Analysis

Population	Efficacy Endpoint	K-M Estimate 24-month Rate % (95% CI)		Unstratified Hazard Ratio (95% CI)	Unstratified Log Rank Test p-value (1-sided)
		Neratinib	Placebo		
HRc-positive	DFS-DCIS	95.6 (93.8,96.9)	90.8 (88.5,92.7)	0.45 (0.29,0.69)	<0.001
	DDFS	96.4 (94.6,97.5)	93.3 (91.3,94.9)	0.52 (0.32,0.84)	0.004

Subgroup Analyses					
Population	Efficacy Endpoint	K-M Estimate 24-month Rate % (95% CI)		Unstratified Hazard Ratio (95% CI)	Unstratified Log Rank Test p-value (1-sided)
		Neratinib	Placebo		
HRc-negative	DFS-DCIS	92.2 (89.4,94.3)	91.8 (89.2,93.8)	0.86 (0.56,1.32)	0.250
	DDFS	94.0 (91.5,95.8)	95.0 (92.8,96.5)	1.13 (0.68,1.91)	0.683
Centrally-confirmed ERBB2-positive and HRc-positive	DFS-DCIS	97.3 (94.8,98.6)	88.7 (84.9,91.6)	0.23 (0.10,0.45)	<0.001
Centrally-confirmed ERBB2-positive and HRc-negative	DFS-DCIS	92.3 (88.6,94.9)	92.5 (89.0,94.9)	0.93 (0.52,1.65)	0.398

[a] Compared with placebo based upon a Cox proportional hazards model stratified by factors used in randomization.
[b] Gray's method (Gray, 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 or ≥4) and ER/PR status (positive or negative).

Health Outcome Results and Analyses

FACT-B

The average FACT-B Total Score over time is shown graphically and FACT-G Total Score over time are shown in the two figures below.

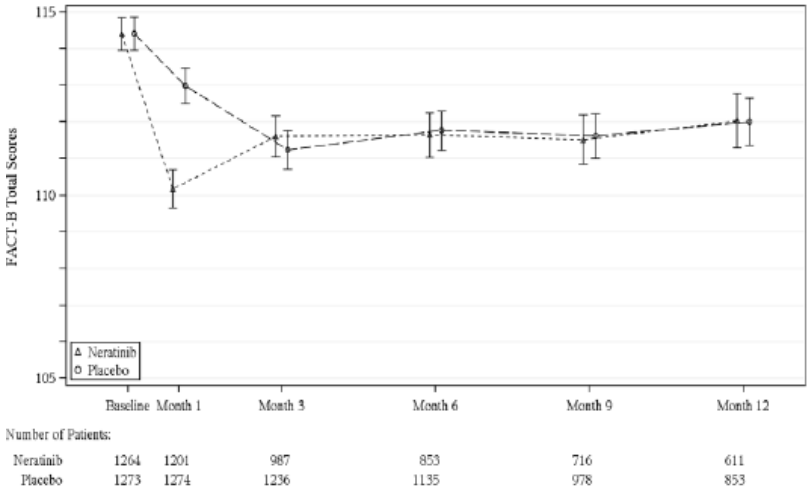


Figure 5 Average FACT-B Total Scores Over Time, ITT Population

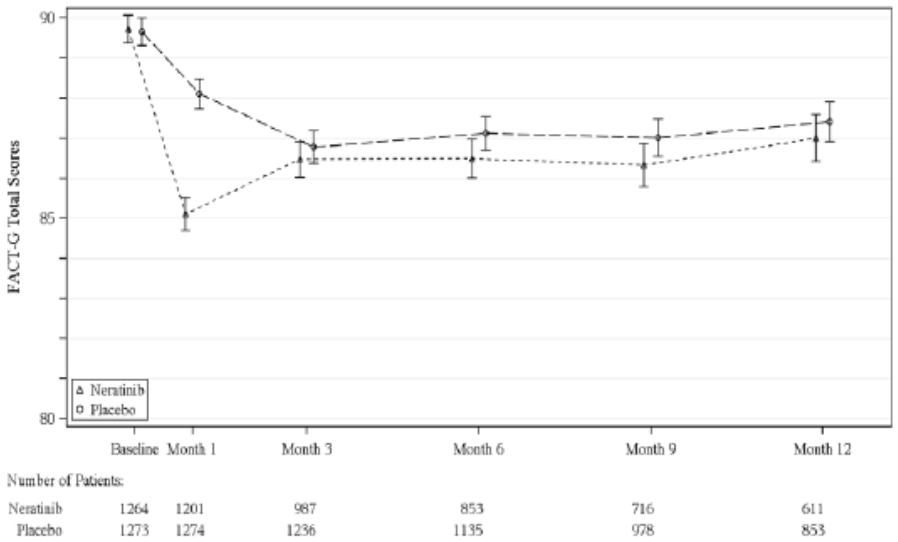


Figure 6 Average FACT-G Total Scores Over Time, ITT Population

There was a decrease in FACT-B mean Total Score in the first month in the neratinib arm of 4.6 points and 1.7 point in the placebo arm. At month 3 and thereafter, there were decreases in mean scores of about 3 points from baseline in both arms. These changes were mirrored closely by the mean FACT-G Total Score. Among the individual scores, physical well-being showed the biggest difference between the 2 arms in the first month and over time, whereas functional well-being, emotional well-being, social/family well-being, and cancer-specific subscales were not impacted as much.

EQ-5D

The average EQ-5D Health State over time and the average EQ-5D Index Score over time are shown the two figures below.

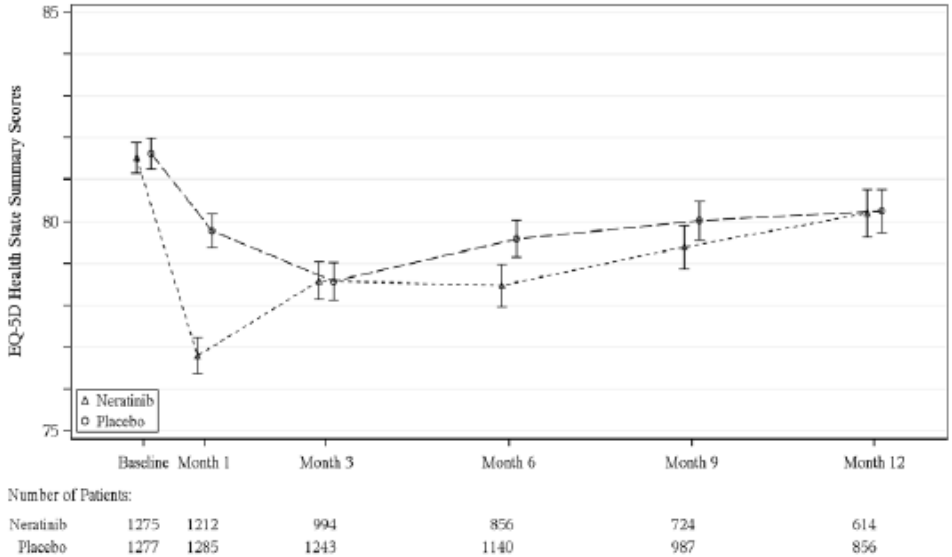


Figure 7 Average EQ-5D Health State Summary Scores Over Time, ITT Population

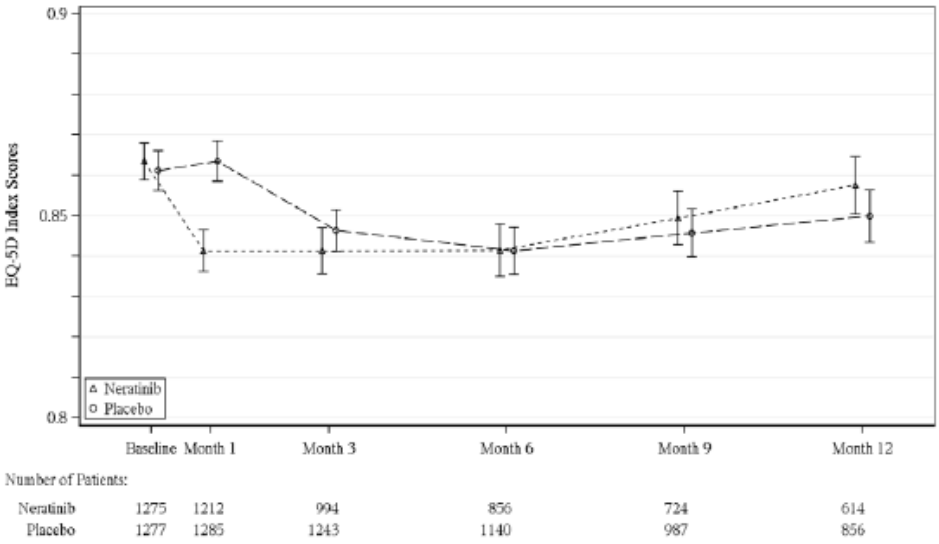


Figure 8 Average EQ-5D Index Scores Over Time, ITT Population

The average EQ-5D Health State scores declined from baseline by 4.9 points in the neratinib arm and by 2.3 points in the placebo arm at month 1. Thereafter, the score rebounded closer to baseline, with a decrease in mean scores of about 2 to 3 points to month 12. These changes over time were similar to those observed in the Index Score.

- **Part A: updated primary analysis of 2-years iDFS (cut-off date: 15 April 2016)**

The Applicant provided with this application an addendum to the final CSR for study 3144A2-3004-WW with an update of the primary analysis of 2 year iDFS, and longer term follow-up for up to 5 years post-randomisation (Part B) (described further below).

Numbers analysed

Amendment 13 re-instated extended follow-up for disease recurrence and survival which is ongoing at the time of this submission. This required an attempt to re-consent all randomized patients, in order to review their medical records for recurrent disease events and deaths. Additional consent from patients who dropped out early in Part A may further reduce the amount of censoring within the first 2 years.

A limitation of the original primary analysis was that the number of patients followed for 24 months was relatively low in each arm with 662 (47%) patients in the neratinib arm and 704 (50%) patients in the placebo arm. Although 130 patients in the neratinib arm ended study within the first 3 months, a large amount of censoring occurred between months 21 and 24 as a result of the protocol-defined visit window and truncation of the primary analysis at 24 months + 28 days. In Part A analysis, 2655 patients (1288 in neratinib arm and 1367 in placebo arm) were at risk at month 3. With the additional follow-up data in the updated 2-year analysis, the number increased to 2708 patients (1325 in neratinib arm and 1383 in placebo arm). In the updated long-term analysis that includes additional data from 1952 re-consented patients and does not truncate data at 24 months, the number of patients with at least 24-month follow-up has increased to 1060 (75%) patients in the neratinib arm and 1107 (78%) patients in the placebo arm.

Primary Analysis of iDFS, ITT Population

In the updated 2-year analysis, an additional 11 events were observed, totaling 184; 74 (5.2%) events were in the neratinib arm and 110 (7.7%) in the placebo arm. The updated 2-year iDFS rate was greater in the neratinib arm than the placebo arm, 94.3% and 91.9%, respectively. In the updated 2-

year analysis, the stratified HR was 0.69 (95% CI, 0.51-0.93) indicating a 31% reduction in risk of iDFS events in the neratinib arm. In the updated 2-year analysis, iDFS was also prolonged in the neratinib arm compared with the placebo arm.

The following table compares the updated 2 year and interim 5 year analyses with the primary 2 year analysis already described in this report:

Table 20 Primary Analysis of 2-year, Updated 2-year, and the Interim 5-year iDFS, ITT Population

	Primary 2-Year		Updated 2-Year		Interim 5-Year	
	Neratinib (N=1420)	**Placebo (N=1420)**	**Neratinib (N=1420)**	**Placebo (N=1420)**	**Neratinib (N=1420)**	**Placebo (N=1420)**
Patients With Events - n (%)	67 (4.7)	106 (7.5)	74 (5.2)	110 (7.7)	107 (7.5)	149 (10.5)
Patients Censored - n (%)	1353 (95.3)	1314 (92.5)	1346 (94.8)	1310 (92.3)	1313 (92.5)	1271 (89.5)
Kaplan-Meier Estimate (%)						
12 Month (95% CI)	97.9 (97.0, 98.6)	95.6 (94.3, 96.5)	97.9 (96.9, 98.5)	95.6 (94.4, 96.5)	97.9 (96.9, 98.5)	95.6 (94.4, 96.5)
24 Month (95% CI)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	94.3 (92.8, 95.4)	91.9 (90.4, 93.3)	94.3 (92.8, 95.4)	91.9 (90.4, 93.3)
36 Month (95% CI)	NA	NA	NA	NA	92.5 (90.8, 93.8)	90.3 (88.6, 91.8)
48 Month (95% CI)	NA	NA	NA	NA	91.4 (89.6, 92.9)	89.2 (87.4, 90.8)
60 Month (95% CI)	NA	NA	NA	NA	90.4 (88.4, 92.0)	87.9 (85.9, 89.7)
Stratified Log-rank Test P-value (one-sided)	0.004		0.007		0.008	
Stratified Cox Proportional Hazards Model Hazard Ratio (95% CI)	0.66 (0.49, 0.90)		0.69 (0.51, 0.93)		0.74 (0.58,0.95)	

NA, not applicable

- **Part B: interim analysis of 5-years iDFS (cut-off date: 15 April 2016)**

Numbers analysed

The interim 5-year iDFS analysis included additional data from a total of 1952 re-consented patients; 945 in the neratinib arm and 1007 in the placebo arm. Patient demographics were comparable between the 2 arms and similar to the Part A population used for the primary 2 year analysis. At the time of the 15/04/2016 cut-off, central confirmation of HER2 status was available for 2138 (75.3%) of the ITT population. Of these, 908 in the neratinib arm (63.9%) and 869 in the placebo arm (61.2%) were confirmed to be ERBB2 positive.

For the ITT population, the median follow-up time was 4.3 years. The number of patients with 24-month follow-up has increased to 1060 (75%) patients in the neratinib arm and 1107 (78%) patients in the placebo arm.

Of the 1952 re-consented patients, a total of 1811 had physical examination data available: 884 in the neratinib arm and 927 in the placebo arm. The median number of physical examinations between years 2-5 of follow-up (Part B) were 5.95 for the neratinib arm and 5.91 for the placebo arm.

Primary Analysis of iDFS, ITT Population

The number of patients with an iDFS event that occurred within 5 years + 90 days after randomization was 256, representing an additional 83 events over the 2-year data. There were 107 (7.5%) events in the neratinib arm and 149 (10.5%) in the placebo arm. The rate of iDFS at 5 years of follow-up was greater in the neratinib arm than the placebo arm, 90.4% and 87.9%, respectively. The stratified HR for neratinib versus placebo was 0.74 (95% CI, 0.58-0.95). Therefore, at 5 years of follow-up, neratinib reduced the risk of iDFS events by 26% compared with placebo, and iDFS was prolonged for patients randomized to the neratinib arm compared with the placebo arm.

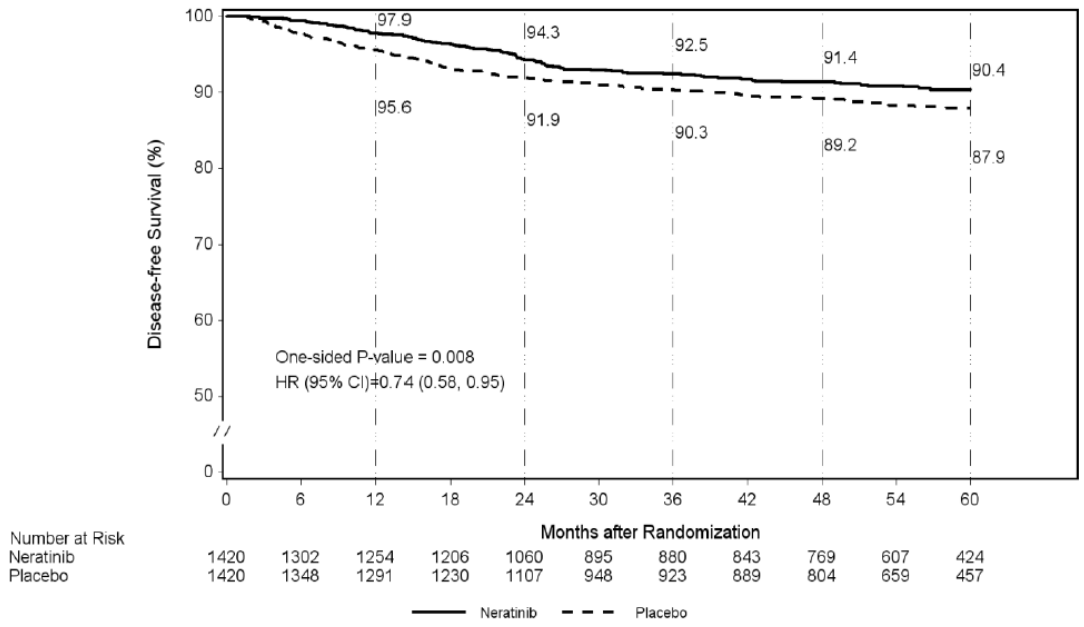
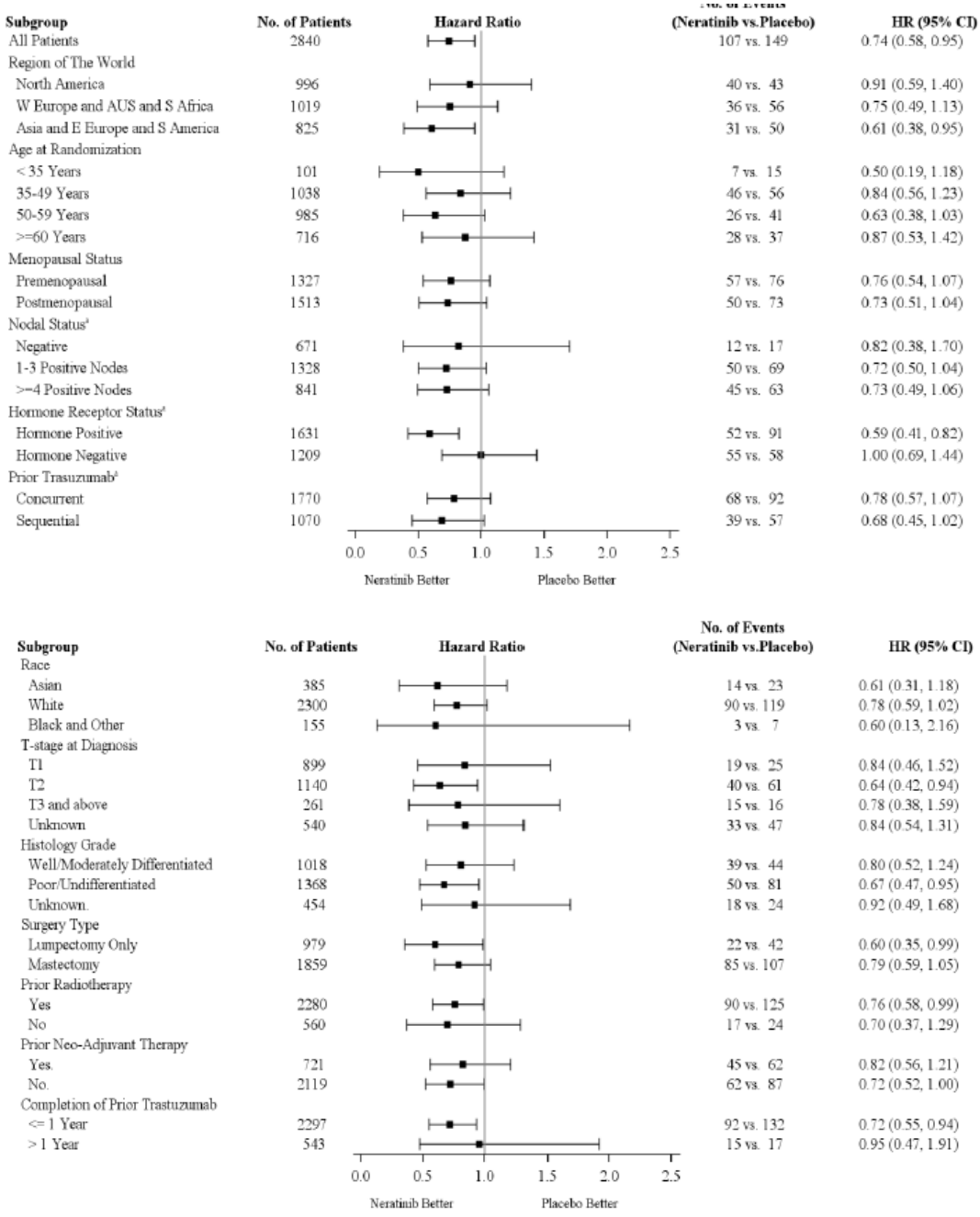


Figure 9 Kaplan-Meier-Plot of Interim 5-year iDFS, ITT Population

Other analyses

The applicant has conducted corresponding analyses for the aITT population. The 5 year K-M % estimate of iDFS (95% CI) was 88.9 (86.3, 91.0) and 85.3 (82.5, 87.7) in the neratinib and placebo groups respectively, hazard ratio 0.73 (0.55, 0.96).

The Applicant has also conducted corresponding analyses for the centrally-confirmed HER2-positive population. The 5 year K-M % estimate of iDFS (95% CI) was 90.8 (88.4, 92.7) and 88.1 (85.5, 90.2) in the neratinib and placebo groups respectively, hazard ratio 0.70 (0.51, 0.96). The Applicant provided a Forest Plot of the interim 5-year iDFS by subgroup:



[a] From stratification factor

Figure 10 Forest Plot of Interim 5-year iDFS by Subgroups, ITT Population

The subgroup analysis is in line with the primary 2-year analysis.

The 5-year interim analyses for the secondary efficacy endpoints are summarised in the following table:

Table 21 Analysis of the interim 5-year secondary endpoints, ITT population

Efficacy endpoint	K-M Estimate 5-year rate % (95% CI)		Stratified Hazard ratio (95% CI)	Stratified Log Rank Test p-value (1-sided)
	Neratinib (n=1420)	Placebo (n=1420)		
DFS-DCIS	89.9 (87.9, 91.6)	87.0 (84.9, 88.8)	0.71 (0.56, 0.90)	0.003
DDFS	92.2 (90.4, 93.7)	90.9 (89.0, 92.4)	0.83 (0.63, 1.10)	0.100
TTDR	92.4 (90.6, 93.8)	91.4 (89.6, 92.9)	0.85 (0.64, 1.13)	0.135
CNS recurrence cumulative incidence estimate[a]	1.34 (0.80, 2.14)	1.45 (0.88, 2.27)		0.420

The results of the secondary endpoint interim analyses at 5 years are broadly in line with the results at 2 years, favouring neratinib.

- **Part B final 5-years iDFS analysis (cut-off date: 1 March 2017)**

The Applicant provided during the evaluation the planned final analysis of invasive disease-free survival (iDFS) at 5 years post-randomization for study 3144A2-3004-WW.

Summary of Primary Endpoint

As of 1 March 2017, 2117 (74.5%) patients have been re-consented for follow-up of iDFS up to 5 years post-randomization: 1028 in the neratinib arm and 1089 in the placebo arm. In the Part A primary analysis of the trial there were 1366 (48% of ITT) patients at risk at month 24. With the re-consenting of 2117 patients included in this update, there are 2248 (79% of ITT) patients now at risk at month 24.

In the primary analysis there were 174 patients censored within the first 3 months of randomization. With the reconsenting of the 2117 in this update the number of patients censored early (within the first 3 months) has dropped to 105. Baseline characteristics are comparable between the re-consented patients (n=2117) and ITT population (n=2840). The median follow-up time is comparable between the two treatment arms: 5.22 years (range, 0.00 to 5.25 years) in the neratinib arm and 5.25 years (range, 0.00 to 5.25 years) in the placebo arm. A total of 885 (62.3 %) and 927 (65.3%) patients in the two arms, respectively, have been followed for 5 or more years for disease recurrence.

Data for the analysis for 2-year and 5-year iDFS in the ITT population are presented in the two tables below (data cut-off of 01 March 2017). For comparison, results for the original primary analysis of 2-year iDFS and 15 April 2016 Update that were in the submission are included in the below table. In this updated 2-year analysis for iDFS (data cut-off of 01 March 2017), a total of 190 events were observed: 76 (5.4%) and 114 (8.0%) in the neratinib and placebo groups, respectively. The updated 2-year iDFS rates for the neratinib arm and the placebo arm were 94.3% and 91.7%, respectively, representing a 32% relative reduction in risk of disease recurrence or death (HR 0.68; 95% CI, 0.51, 0.91; stratified one-sided log-rank test P = 0.004). With this reduction in the number of early censored patients, the updated HR and magnitude of benefit did not change.

At 5 years post-randomization, 279 patients had an iDFS event in the ITT population: 116 (8.2%) and 163 (11.5%) in the neratinib and placebo groups, respectively, representing an additional 106 events over the 2-year data. The 5-year iDFS rate was higher in the neratinib than placebo group (90.2% and 87.7%, respectively), representing a 27% relative reduction in the risk of disease recurrence or death (HR 0.73; 95% CI, 0.57, 0.92; stratified one-sided log-rank test P = 0.004).

Table 22 IDFS at 07 July 2014 (Primary Analysis), 15 April 2016 and 01 March 2017[a]

	Primary 2-year iDFS [b] (07Jul2014)		Updated 2-year iDFS #1[b] (15Apr2016)		2-year iDFS #2[b] (1Mar2017)	
	Neratinib (N=1420)	Placebo (N=1420)	Neratinib (N=1420)	Placebo (N=1420)	Neratinib (N=1420)	Placebo (N=1420)
Patients With Events – n (%)	67 (4.7)	106 (7.5)	74 (5.2)	110 (7.7)	76 (5.4)	114 (8.0)
Patients Censored - n (%)	1353 (95.3)	1314 (92.5)	1346 (94.8)	1310 (92.3)	1344 (94.6)	1306 (92.0)
Patients at Risk at 2-year	662 (46.6)	704 (49.6)	1056 (74.4)	1101 (77.5)	1102 (77.6)	1136 (80.0)
Kaplan-Meier Estimate (%)						
24 Month (95% CI)	94.2 (92.6–95.4)	91.9 (90.2–93.2)	94.3 (92.8–95.4)	91.9 (90.4– 93.3)	94.3 (92.9, 95.4)	91.7 (90.1, 93.1)
Stratified Log-rank Test P-value (one-sided)	0.004		0.007		0.004	
Stratified Hazard Ratio (95% CI)[a]	0.66 (0.49–0.90)		0.69 (0.51– 0.93)		0.68 (0.51, 0.91)	

[a]Log-rank test and Cox model are stratified by randomization stratification factors: prior Trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).
[b]The 2-year iDFS analyses include follow-up data within the 2 year, 4 month and 28 day window specified by the SAP for the primary analysis

Table 23 IDFS Updated on 15 April 2016, and 01 March 2017 Analyses[a]

	Interim 5-year iDFS (15Apr2016)		5-year iDFS (1MAR2017)	
	Neratinib (N=1420)	Placebo (N=1420)	Neratinib (N=1420)	Placebo (N=1420)
Patients With Events - n (%)	107 (7.5)	149 (10.5)	116 (8.2)	163 (11.5)
Patients Censored - n (%)	1313 (92.5)	1271 (89.5)	1304 (91.8)	1257 (88.5)
Patients at Risk at 5-year	424 (29.9)	457 (32.2)	885 (62.3)	927(65.3)
Kaplan-Meier Estimate (%)				
60 Month (95% CI)	90.4 (88.4–92.0)	87.9 (85.9–89.7)	90.2 (88.3, 91.8)	87.7 (85.7, 89.4)
Stratified Log-rank Test P-value (one-sided)	0.008		0.004	
Stratified Hazard Ratio (95% CI)[a]	0.74 (0.58–0.95)		0.73 (0.57, 0.92)	

[a]Log-rank test and Cox model are stratified by randomization stratification factors: prior Trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

The figure below shows the results of the Kaplan-Meier 5-year iDFS analyses (data cut-off date of 01 March 2017) for the ITT population. The two curves separate at approximately 3 months and remain separate throughout the 5-year period.

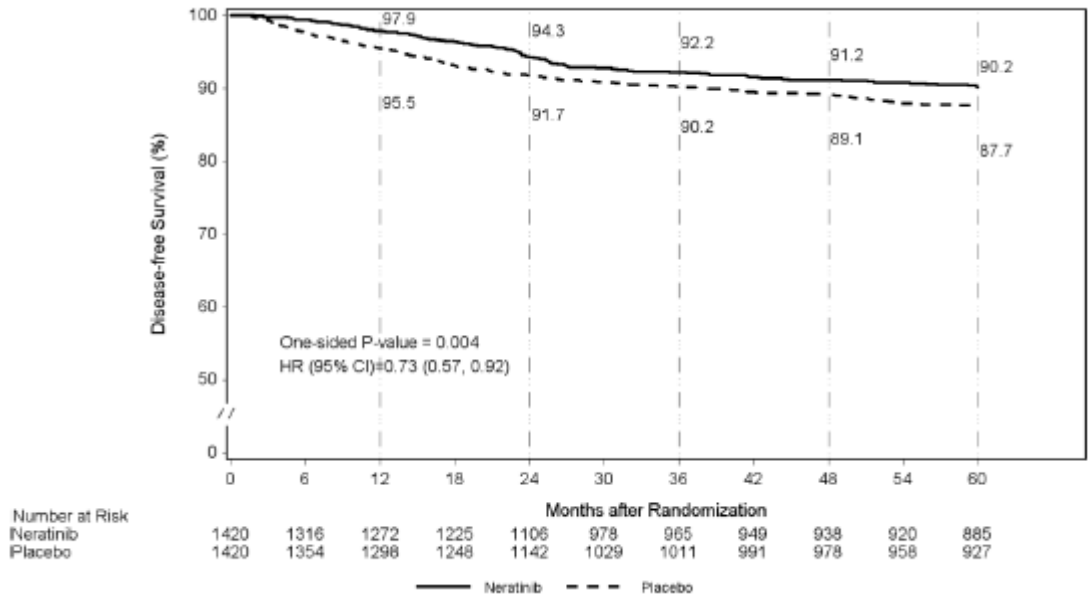


Figure 11 Kaplan-Meier Plot of 5-year Disease-free Survival (All Data for Censoring), ITT Population 01 March 2017

Summary of Secondary Endpoints

For the secondary endpoint of DFS-DCIS, a 29% reduction (HR = 0.71; 95% CI, 0.56, 0.89; P = 0.002, one-sided) was seen in the neratinib arm compared to placebo (see table below). Although limited by a small number of events, TTDR and DDFS appeared favorable for patients treated with neratinib compared to those treated with placebo. CNS recurrence event number was low and no inferences about treatment benefit can be made.

Table 24 Secondary Efficacy Endpoints

	Estimated Event-Free Survival Rate[a]			
	Neratinib (N=1420)	Placebo (N=1420)	HR (95% CI)[b]	P-Value[c]
DFS-DCIS	89.7%	86.8%	0.71 (0.56, 0.89)	0.002
DDFS	91.6%	89.9%	0.78 (0.60, 1.01)	0.032
TTDR	91.8%	90.3%	0.79 (0.60, 1.03)	0.039
CNS Recurrence: cumulative incidence estimate	1.30%	1.82%	NA	0. 166

a Event-free rates for all endpoints except for CNS recurrence for which cumulative incidence is reported.
b Stratified Cox proportional hazards model.
c Descriptive P-value (1-sided)

Summary of Subgroup Analysis

The results of subgroup analyses demonstrate generally consistent treatment effect in the direction favouring the neratinib arm. These findings support similar observations based on the forest plot from the primary 2-year analysis. The pre-specified subgroups were nodal status, hormone receptor status, timing of chemotherapy with trastuzumab (randomization stratification factors) and time since completion of prior trastuzumab.

In the HRc positive subgroup (n=1631), neratinib reduced the 5-year risk of recurrence or death by 40% relative to placebo (HR 0.60; 95% CI, 0.43, 0.83), whereas 5-year iDFS rates were not different in HRc negative women (n=1209) (HR 0.95; 95% CI, 0.66, 1.35). The Kaplan-Meier curves for the 2

treatment groups separate early and remain separate throughout the 5-year study period in the subgroup with HRc positive tumours. In the subgroup of women with HRc negative tumours, the curves also separate early and remain separate throughout receipt of study drug (i.e., 12 months), but begin to converge upon cessation of neratinib treatment, coming together at approximately 24 months.

In the 2 year analysis, in patients who completed trastuzumab treatment within 1 year prior to randomization, neratinib reduced the risk of recurrence or death by 37% relative to placebo (HR 0.63; 95% CI, 0.45, 0.88), but less so in women who completed trastuzumab therapy more than 1 year prior to randomization (HR 0.92; 95% CI, 0.37, 2.23). Similarly in the 5 year analysis, patients who completed trastuzumab treatment within 1 year prior to randomization, there was greater benefit (HR 0.70; 95% CI, 0.54, 0.90), compared to women who completed trastuzumab therapy more than 1 year prior to randomization (HR 1.00; 95% CI, 0.51, 1.94).

Ancillary analyses

Analyses of subgroups were performed, as specified in the SAP, for all stratification factors used in randomization for the ITT population. These stratification factors included the following:

- ER/PR (HRc) status (positive or negative)
- Nodal status (≤3 or ≥4)
- Trastuzumab given sequentially or concurrently with chemotherapy

Subgroup analyses were performed as pre-specified in the SAP to include the following patient subsets:

- Nodal status (negative or positive)
- Patients who completed prior trastuzumab within 1 year or more than 1 year from randomization

For Part A, the efficacy endpoints that were assessed via the aforementioned subgroups are iDFS, DFS-DCIS, TTDR, and DDFS. The incidence of CNS recurrence is not included in the examination of subgroups because there were insufficient events for meaningful statistical analysis.

In addition to above, exploratory subgroup analyses were performed on the following patient subsets:

- Patients who were centrally-confirmed ERBB2-positive by HRc status (positive or negative)
- Patients who were centrally-confirmed ERBB2-positive who completed trastuzumab within 1 year or more than 1 year from randomization
- Patients in the aITT population who completed trastuzumab within 1 year or more than 1 year from randomization
- Patients who completed prior adjuvant trastuzumab within 1 year from randomization by HRc status (positive or negative)
- Patients who were centrally-confirmed ERBB2-positive, HRc-positive, and completed prior adjuvant trastuzumab ≤1 or >1 year from randomization.

Subgroup Analysis of Invasive Disease-free Survival, ITT Population

A Forest plot of a subgroup analysis of 2-year iDFS for the ITT population is shown in the below figure.

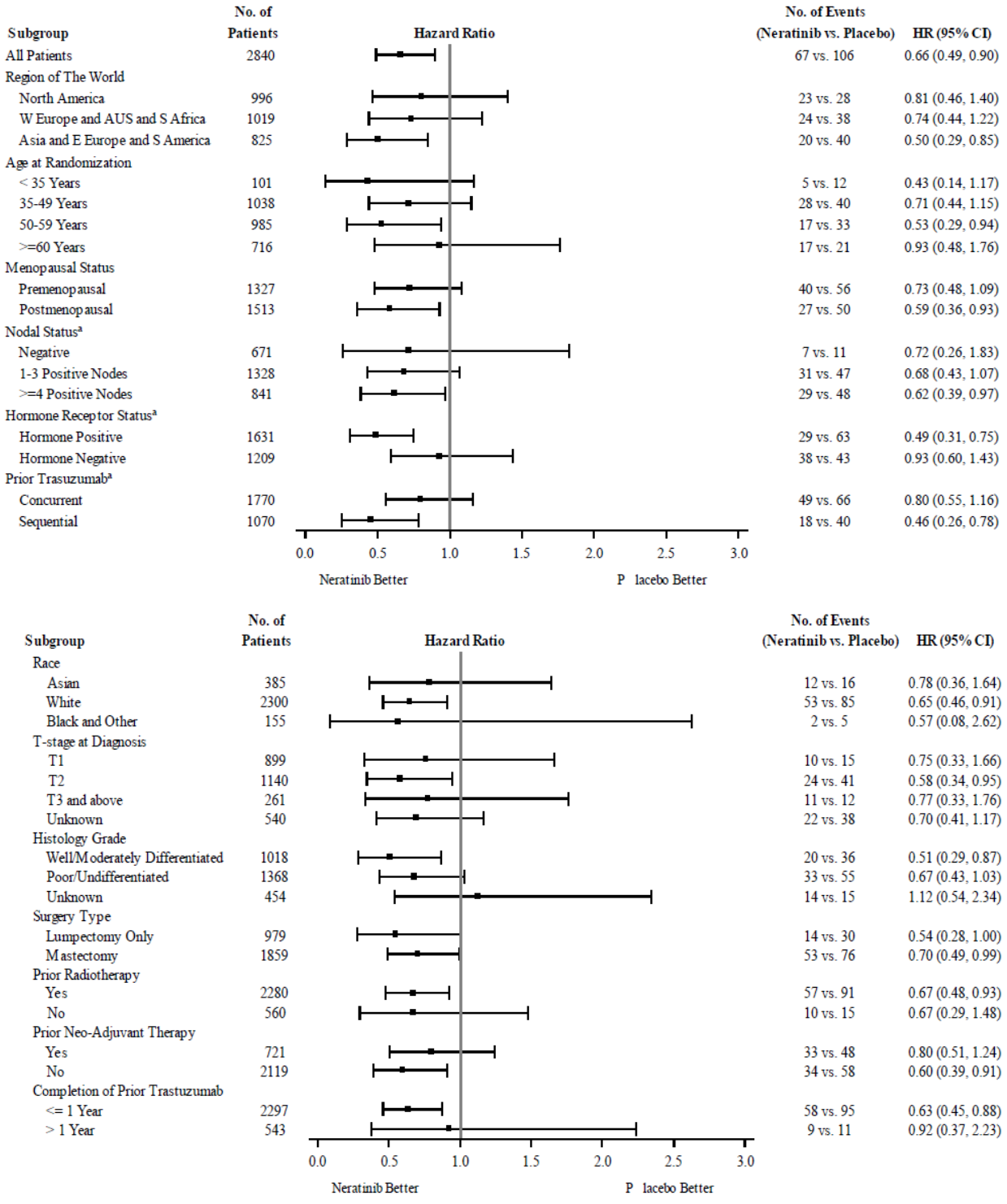


Figure 12 Forest Plot of Disease-free Survival by Subgroups, ITT Population

Generally, in the subgroups analyzed, the treatment effect was in favour of neratinib, and the trends observed were in the same direction as the analysis of the overall ITT population.

In order to evaluate if there is any interaction between the treatment and HRc status, a test of interaction was also performed. The 2-sided p-value for HRc status interaction was 0.045 indicating a potential interaction between treatment and HRc status.

Subgroup Analysis of Invasive Disease-free Survival by Time from Completion of Prior Trastuzumab; ≤1 Year or >1 Year from Randomization

There were 1152 patients in the neratinib arm and 1145 patients in the placebo arm who completed prior adjuvant trastuzumab treatment within 1 year from randomization. The results of iDFS analysis are shown in the below figure. The number of patients with an iDFS event that occurred within 2 years + 28 days after randomization was 58 (5.0%) in the neratinib arm and 95 (8.3%) in the placebo arm. The 2-year iDFS rate was 93.8% in the neratinib arm and 90.9% the placebo arm. The estimated unstratified HR was 0.63 (95% CI, 0.45-0.88), and the 1-sided p-value from the unstratified log rank test was 0.003.

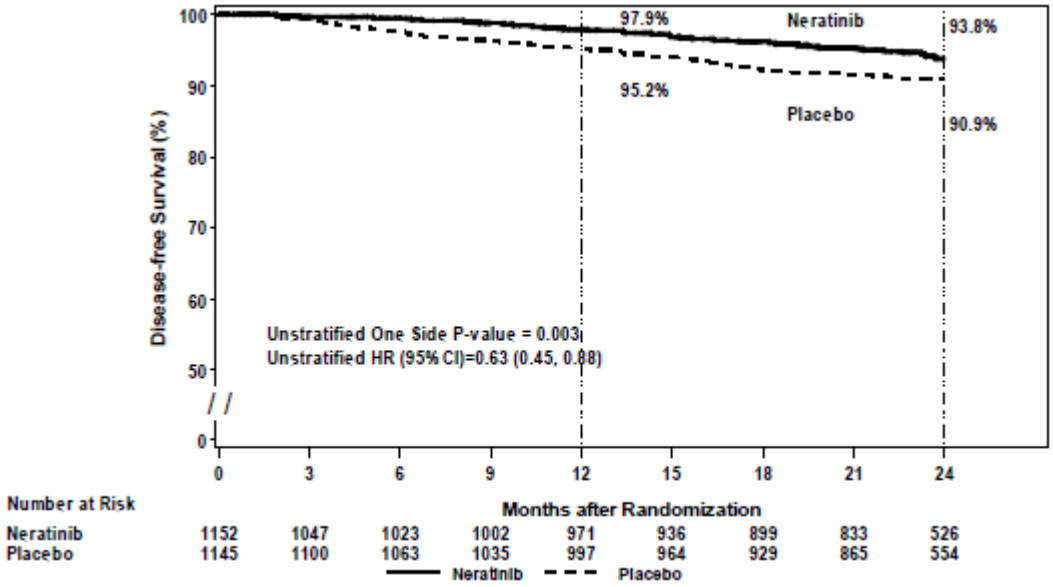


Figure 13 Kaplan-Meier plot of disease-free survival patients who completed trastuzumab within 1 year from randomisation for the ITT population

The results of analysis for the group of patients who completed trastuzumab >1 year from randomization is shown in the below figure. In this group the 2-year iDFS rate was 95.8% and 95.7% in the neratinib and placebo arms, respectively; the unstratified HR was 0.92 (95% CI, 0.37-2.23).

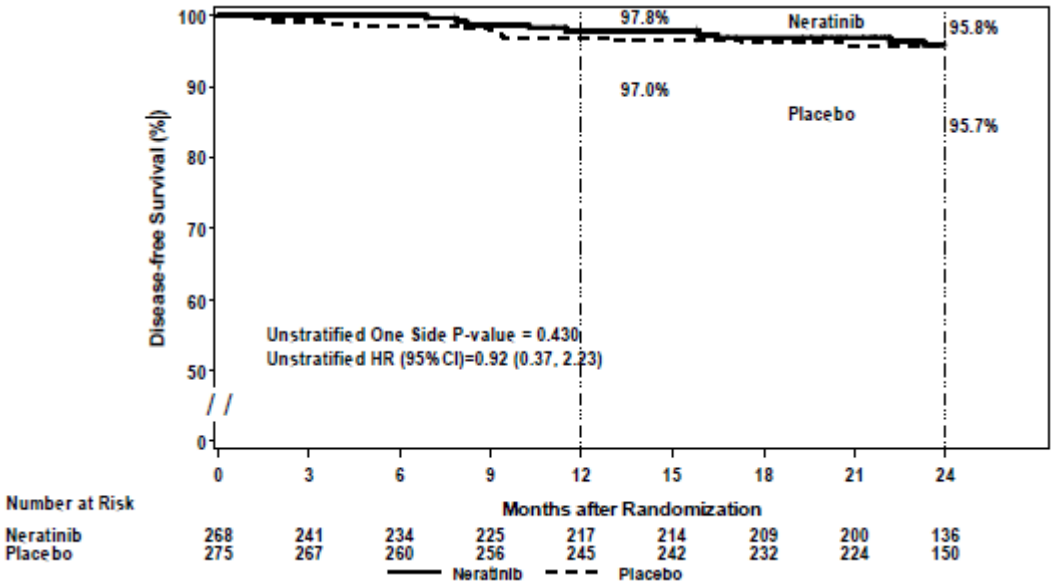


Figure 14 Kaplan-Meier of disease-free survival patients who completed prior adjuvant trastuzumab >1 year from randomisation for the ITT population

Subgroup Analysis of Invasive Disease-free Survival by Hormone Receptor Status

The HRc-positive patient population consisted of 1631 patients randomized to the 2 treatment arms: 816 in the neratinib arm and 815 in the placebo arm. A K-M plot of iDFS for the HRc-positive patients is shown in the figure below.

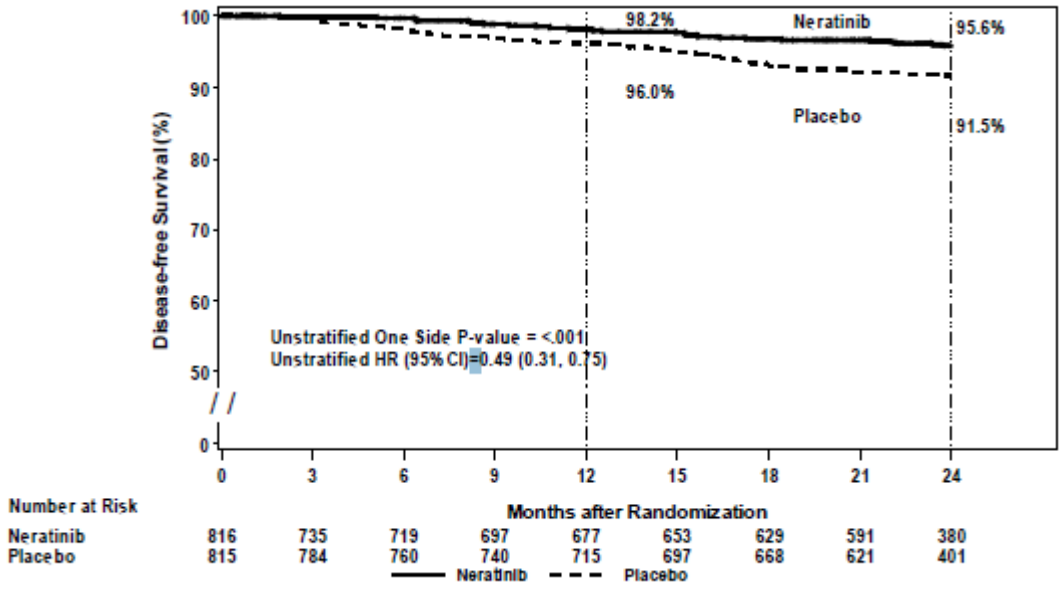


Figure 15 Kaplan-Meier Plot of Disease-free Survival - Hormone Receptor-positive Patients for the ITT Population

A K-M plot of iDFS for HRc-negative patients is shown in the figure below.

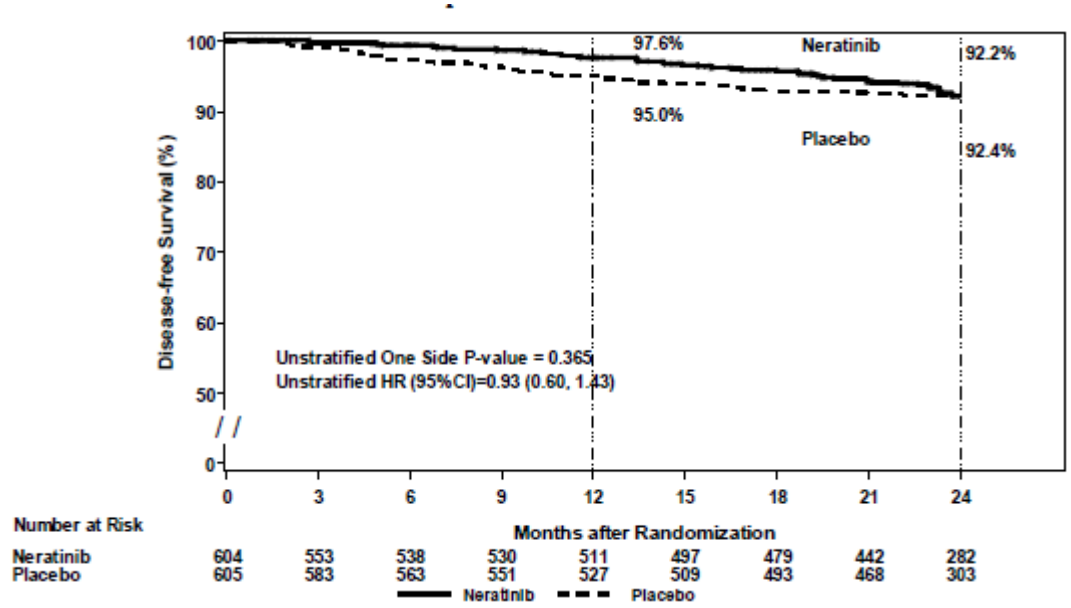


Figure 16 Kaplan-Meier Plot of Disease-free Survival - Hormone Receptor-negative Patients for the ITT Population

For the HRc-positive group, the number of patients with an iDFS event that occurred within 2 years + 28 days after randomization was 92: 29 (3.6%) in the neratinib arm and 63 (7.7%) in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than the placebo arm, 95.6% and 91.5%, respectively. The estimated unstratified HR was 0.49 (95% CI, 0.31-0.75), and the 1-sided p-value from the unstratified log rank test was <0.001.

For the HRc-negative patients, the estimated unstratified HR of neratinib versus placebo was 0.93 (95% CI, 0.60-1.43), with a 1-sided p-value of the unstratified log rank test of 0.365.

Subgroup Analysis of Invasive Disease-free Survival for Patients who Completed Prior Trastuzumab Within Year from Randomization by Hormone Receptor Status

There were 670 patients in the neratinib arm and 664 patients in the placebo arm who completed prior adjuvant trastuzumab treatment within 1 year from randomization and who were HRc-positive. The result of iDFS analysis is shown the figure below.

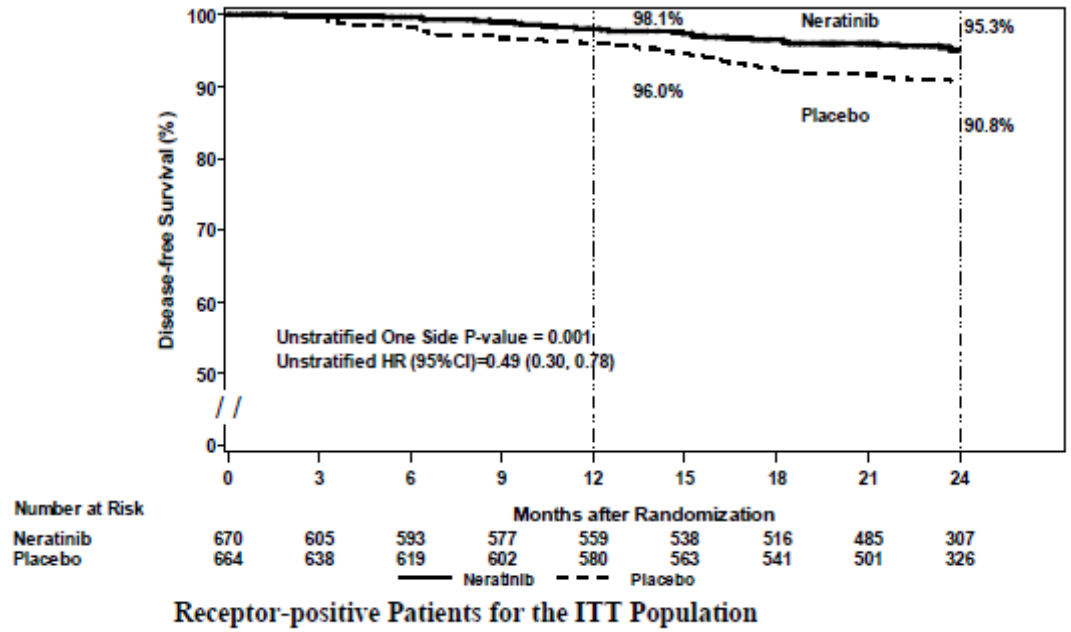


Figure 17 Kaplan-Meier Plot of Disease-free Survival - Patients Who Completed Prior Adjuvant Trastuzumab Within 1 Year from Randomization in Hormone

The number of patients with an iDFS event that occurred within 2 years + 28 days after randomization was 26 (3.9%) in the neratinib arm and 55 (8.3%) in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than the placebo arm, 95.3% and 90.8%, respectively. The estimated unstratified HR was 0.49 (95% CI, 0.30-0.78), and the 1-sided p-value from the unstratified log rank test was 0.001.

The results of analysis for the HRc-negative group of patients who completed trastuzumab within 1 year from randomization is shown in the figure below. In this group, the 2-year iDFS rate was 91.7% in the neratinib arm and 91.1% in the placebo arm; the 2-year iDFS rate was similar in the 2 arms (unstratified HR 0.83; 95%CI, 0.52-1.31).

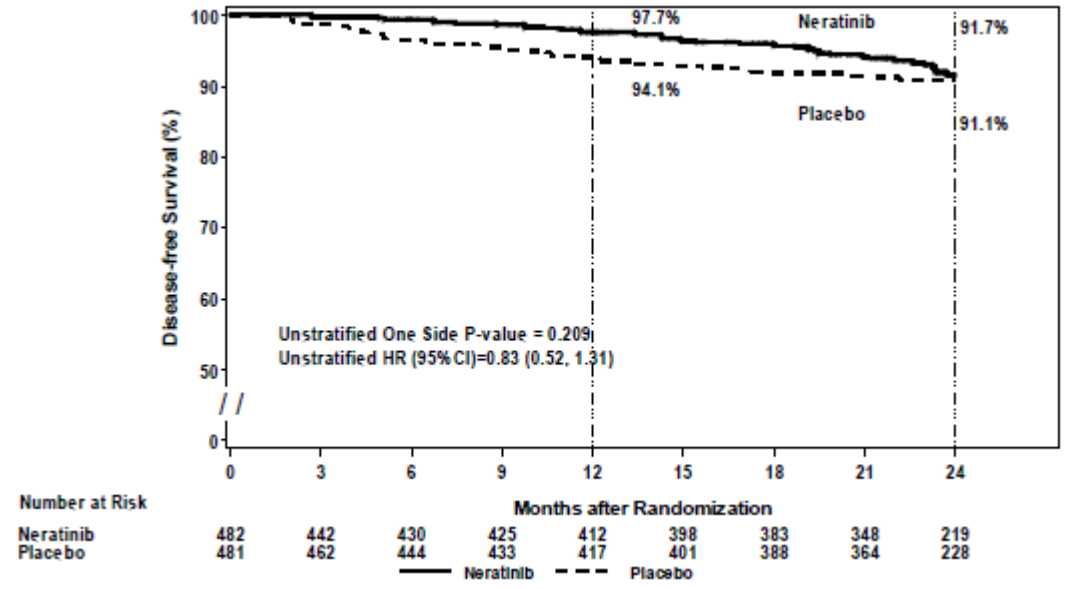


Figure 18 Kaplan-Meier Plot of Disease-free Survival - Patients Who Completed Prior Adjuvant Trastuzumab Within 1 Year from Randomization in Hormone Receptor-negative Patients for the ITT Population

Subgroup Analysis of Invasive Disease-free Survival for the aITT and Centrally-confirmed ERBB2-positive Populations

Generally, in the subgroups analyzed, the treatment effect was in favor of neratinib and the trends observed were in the same direction as the analysis of the total aITT population or centrally-confirmed ERBB2-positive population.

AK-M plot for the patients who completed trastuzumab within 1 year of randomization for the aITT population is shown in the figure below.

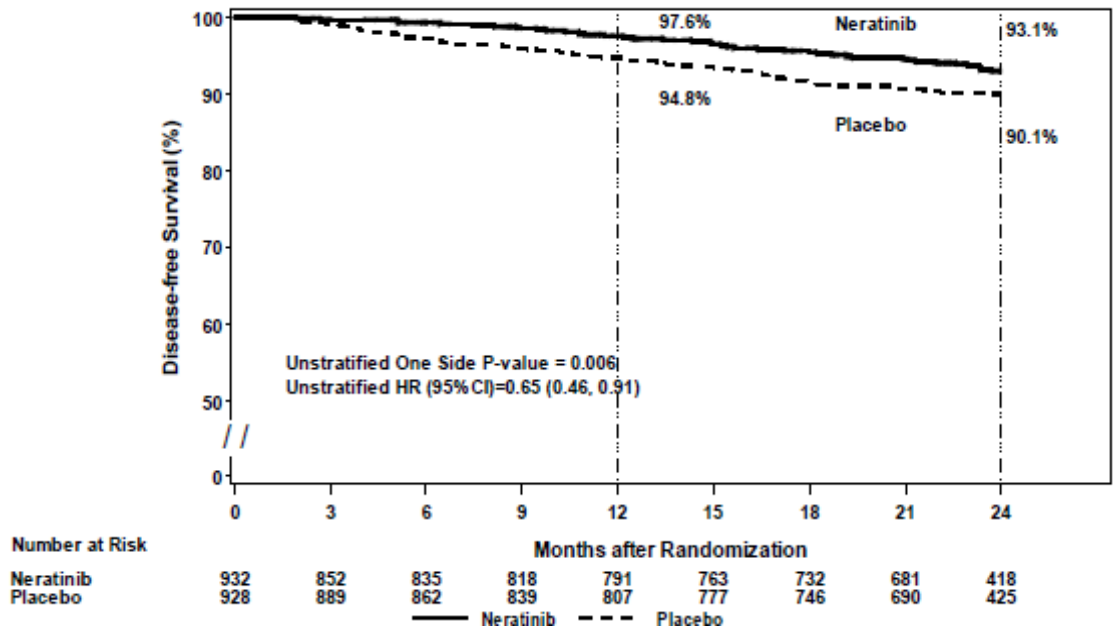


Figure 19 Kaplan-Meier Plot of Disease-free Survival - Patients Who Completed Prior Adjuvant Trastuzumab Within 1 Year from Randomization for the aITT Population

A K-M plot for the patients who completed trastuzumab within 1 year of randomization in the centrally-confirmed ERBB2-positive population is shown in the figure below.

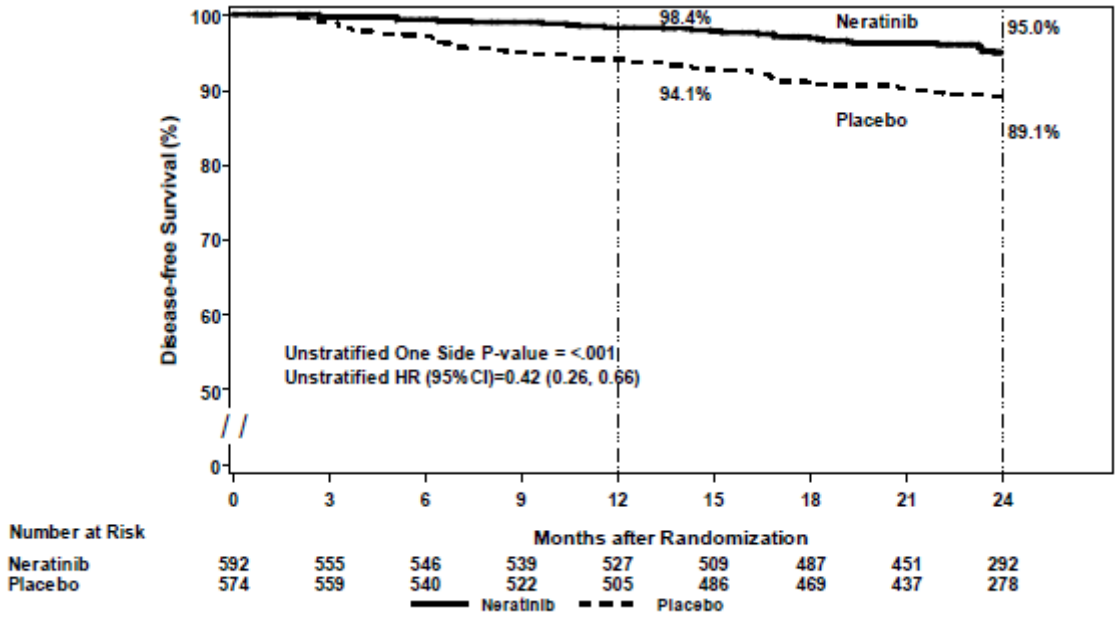


Figure 20 Kaplan-Meier Plot of Disease-free Survival - Patients Who Completed Prior Adjuvant Trastuzumab Within 1 Year from Randomization for the Centrally-confirmed ERBB2-positive Population

In the aITT population, there were 932 patients in the neratinib arm and 928 patients in the placebo arm who completed prior adjuvant trastuzumab treatment within 1 year from randomization. The number of patients with an iDFS event that occurred within 2 years + 28 days after randomization was 53 (5.7%) in the neratinib arm and 84 (9.1%) in the placebo arm. The 2-year iDFS rate was greater in the neratinib arm than the placebo arm, 93.1% and 90.1%, respectively. The estimated unstratified HR was 0.65 (95% CI, 0.46-0.91), and the 1-sided p-value from the unstratified log rank test was 0.006. For the patients who completed trastuzumab >1 year from randomization, there were no iDFS events for analysis.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25 Summary of efficacy for trial 3144A2-3004-WW (study 3004)

Title: 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		
Study identifier	3144A2-3004-WW (3004)	
Design	A phase 3, multi-centre, randomized, double-blind, placebo-controlled study of neratinib monotherapy in women with early-stage HER2-overexpressed /amplified breast cancer who have received adjuvant treatment with trastuzumab.	
	Duration of main phase:	2 years
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	3 years
Hypothesis	Superiority	
Treatments groups	Neratinib	240 mg once daily for one year, N=1420 randomized

	Placebo		Matched placebo once daily for one year, N=1420 randomized
Endpoints and definitions	Primary endpoint	Invasive disease-free survival (iDFS)	Time from randomization to the first occurrence of invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence or death from any cause.
	Secondary:	DFS-DCIS	DFS including ductal carcinoma in situ
	Secondary:	Distant disease-free survival (DDFS)	Time from randomization to the first distant tumour recurrence or death from any cause.
	Secondary:	Time to distant recurrence (TTDR)	Time between randomization and the date of the first distant tumour recurrence, or death from breast cancer.
	Secondary:	Incidence of CNS recurrence	Cumulative incidence of CNS recurrence as a site of distant recurrence
	Secondary:	Overall survival (OS)	Time from the date of randomization until the date of death, censored at the last date known alive.
Database lock	07/07/2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, 2 years		
Descriptive statistics and estimate variability	Treatment group	Neratinib	Placebo
	Number of subjects	1420	1420
	iDFS (Kaplan-Meier Estimate 24 Month) Point estimate (%)	94.2	91.9
	95% confidence interval	92.6, 95.4	90.2, 93.2

Effect estimate per comparison	Primary endpoint: **iDFS**	Comparison groups	Neratinib / Placebo
		Stratified Cox Proportional Hazards Model: Hazard ratio	0.66
		95% confidence interval	0.49, 0.90
		P-value one sided	0.004

Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat, 2 years		
Descriptive statistics and estimate variability	Treatment group	Neratinib	Placebo
	Number of subjects	1420	1420

	DFS-DCIS (Kaplan-Meier Estimate 24 Month) Point estimate (%)	94.2	91.3
	95% confidence interval	92.6, 95.4	89.6, 92.7

Effect estimate per comparison	Secondary endpoint: **DFS-DCIS**	Comparison groups	Neratinib / Placebo
		Stratified Cox Proportional Hazards Model: Hazard ratio	0.61
		95% confidence interval	0.45, 0.83
		P-value one sided	<0.001

Descriptive statistics and estimate variability	Treatment group	Neratinib	Placebo
	Number of subjects	1420	1420
	DDFS (Kaplan-Meier Estimate 24 Month) Point estimate (%)	95.3	94.0
	95% confidence interval	93.9, 96.4	92.6, 95.2

Effect estimate per comparison	Secondary endpoint: **DDFS**	Comparison groups	Neratinib / Placebo
		Stratified Cox Proportional Hazards Model: Hazard ratio	0.74
		95% confidence interval	0.52, 1.05
		P-value one sided	0.047

Descriptive statistics and estimate variability	Treatment group	Neratinib	Placebo
	Number of subjects	1420	1420
	TTDR (Kaplan-Meier Estimate 24 Month) Point estimate (%)	95.5	94.2
	95% confidence interval	94.1, 96.6	92.8, 95.3

Effect estimate per comparison	Secondary endpoint: **TTDR**	Comparison groups	Neratinib / Placebo
		Stratified Cox Proportional Hazards Model: Hazard ratio	0.73
		95% confidence interval	0.51, 1.04
		P-value one sided	0.043

Descriptive statistics and estimate variability	Treatment group	Neratinib	Placebo
	Number of subjects	1420	1420
	CNS Recurrence Cumulative Incidence Estimate	0.92	1.16

	95% confidence interval		0.49, 1.59	0.68, 1.87
Effect estimate per comparison	Secondary endpoint: **CNS recurrence**	Comparison groups	Neratinib / Placebo	
		P-value one sided	0.274	
Notes	An OS analysis has not been conducted because the required number of deaths has not been reached.			

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

The Applicant has not conducted clinical efficacy studies in special populations. The pivotal study 3004 included 348 patients ≥ 65 years (173 on neratinib and 175 on placebo) and 43 patients ≥ 75 years (25 on neratinib and 18 on placebo).

Table 26 Summary of number of subjects by age (subjects in monotherapy breast cancer safety analysis set

	Age <65	Age 65 to 74	Age 75 to 84	Age 85+	Total
Overall	2830 (87.5)	348 (10.8)	54 (1.7)	1 (0.0)	3233 (100.0)
3004	2471 (87.7)	302 (10.7)	43 (1.5)	0 (0.0)	2816 (100.0)
Neratinib	1236 (87.8)	147 (10.4)	25 (1.8)	0 (0.0)	1408 (100.0)
Placebo	1235 (87.7)	155 (11.0)	18 (1.3)	0 (0.0)	1408 (100.0)
3003	196 (84.8)	29 (12.6)	6 (2.6)	0 (0.0)	231 (100.0)
Neratinib	102 (87.9)	12 (10.3)	2 (1.7)	0 (0.0)	116 (100.0)
Control	94 (81.7)	17 (14.8)	4 (3.5)	0 (0.0)	115 (100.0)
6201	40 (80.0)	7 (14.0)	2 (4.0)	1 (2.0)	50 (100.0)
201	123 (90.4)	10 (7.4)	3 (2.2)	0 (0.0)	136 (100.0)

Supportive studies

Study 3144A1-201-WW/B1891012 was an open-label uncontrolled one year study of neratinib 240 mg daily in women with HER2 positive advanced breast cancer. The primary objective was to determine the 16-week PFS rate. A total of 136 patients were enrolled. In the sub-group which had received trastuzumab (n=66), the independently assessed 16-week PFS rate was 58.9% (95% CI: 45.8%,

71.9%). The overall response rate (ORR) was 25.4% (95% CI, 15.3%, 37.9%), all partial responses (n=16). The median duration of response was 40.3 weeks. The applicant has also provided the ORR per HRc status. In patients with no prior trastuzumab, the ORR was 61% (95% CI: 43%, 77%) in HRc positive patients (n=36) compared to 59% (41%, 76%) in HRc negative patients (n=32). In patients after prior trastuzumab, the ORR was 23% (95% CI: 9%, 44%) in HRc positive patients (n=26) compared to 37% (22%, 54%) in HRc negative patients (n=38).

Study 3144A2-3003-WW/ B1891003 was a phase 2 randomized open-label study of neratinib vs lapatinib + capecitabine for the treatment of HER2 + locally advanced or metastatic breast cancer in patients who have received prior therapy including a taxane and trastuzumab. The primary objective of this study was to compare the PFS. A total of 233 patients were randomized 1:1 to receive neratinib 240 mg daily or lapatinib 1250 mg daily + capecitabine 2000 mg/m2 daily days 1-14 of a 21-day cycle) for 9 months. The HR (neratinib arm compared to lapatinib + capecitabine arm) was 1.30 (95% CI: 0.96 - 1.77). Non-inferiority of neratinib compared to lapatinib + capecitabine was not established. For the secondary endpoint of ORR, the investigator assessments indicated that 34 subjects (29.1%; 95% CI, 21.0-38.2) in the neratinib treatment group and 47 subjects (40.5%; 95% CI, 31.5-50.0) in the lapatinib + capecitabine treatment group of the ITT population had an objective response. The median duration of response was 12.5 months for those responding to neratinib. The applicant has also provided the ORR for neratinib per HRc status. In 52 HRc positive patients, the ORR was 23% (95% CI: 13%, 37%). In 63 HRc negative patients, the ORR was 32% (21%, 45%). This study did not demonstrate non-inferiority of neratinib to a combination of lapatinib and capecitabine. However, this study provides evidence for the clinical activity of neratinib in HER2 positive advanced breast cancer, both in HRc positive and HRC negative disease, and therefore some supportive evidence for efficacy in the extended adjuvant treatment of early breast cancer, at the 240 mg daily dose.

The Applicant has submitted an abstract from the American Association for Cancer Research Annual Meeting 2014 which summarises the efficacy results from the I-SPY 2 trial, an adaptive umbrella study. Neratinib 240 mg daily was compared to trastuzumab, both in combination with standard neoadjuvant therapy, for the treatment of high-risk breast cancer. The primary endpoint was pathological complete response (pCR). The estimated pCR rate was calculated for molecular subgroups. For the HER2+/HRc- subgroup the estimated pCR rate was 56% for the neratinib group compared to 33% for the control group. For the HER2+/HRc+ subgroup, the respective pCRs were 30% and 17%. The dual blockade by endocrine therapy and Anti-HER2 in study 3004 may explain the different antitumoral activity against HRc-positive patients between this study and study ISpy2.

The Applicant has submitted reports of a number of ongoing or completed monotherapy and combination studies of neratinib in patients with solid tumours including breast cancer. These studies do not provide supportive evidence of efficacy in the breast cancer monotherapy setting.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose response studies

The dose finding was based on data from three early phase studies, two of which were of ascending single and multiple dose design. The dose limiting toxicity was diarrhoea. The proposed phase 3 dose of 240 mg once daily with food was the maximum tolerated dose. The dose selection was also based on PK and PK/PD considerations. The applicant's rationale is agreed.

Pivotal study 3004

The Applicant has submitted data from a single pivotal trial to support this application. Study 3004 was a multicentre, randomized, double-blind, placebo-controlled trial of neratinib in women with early stage HER2 over-expressed (+) breast cancer. The primary objective of this study was to compare invasive disease-free survival (iDFS) of women with early-stage HER2+ breast cancer who received neratinib or placebo, following trastuzumab in the adjuvant setting. Eligible patients were randomized in a 1:1 ratio to treatment with either neratinib 240 mg or placebo daily with food for a period of 1 year. Comparison against placebo is considered acceptable, since there is no standard comparator in this setting. The study consisted of 3 parts: (A) follow-up period of 2 years post randomization to provide data for the primary analysis (iDFS); (B) extended follow-up for 2-5 years based on medical records upon re-consent; (C) long-term follow-up of overall survival (OS).

After Amendment 9, follow-up was truncated from 5 years to 2 years post-randomization. This was not in line with the scientific advice provided to the Applicant in which CHMP recommended four monthly visits for 3 years after randomization. After amendment 13, patients were re-consented for long-term follow-up to allow a 5 year analysis of iDFS and long-term analysis of OS. These amendments could result in an increase proportion of patients lost to follow-up during Parts B and C, due to the need to obtain new consent. The eligibility criteria defined a HER2+ early breast cancer population who had received loco-regional surgery ± radiotherapy, as well as standard of care chemotherapy and trastuzumab. Following Amendment 3, patients who were node negative were excluded. This was designed to exclude lower risk patients who may be less likely to benefit from neratinib therapy. This reduced the generalisability of the study results. In a real world setting, it is likely that adjuvant neratinib treatment would be sequenced immediately following trastuzumab treatment.

The primary endpoint of iDFS was agreed with the CHMP. The chosen secondary endpoints of DFS-DCIS, DDFS, TTDR, incidence of CNS recurrence and overall survival were considered appropriate.

The statistical methods, including the choice of ITT for the primary analysis, were generally acceptable. Due to the imbalance in discontinuations from the treatment arms in this study, alternative analyses have been conducted to handle this issue (see below).

Overall, considering the number of significant protocol amendments, there are no major methodological issues. However, opportunities to systematically follow-up patients for a clinically relevant period, have been lost.

Efficacy data and additional analyses

A total of 2840 patients were randomized, 1420 to each treatment arm. The study population was generally representative of an early breast cancer population. However, there was a lower proportion of node negative patients than expected. In addition, the inadequacy of the chemotherapy combination and duration of trastuzumab therapy could hamper the external validity. The baseline demographic, disease and prior therapy characteristics were well-balanced between treatment groups.

At 24 months from randomisation (12 months after stopping study drug) the Kaplan-Meier point estimate for iDFS is 94.2% for the neratinib arm compared to 91.9% for the placebo arm, a difference of 2.3%. The HR is 0.66 (0.49, 0.90), p=0.004. One-sided p-values are being presented. If 2-sided p-values were used the p-value would be 0.008, and while this is statistically significant it is not of the extreme level that might be hoped for in an application with a single pivotal trial. This is also revealed by the confidence interval upper-bound for the hazard ratio, which at 0.90 is not substantially below 1.0.

There is an imbalance in the number of patients leaving the trial early, with 325 discontinuing the trial prematurely on neratinib, compared to only 237 on placebo. The requested sensitivity analyses to address this issue have been conducted; the results seem robust to the method of handling missing data.

In order to provide context for the efficacy results observed with neratinib, the applicant has provided a summary of absolute 2-year and 5-year DFS, and hazard ratios, for approved adjuvant therapies (table 14 of the response to question 8 - joint clinical AR). Apart from paclitaxel and extended adjuvant letrozole (after 5 years of tamoxifen), the studies included active comparators rather than placebo, and therefore are not relevant for comparison with study 3004. Paclitaxel as add-on therapy is associated with an increase absolute DFS benefit of 4% at 2 years (CALGB) or 5 years (NSABP B-28).

There is considerable inconsistency according to hormone receptor status. The HRc negative subgroup does not appear to benefit from neratinib, although a benefit in the HRc negative subgroup is not excluded. The applicant attributes this finding to dual inhibition of the ER-HER2 cross talk, supported by non-clinical and clinical data. It is also possible that due to early recurrences in HRc negative patients, those recruited into the study were a lower risk sub-group compared to the recruited HRc positive patients. It should be noted that there is evidence of the clinical activity of neratinib in HRc negative HER2+ advanced breast cancer; based on the results of studies 201 and 3003. The results of the pre-specified primary analysis, combining HRc+ and HRc- sub-populations, is the most relevant when assessing benefit-risk. We must be cautious about basing decisions on the results of subgroups when the overall result is of borderline clinical relevance.

Although the outcomes for the secondary endpoints of DFS-DCIS, DDFS, TTDR and CNS recurrence favoured neratinib, only DFS-DCIS achieved statistically significance. For the more clinically relevant endpoint of DDFS, statistical significance was not achieved. The secondary outcomes provide some support for the positive primary analysis, but not the clear consistency which would be hoped for in a single pivotal trial. Although quality of life data was not collected consistently, there is evidence of a clinically relevant difference during Month 1 favouring placebo. This is likely to be due to the high incidence of gastrointestinal toxicity.

An updated 5-year analysis is provided. This is based on incomplete data since patients had to be re-consented, and their medical records checked for recurrence or death retrospectively. To date, about 75% of patients have been re-consented for 5-year follow-up. During Part B (2-5 years post-randomization) there were on average 2 physical examinations a year. Although this is in line with standard clinical practice, it is more difficult to estimate the timing of any recurrence, compared to the 4-monthly study visits recommended by CHMP for 3 years post-randomization. Based on sensitivity analyses, the missing data due to incomplete follow-up are unlikely to have affected the study conclusions. The results from this updated analysis are not overwhelming, and are less impressive than the 2-year results. The absolute treatment difference in iDFS at 5 years is 2.5%, very similar to that seen at year 2, while the hazard ratio is less favourable at 0.73 (0.57, 0.92), p=0.004 1-sided (0.008 2-sided). This is a reflection of the shape of the Kaplan-Meier curves which initially separate and then run parallel from around 12 months onwards rather than continuing to diverge. Therefore the hazard ratio is not a particularly good summary statistic (and is likely to continue to decrease with duration of follow-up) and the size of benefit is better represented by the around 2.5% absolute difference.

Protocol amendment 3 had the effect of reducing the external validity of the study, since the study population overall was higher risk than that for which neratinib is intended. However, the result of the sensitivity analysis on the aITT population (those enrolled per amendment 3) was in line with the overall result, and subgroup analyses according to nodal status were consistent with the primary outcome. Furthermore, it is acknowledged that there exist other influential studies in this setting with similar proportions of node negative patients. Information on the proportion of patients with node

negative disease, and outcomes in this subgroup, are reflected in section 5.1 of the proposed SmPC. This is acceptable.

The delay between completing trastuzumab and starting neratinib, even when reduced to one year by amendment 3, does not reflect likely clinical practice, since neratinib would be sequenced as soon as possible after trastuzumab. This issue affects the external validity of the study, but is unlikely to favour neratinib. Section 4.2 of the SmPC now includes the recommendation: Patients should initiate treatment within 1 year after completion of trastuzumab therapy.

The Applicant argued that the results from the pivotal trial study 3004 are compelling from both a statistical and clinical point of view.

- Study 3004 is the first trial in extended adjuvant early stage HER2 positive breast cancer to reduce the risk of invasive disease free survival for patients who have previously been treated with adjuvant trastuzumab. The hazard ratio of 0.66 reflects a 34% reduction of risk of iDFS and is clinically meaningful. It is important to put the 2-year treatment difference of 2.3% into the appropriate clinical context. The use of adjuvant trastuzumab and endocrine therapies has led to an additive reduction in the risk of disease recurrence. Due to this, it is important to look at the absolute iDFS benefit relative to the maximum difference that would be achieved if the goal is to cure 100% of the patients. In study 3004, the placebo group demonstrated a 91.6% iDFS at 2 years which would indicate that the maximum achievable improvement would be 8.4% (which would result in 100% of the patients being cured). In that context, a 2.3% absolute increase represents a 27% relative iDFS improvement if the goal was to cure 100% of the patients.
- The Applicant however acknowledged that in certain pre-defined subgroups of study 3004 the magnitude of the clinical benefit was much greater. In the predefined subgroup of patients who were treated with neratinib less than one year after the completion of adjuvant trastuzumab, the 2 year iDFS hazard ratio was 0.63 which translated into an absolute 2-year treatment difference of 2.9%, which is of much greater clinical significance. Again it is important to look at this in the context of the maximum difference that would be achieved if the goal is to cure 100% of the patients. In study 3004, in the subgroup of patients treated with neratinib less than one year after the completion of adjuvant trastuzumab, the placebo arm of the trial demonstrated a 90.9% iDFS at 2 years which would indicate that the maximum achievable improvement would be 9.1%. If the goal was to cure 100% of the patients, then in this subgroup the 2.9% increase would represent a 32% relative iDFS improvement.
- In addition, in the predefined subgroup of patients with HRc positive disease, the 2-year iDFS hazard ratio was 0.49 which translated into an absolute 2-year treatment difference of 4.1%, which is of much greater clinical significance. Again it is important to look at this in the context of the maximum difference that would be achieved if the goal is to cure 100% of the patients. In study 3004, in the subgroup of patients with HRc positive disease, the placebo arm of the trial demonstrated a 91.5% iDFS at 2 years which would indicate that the maximum achievable improvement would be 8.5% if the goal was to cure 100% of the patients. In that context, a 4.1% increase represents a 48% relative iDFS improvement if the goal is to cure 100% of the patients.
- The Applicant discussed the clinical relevance in terms of the maximum absolute treatment difference that could have been achieved, i.e. the improvement that would equate to a cure for 100% of patients.

The Applicant acknowledged that for the ITT population, the only secondary endpoint that achieves statistical significance is invasive disease free survival that includes ductal carcinoma in situ (DFS-DCIS). A higher level of internal consistency might be expected for a single pivotal trial.

Additional expert consultation

The SAG Oncology was asked to provide their view on the following issues:

1. **The benefit of neratinib in HER2 positive early breast cancer, as measured by iDFS, is currently uncertain due to:**

    a. Wide confidence intervals for absolute difference and hazard ratio

    b. Incompleteness of 5-year data due to need to re-consent subjects

    c. Incomplete quality of life (QoL) data due to protocol amendment

    d. Limitations in external validity of study population (higher risk, neratinib not immediately sequenced after trastuzumab)

    e. Inconsistent outcomes for subgroups by hormone receptor status

    Is the point estimate (5-year absolute treatment difference in iDFS of 2.5%) of clinical relevance in this population?

The SAG agreed that based on objective responses reported from small trials in the metastatic setting, neratinib appears to be associated with relevant antitumour activity. The SAG also agreed that the conduct of the main study for this application (Study 3004), due to various reasons (including administrative reasons) has a number of limitations, including missing data that are not possible to correct and result in uncertainties about the magnitude of the effect. However, the views of the SAG diverged on a number of key conclusions such as the importance of uncertainties, the strength of the evidence for clinical efficacy, the clinical relevance of the primary endpoint iDFS (time between the date of randomization to the first occurrence of invasive recurrence, i.e. local/regional, ipsilateral, or contralateral breast cancer; distant recurrence, or death from any cause), the observed magnitude of effect in terms of iDFS, and the importance of the observed toxicity.

According to one view, the observed benefit of about 2.5% difference in patients alive and free from invasive disease at 5 years is significant in terms of the absolute number of patients who may actually benefit as breast cancer is not a rare disease. An additive effect of this magnitude is consistent with the additive effect of other agents used in the adjuvant setting. iDFS is of clinical relevance even acknowledging that in rare cases, local recurrences could still be completely resected. The effect on distant metastases (expectedly less statistically significant due to the fewer events) was consistent with the primary endpoint. Given the relatively small magnitude of effect, the long duration of survival and many potential confounders, an effect in terms of OS is not expected to be observable (however, visual exploration of OS curves should allow to rule out important detriment in OS – such data were not presented to the SAG). Concerning the limitations described above, the confidence interval for the so far reported end-points (regardless of its size) clearly rules out “no-difference”. Censoring mechanisms have been shown to be largely administrative and similar across treatment arms. Even acknowledging the lack of proportional hazards around the 2-year timepoint, the threshold analysis presented is reassuring about the existence of an effect. A transient detriment in QoL is to be expected due to toxicity (compared to no treatment) and is likely self-limiting considering treatment interruptions and discontinuations. Although the effect of dropout on QoL is difficult to ascertain, differences in QoL did not appear to be major. Limitations in external validity of the efficacy results are

not expected (although the association between anthracycline-taxane trastuzumab dose-intensity and neratinib effect should be further explored). Inconsistency between subgroups based on HR status in exploratory subgroup analyses lack convincing biological rationale and would need to be confirmed after long follow-up, 10 years or more for the Er+ subgroup. From a patient and clinical perspective, as long as benefits, risks, and uncertainties were clearly understood by patients and clinicians, it was considered that meaningful treatment decisions could be made and that treatment with neratinib could be a good option for some patients (e.g., based on risk factors such as patients with many involved lymph nodes).

According to an opposing view, the limitations stated above, although individually not considered critical, in the context of a poorly conducted clinical trial with only a very small difference observed raises serious doubts on whether clinical efficacy has been demonstrated. In particular, the small difference observed and high number-needed-to-treat is not considered a clear benefit; the intermediate endpoint of iDFS includes local recurrences that are operable and do not represent a clearly worse prognosis; no data on OS have been presented and are very unlikely to ever be observed in this trial; no statistically significant effect has been demonstrated in terms of distant metastases; there is substantial uncertainty about the magnitude of the effect in view of the poor conduct of the study and unpredictable effect of censoring, both in the iDFS and QoL results. Concerning iDFS, the shape of the survival curve for neratinib shows a drop around the 2-year timepoint that is difficult to explain from a clinical point of view and is likely due to a data collection issue, introducing possible bias and further uncertainty about the magnitude of the effect. In conclusion, due to the limitations of the study and many remaining uncertainties, the efficacy cannot be considered convincingly demonstrated. Taking the non-negligible toxicity into account (gastrointestinal toxicity; fatigue), the high cure rate given available adjuvant treatments, the balance of risks and benefits cannot be considered positive for any clearly defined patient population.

Both views agreed on the recommendation for further data and studies, including biomarker research also in the neoadjuvant and metastatic setting (e.g., genome sequencing of tissue from patients with dramatic responses and studies on patients with “Her-2 like biology” (no HER-2 amplification/increased protein expression) but with mutations in the Her-2 thyrosine kinase domain; serial next-generation sequencing of circulating cell-free DNA to detect minimal residual disease), association between anthracycline-taxane trastuzumab dose-intensity and efficacy, long-term follow-up for ER+/ER- subgroups, and long-term OS results.

Supportive data

Data from two uncontrolled studies (3144A1-201-WW/B1891012, 3144A2-3003-WW/ B1891003), provide some evidence of the activity of neratinib in the advanced breast cancer setting.

2.5.4. Conclusions on the clinical efficacy

The evidence of efficacy, from a single pivotal trial, is not compelling. The hazard ratio point estimate is 0.66 for 2-year iDFS. This translates to an absolute 2-year treatment difference of 2.3%, which is modest, although of clinical relevance. The 95% confidence interval upper bound for the hazard ratio is 0.90, and the 2-sided p value is 0.008. Therefore, there remains uncertainty regarding the magnitude of the iDFS benefit. Secondary endpoints DDFS and TTDR give smaller treatment effects which do not reach statistical significance. There is considerable inconsistency according to hormone receptor status. The hazard ratio for the 5-year iDFS interim analysis is less favourable at 0.73 (95% CI: 0.57, 0.92), and the absolute difference does not increase at the later time-points.

The applicant modified the initially applied indication to patients at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy). Although the absolute benefit in this subgroup is increased relative to the ITT population, as would be expected in a higher risk population, the 95% confidence intervals remain wide. Therefore, the uncertainty remains regarding the magnitude of the iDFS benefit.

For a further discussion, refer to section "3 - Benefit-risk balance".

2.6. Clinical safety

Neratinib has been investigated in a total of 31 studies, including studies in healthy volunteers (12 studies); neratinib monotherapy in breast cancer (4 studies); neratinib monotherapy in solid tumours including breast cancer (4 studies); neratinib combination therapy in breast cancer (3 studies); and neratinib combination therapy in solid tumours including breast cancer (8 studies). The applicant has focused the safety evaluation on the Monotherapy Breast Cancer Safety Analysis Set. This includes study 3004 and ongoing study 6201 in the early breast cancer adjuvant setting, and studies 201 and 3003 in the metastatic setting. Pivotal study 3004 was the only study in this dataset with a placebo arm, and contributed 1408 out of 1710 (82.3%) of the neratinib patients in the Monotherapy Breast Cancer Safety Analysis Set. Therefore, the focus of the safety assessment is the data generated by this study.

Patient exposure

Table 27 Summary of patient exposure – neratinib monotherapy in breast cancer

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose (240 mg daily)	Patients with long term* safety data (months)		Data cut-off date
				≥6 to <12	≥12	
Placebo-controlled (study 3004)	1420	1408	1408	742	191	07/07/2014
Active – controlled (study 3003)	117	116	116	17	23	26/07/2013
Open study (study 201)	136	136	136	31	37	23/07/2012
Open study (study 6201)	50	50	50	3	0	22/09/2015
Total	1723	1710	1710	793	251	

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

A total of 2079 patients have been exposed to neratinib monotherapy and 816 patients to neratinib combination therapy. In addition, 357 healthy volunteers have been exposed to neratinib. A total of 1710 patients with breast cancer have been exposed to neratinib monotherapy at the proposed dose of 240 mg daily, 1408 from study 3004. This includes 793 patients exposed for ≥6 to <12 months and 251 patients exposed for ≥12 months, of which the majority were from study 3004. The median treatment duration (range) of neratinib was 49.6 weeks (0.1, 260.1) for the Monotherapy Breast Cancer Safety Analysis Set. The mean dose intensity (cumulative dose ÷ treatment duration) was 212.0 (42.5) mg/day. The neratinib exposure during the pivotal study 3004 is summarised in the following table:

Table 28 Summary of Investigational Product Exposure, Safety Population

	Neratinib (N=1408)	**Placebo (N=1408)**
Duration Of Treatment (month)		
n	1408	1408
Mean (SD)	8.23 (4.88)	10.71 (2.85)
Median	11.60	11.83
Q1, Q3	2.48, 11.93	11.50, 11.99
Min, Max	0.03, 13.34	0.13, 13.17
Cumulative Actual Dose (mg)		
n	1408	1408
Mean (SD)	54193.93 (34205.17)	76749.32 (20841.81)
Median	70200	85200
Q1, Q3	13920, 85200	80640, 87120
Min, Max	240, 92400	960, 95040
Cumulative Prescribed Dose (mg) During Treatment Period		
n	1408	1408
Mean (SD)	54994.28 (34409.86)	77544.55 (20914.05)
Median	72160	86160
Q1, Q3	14040, 85680	82320, 87600
Min, Max	240, 92400	960, 96240
Prescribed Dose Intensity (mg/day) [a]		
n	1408	1408
Mean (SD)	214.33 (40.95)	237.89 (8.70)
Median	240.00	240.00
Q1, Q3	199.68, 240.00	240.00, 240.00
Min, Max	27.88, 240.00	109.29, 240.00

Relative Prescribed Dose Intensity (%) [b]		
n	1408	1408
Mean (SD)	89.30 (17.06)	99.12 (3.62)
Median	100.00	100.00
Q1, Q3	83.20, 100.00	100.00, 100.00
Min, Max	11.62, 100.00	45.54, 100.00
Actual Dose Intensity (mg/day) [c]		
n	1408	1408
Mean (SD)	210.35 (43.04)	235.33 (11.70)
Median	235.40	240.00
Q1, Q3	193.82, 240.00	236.65, 240.00
Min, Max	19.39, 240.67	109.29, 241.33
Relative Actual Dose Intensity (%) [d]		
n	1408	1408
Mean (SD)	87.64 (17.93)	98.05 (4.87)
Median	98.08	100.00
Q1, Q3	80.76, 100.00	98.60, 100.00
Min, Max	8.08, 100.28	45.54, 100.56
Compliance (%) [e]		
n	1408	1408
Mean (SD)	98.09 (6.52)	98.91 (3.11)
Median	100.00	100.00
Q1, Q3	99.10, 100.00	99.22, 100.00
Min, Max	17.82, 103.33	59.09, 100.56

[a] Prescribed dose intensity is defined as cumulative prescribed dose during treatment period divided by treatment duration
[b] Relative prescribed dose intensity is defined as the prescribed dose intensity/240.
[c] Actual dose intensity is defined as the actual cumulative dose divided by the treatment duration.
[d] Relative actual dose intensity is defined as actual dose intensity/240.
[e] Compliance= actual dose intensity/prescribed dose intensity x100%.
Source: Table 154

Adverse events

The Applicant defined a treatment-emergent adverse event (TEAE) as an AE that occurs or worsens on or after the first administration of study drug and up to 28 days after last dose. In this report AE means TEAE.

Of the 1710 neratinib patients included in the Monotherapy Breast Cancer Safety Analysis Set, 1680 (98.2%) reported any AE, 835 (48.8%) reported a grade 3 or 4 (NCI CTCAE) AE, 14 (0.8%) reported a fatal AE and 173 (10.1%) reported a serious AE (SAE).

Pivotal study 3004 was the only study in this dataset with a placebo arm, and contributed 1408 out of 1710 (82.3%) of the neratinib patients in the Monotherapy Breast Cancer Safety Analysis Set. For neratinib vs placebo in study 3004, the respective incidences were 98.5% versus 88.1% for any AE, 49.7% versus 13.1% for grade 3 or 4 AEs, 0.1% versus 0.1% for fatal AEs, 7.3% versus 6.0% for serious AEs, and 27.6% versus 5.4% for AEs leading to treatment discontinuation.

The following table summarises the most frequently reported AEs:

Table 29 AEs in ≥ 5% of patients in descending order of frequency by preferred term (Study 3004), and corresponding ≥ grade 3 events (occurring in ⩾1.0%)

Preferred terms	All grades		≥ Grade 3	
	Neratinib N=1408 n (%)	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Placebo N=1408 n (%)
Diarrhoea	1343 (95.4)	499 (35.4)	562 (39.9)	23 (1.6)
Nausea	605 (43.0)	303 (21.5)	26 (1.8)	2 (0.1)
Fatigue	382 (27.1)	283 (20.1)	23 (1.6)	6 (0.4)
Vomiting	369 (26.2)	113 (8.0)	47 (3.3)	5 (0.4)
Abdominal pain	340 (24.1)	144 (10.2)	24 (1.7)	3 (0.2)
Headache	278 (19.7)	275 (19.5)	-	-
Abdominal pain upper	212 (15.1)	96 (6.8)	-	-
Rash	211 (15.0)	100 (7.1)	-	-
Decreased appetite	170 (12.1)	40 (2.8)	-	-
Muscle spasms	159 (11.3)	45 (3.2)	-	-
Dizziness	146 (10.4)	128 (9.1)	-	-
Dyspepsia	139 (9.9)	59 (4.2)	-	-
ALT increased	120 (8.5)	45 (3.2)	18 (1.3)	3 (0.2)
Constipation	115 (8.2)	135 (9.6)	-	-
Asthenia	108 (7.7)	110 (7.8)	-	-
AST increased	104 (7.4)	46 (3.3)	10 (0.7)	4 (0.3)
Arthralgia	86 (6.1)	162 (11.5)	-	-
Stomatitis	85 (6.0)	29 (2.1)	-	-
Dry skin	85 (6.0)	33 (2.3)	-	-
Nasopharyngitis	84 (6.0)	126 (8.9)	-	-
Back pain	79 (5.6)	134 (9.5)	-	-
Pyrexia	79 (5.6)	55 (3.9)	-	-
Urinary tract infection	72 (5.1)	23 (1.6)	-	-
Cough	69 (4.9)	92 (6.5)	-	-

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Grade 3 or 4 adverse events

Table 30 Grade 3 or 4 Treatment-emergent Adverse Events Occurring in ≥1.0% of All Neratinib Monotherapy Patients (Monotherapy Breast Cancer Safety Analysis Set)

	Study 3004		Study 3003	Study 201	Study 6201	All Neratinib Monotherapy
Preferred Terms	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib N=116 n (%)	Neratinib N=136 n (%)	Neratinib N=50 n (%)	N=1710 n (%)
Diarrhoea	23 (1.6)	562 (39.9)	34 (29.3)	31 (22.8)	8 (16.0)	635 (37.1)
Grade 3	23 (1.6)	561 (39.8)	32 (27.6)	30 (22.1)	8 (16.0)	631 (36.9)
Grade 4	0	1 (0.1)	2 (1.7)	1 (0.7)	0	4 (0.2)
Vomiting	5 (0.4)	47 (3.3)	6 (5.2)	6 (4.4)	0	59 (3.5)
Grade 3	5 (0.4)	47 (3.3)	5 (4.3)	6 (4.4)	0	58 (3.4)
Grade 4	0	0	1 (0.9)	0	0	1 (0.1)
Nausea	2 (0.1)	26 (1.8)	6 (5.2)	2 (1.5)	0	34 (2.0)
Grade 3	2 (0.1)	26 (1.8)	5 (4.3)	2 (1.5)	0	33 (1.9)
Grade 4	0	0	1 (0.9)	0	0	1 (0.1)
Fatigue	6 (0.4)	23 (1.6)	3 (2.6)	2 (1.5)	2 (4.0)	30 (1.8)
Grade 3	6 (0.4)	23 (1.6)	3 (2.6)	2 (1.5)	2 (4.0)	30 (1.8)
Abdominal pain	3 (0.2)	24 (1.7)	2 (1.7)	1 (0.7)	1 (2.0)	28 (1.6)
Grade 3	3 (0.2)	24 (1.7)	2 (1.7)	1 (0.7)	1 (2.0)	28 (1.6)
Alanine aminotransferase increased	3 (0.2)	18 (1.3)	5 (4.3)	5 (3.7)	0	28 (1.6)
Grade 3	3 (0.2)	15 (1.1)	5 (4.3)	4 (2.9)	0	24 (1.4)
Grade 4	0	3 (0.2)	0	1 (0.7)	0	4 (0.2)
Dehydration	1 (0.1)	13 (0.9)	4 (3.4)	6 (4.4)	0	23 (1.3)
Grade 3	1 (0.1)	12 (0.9)	3 (2.6)	6 (4.4)	0	21 (1.2)
Grade 4	0	1 (0.1)	1 (0.9)	0	0	2 (0.1)
Aspartate aminotransferase increased	4 (0.3)	10 (0.7)	4 (3.4)	4 (2.9)	0	18 (1.1)
Grade 3	4 (0.3)	7 (0.5)	4 (3.4)	3 (2.2)	0	14 (0.8)
Grade 4	0	3 (0.2)	0	1 (0.7)	0	4 (0.2)

The incidence of grade 3 diarrhoea was markedly increased for the neratinib arm of study 3004 relative to placebo. The incidence was lower in study 6201 in which prophylactic loperamide was mandated in the protocol (see additional comments below under AEs of special interest). Other grade 3 GI AEs were increased for neratinib vs placebo, but to a lesser extent. The cases of grade 3 dehydration in the neratinib group are likely to be secondary to diarrhoea.

Under the renal and urinary disorders SOC, there were 10 (0.7%) grade 3 or 4 AEs in the neratinib arm of study 3004 compared to 1 (0.1%) in the placebo arm. This included 3 reports of renal failure and 3 reports of renal failure acute compared to no reports of renal failure in the placebo arm (for discussion see below SAEs).

There was one case of grade 3 or 4 hepatotoxicity in the neratinib arm of study 3004 (for discussion see below AEs of special interest).

Serious adverse event/deaths/other significant events

Serious adverse events and deaths

A total of 173 (10.1%) breast cancer patients treated with neratinib monotherapy had at least 1 SAE. The SAEs with the highest incidence in the Monotherapy Breast Cancer Safety Analysis Set were gastrointestinal or hepatic. SAEs from these SOCs were also increased for neratinib vs placebo in study 3004:

Table 31 SAEs occurring in ≥3 patients (study 3004)

Preferred term	**Neratinib N=1408** **n (%)**	**Placebo N=1408** **n (%)**
Diarrhoea	22 (1.6)	1 (0.1)
Vomiting	12 (0.9)	1 (0.1)
Dehydration	9 (0.6)	1 (0.1)
Nausea	4 (0.3)	1 (0.1)
ALT increased	4 (0.3)	0
AST increased	4 (0.3)	0
Cellulitis	6 (0.4)	4 (0.3)
Erysipelas	5 (0.4)	0
Fatigue	3 (0.2)	0
Pulmonary embolism	3 (0.2)	3 (0.2)
Non-cardiac chest pain	3 (0.2)	0
Renal failure acute	3 (0.2)	0
Syncope	3 (0.2)	2 (0.1)

In study 3004, nine patients reported SAEs of dehydration compared to one on placebo. Of the nine patients from the neratinib arm, eight reported SAEs of dehydration in association with diarrhoea. There were five SAEs of renal failure/acute renal failure in the neratinib arm of study 3004. In four subjects, this was associated with diarrhoea of which two subjects also reported dehydration SAEs. Therefore, ten subjects out of 1408 (0.7%) in the neratinib arm of study 3004 reported SAEs of dehydration and/or renal failure in association with diarrhoea.

On review of narratives, the SAEs for erysipelas are unrelated to study drug. Hepatic SAEs are discussed below under *Adverse events of special interest*.

There were 14 AEs with a fatal outcome in the Monotherapy Breast Cancer Safety Analysis Set. The majority of deaths were due to events occurring in 2 SOCs: *Respiratory, thoracic and mediastinal disorders* and *Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)*. Twelve fatal TEAEs occurred in studies 3003 and 201 in a metastatic setting. Two fatal TEAEs occurred in the neratinib

arm of pivotal study 3004, one due to acute myeloid leukaemia and one due to metastatic breast cancer. A single death in the placebo arm was due to gastric cancer. Overall, there was a low incidence of fatal TEAEs in the adjuvant early breast cancer setting; no neratinib-related safety concerns are raised following review of study deaths.

Adverse events of special interest

Diarrhoea

In the Monotherapy Breast Cancer Safety Analysis Set the overall incidence of AEs for the PT diarrhoea was 94.6% (grade 3: 37.5%), largely driven by the pivotal study 3004. The incidence of diarrhoea SAEs was 1.9%. For the 1571 patients with treatment-emergent diarrhoea, the median time to first onset was 2 days. The median cumulative duration was 59 days for any grade, 10 days for grade 2 and above, and 5 days for grade 3 and above.

In study 3004, the largest proportion of subjects was affected by diarrhoea during the first month. Anti-diarrhoeal prophylaxis was not mandated. However, the protocol included dose reduction schedules and recommendations for pharmacological intervention in the event of diarrhoea, according to severity. Patients were advised to take loperamide at the first occurrence of diarrhoea, 4 mg initially, then 2 mg every 4 hours or after each loose stool until diarrhoea-free for at least 12 hours. Investigators had to ensure that subjects had loperamide available when taking the first dose of neratinib. 91.6% of neratinib patients took anti-diarrheal medication compared to 43.5% of placebo patients, mainly loperamide. The median time to first use of antidiarrheal medication was 3 days (range: 1-598 days). Loperamide as secondary prophylaxis was used by 38.9% of the neratinib arm vs 16.5% of the placebo.

Study PUMA-NER-6201 (6201)

An Open Label Study to Characterize the Incidence and Severity of Diarrhoea in Patients with Early Stage HER2 Breast Cancer Treated with Neratinib and Intensive Loperamide Prophylaxis

The Applicant is sponsoring an ongoing open-label single arm study to characterize the incidence and severity of diarrhoea in patients with early stage HER2 breast cancer treated with neratinib 240 mg daily for up to one year, and intensive anti-diarrhoeal prophylaxis (study PUMA-NER-6201). An interim synopsis safety report with a cut-off date of 18 August 2017 has been submitted during the evaluation. Compared to the pivotal study 3004, the inclusion criteria for this study define a lower risk early breast cancer population: patients with stage I disease, negative lymph nodes, or a pathological complete response following neoadjuvant therapy were permitted. The primary endpoint is the incidence of ≥ grade 3 diarrhoea. Amendment 2 (6 November 2015) added patient reported outcomes as an endpoint, to be analysed once all patients have completed 12 months of neratinib.

The anti-diarrhoeal prophylaxis regimens included (1) loperamide for the first 2 cycles of neratinib; (2) the combination of loperamide (for first 2 cycles) and budesonide extended release (9 mg tablets once daily for first cycle); and (3) the combination of loperamide plus colestipol (2g twice daily), both given during the 1st cycle. Regimens (2) and (3) were added as amendment 3 (24 March 2016). Loperamide 4 mg is taken 3 times daily (the first dose of loperamide with the first dose of neratinib) for 14 days. After this, the dose is reduced to 4 mg 2 times daily until the end of the second cycle. Then, loperamide is taken as required, not exceeding 16 mg daily. The dose can be individually titrated up to a maximum of 16 mg daily, to achieve 1-2 bowel movements a day. However, prior to a protocol amendment, 28 subjects in the loperamide only cohort were dosed as follows: Initial dose of 4 mg was taken with the first dose of neratinib, followed by 2 mg every 4 hours for the first 3 days. After the first 3 days, loperamide 2 mg was taken every 6 to 8 hours through the first 2 cycles of therapy (56 days)

from start of neratinib. Other than mandatory anti-diarrhoeal prophylaxis, and the lack of blinding, the diarrhoea-related protocol aspects were similar to study 3004.

The loperamide cohort is considered of most relevance, since all patients in this cohort have completed the study, and taking into account that anti-diarrhoeal prophylaxis with loperamide is recommended with the first dose of neratinib treatment and during the first two cycles in the proposed SmPC.

The mean (SD) duration of exposure was 7.3 (5.4) months and the mean dose intensity was 213.8 (46.3) mg/day. All patients in the loperamide cohort reported at least one TEAE, 42.3% reported grade 3 or 4 TEAES and 6.6% reported SAEs. There were no fatal TEAEs. The proportion reporting TEAES leading to study drug discontinuation, dose reduction or dose hold were 40.9%, 14.6% and 32.1%. The proportion discontinuing due to a TEAE in the loperamide cohort is higher than that reported for study 3004 (27.6%). Diarrhoea was the most common TEAE (78.5%). In the loperamide cohort, the maximum severity of diarrhoea was grade 1, grade 2 or grade 3 for 24.8%, 24.1% and 30.7% (95% CI: 23.1%, 39.1%), respectively. The figure below provides an analysis of prevalence (of grade 2-3 diarrhoea) during each cycle of neratinib treatment:

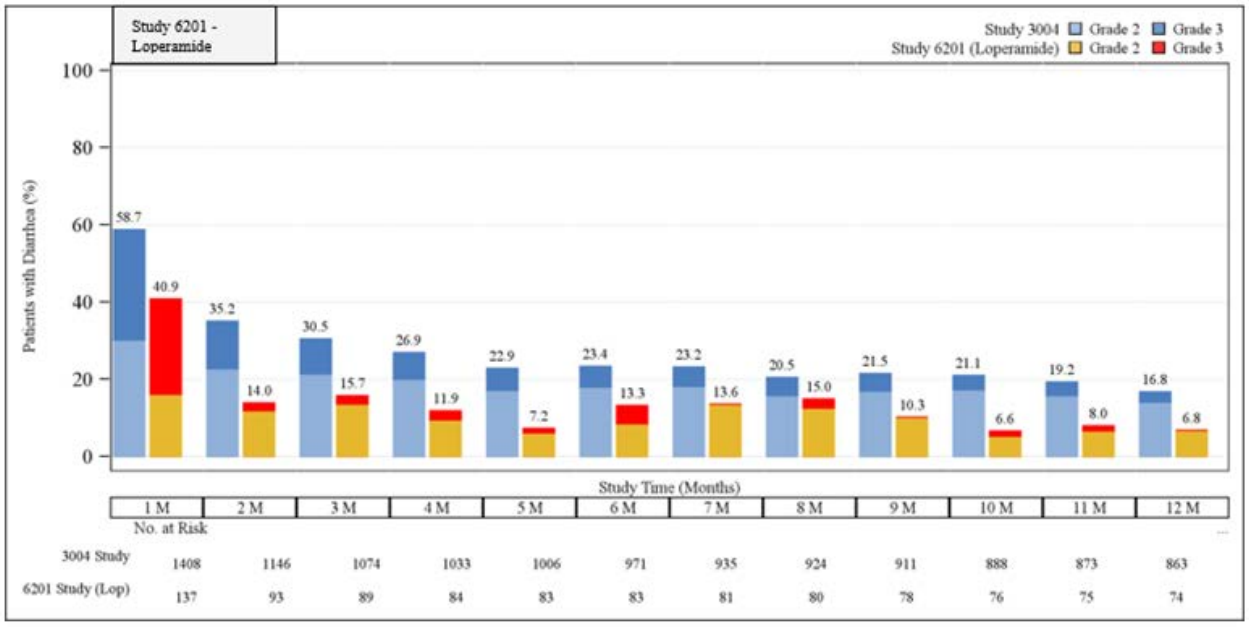


Figure 21 Prevalence of treatment-emergent diarrhoea as a preferred term by treatment month (all patients who received neratinib in study 3004 and neratinib plus loperamide prophylaxis in study 6201)

Other frequently reported TEAEs included constipation (63.8%), nausea (54.9%), fatigue (49.5%), vomiting (25.3%) and abdominal pain (21.2%). The incidence of constipation was much higher than study 3004 (8.2%), presumably due to increased loperamide use. For all cohorts, 14 patients reported SAEs including two reports of diarrhoea and one report of elevated AST and ALT. The following table summarises the incidence of treatment-emergent adverse events other than diarrhoea (>10%) by PT and Grade (Safety Population):

Table 32 Incidence of Treatment-emergent Adverse Events Other than Diarrhoea

(>10%) by PT and Grade (Safety Population)

	Loperamide Cohort (N=137) n (%)	Loperamide plus Budesonide XR Cohort (N=64) n (%)	Loperamide plus Colestipol Cohort (N=26) n (%)	Total (N=227) n (%)
Constipation	77 (56.2)	45 (70.3)	17 (65.4)	139 (61.2)
Grade 1	57 (41.6)	38 (59.4)	16 (61.5)	111 (48.9)
Grade 2	20 (14.6)	7 (10.9)	1 (3.8)	28 (12.3)
Nausea	76 (55.5)	30 (46.9)	15 (57.7)	121 (53.3)
Grade 1	49 (35.8)	24 (37.5)	10 (38.5)	83 (36.6)
Grade 2	26 (19.0)	6 (9.4)	5 (19.2)	37 (16.3)
Grade 3	1 (0.7)	0	0	1 (0.4)
Fatigue	73 (53.3)	30 (46.9)	12 (46.2)	115 (50.7)
Grade 1	44 (32.1)	17 (26.6)	8 (30.8)	69 (30.4)
Grade 2	24 (17.5)	9 (14.1)	4 (15.4)	37 (16.3)
Grade 3	5 (3.6)	4 (6.3)	0	9 (4.0)
Vomiting	34 (24.8)	13 (20.3)	5 (19.2)	52 (22.9)
Grade 1	21 (15.3)	9 (14.1)	3 (11.5)	33 (14.5)
Grade 2	11 (8.0)	2 (3.1)	2 (7.7)	15 (6.6)
Grade 3	2 (1.5)	2 (3.1)	0	4 (1.8)
Abdominal Pain	36 (26.3)	10 (15.6)	1 (3.8)	47 (20.7)
Grade 1	25 (18.2)	8 (12.5)	0	33 (14.5)
Grade 2	9 (6.6)	2 (3.1)	0	11 (4.8)
Grade 3	2 (1.5)	0	1 (3.8)	3 (1.3)
Decreased Appetite	26 (19.0)	9 (14.1)	3 (11.5)	38 (16.7)
Grade 1	22 (16.1)	5 (7.8)	3 (11.5)	30 (13.2)
Grade 2	4 (2.9)	4 (6.3)	0	8 (3.5)

	Loperamide Cohort (N=137) n (%)	Loperamide plus Budesonide XR Cohort (N=64) n (%)	Loperamide plus Colestipol Cohort (N=26) n (%)	Total (N=227) n (%)
Headache	26 (19.0)	9 (14.1)	2 (7.7)	37 (16.3)
Grade 1	20 (14.6)	7 (10.9)	2 (7.7)	29 (12.8)
Grade 2	6 (4.4)	2 (3.1)	0	8 (3.5)
Dizziness	19 (13.9)	5 (7.8)	4 (15.4)	28 (12.3)
Grade 1	16 (11.7)	3 (4.7)	3 (11.5)	22 (9.7)
Grade 2	3 (2.2)	2 (3.1)	1 (3.8)	6 (2.6)
Dry mouth	18 (13.1)	6 (9.4)	3 (11.5)	27 (11.9)
Grade 1	16 (11.7)	6 (9.4)	2 (7.7)	24 (10.6)
Grade 2	2 (1.5)	0	1 (3.8)	3 (1.3)
Abdominal distension	21 (15.3)	3 (4.7)	1 (3.8)	25 (11.0)
Grade 1	13 (9.5)	0	1 (3.8)	14 (6.2)
Grade 2	8 (5.8)	3 (4.7)	0	11 (4.8)

Note: For loperamide, if applicable, a patient is counted under the Amendment subgroup based on their latest consent or reconsent date that is prior to or on the start date of neratinib. For budesonide XR and colestipol, a patient is counted under the enrollment cohort.

Table 33 Characteristics of diarrhoea in studies 3004 and 6201 (December 2017 cut-off)

	Study 3004		Study 6201 (December 2017 data cut off)		
	Neratinib arm (N=1408)	Placebo arm (N=1408)	Loperamide (N=137)	Loperamide +Budesonide (N=64)	Loperamide +Colestipol (N=129)
Duration of treatment (month)					
Median (Min, Max)	11.6 (0.03, 13.3)	11.8 (0.1, 13.2)	11.5 (0.1, 13.1)	11.8 (0.2, 13.9)	4.3 (1.7, 8.2)
Incidence of diarrhoea by worst grade – n (%)					
Any Grade	1343 (95.4)	499 (35.4)	109 (79.6)	55 (85.9)	97 (75.2)
Grade 1	323 (22.9)	382 (27.1)	34 (24.8)	16 (25.0)	42 (32.6)
Grade 2	458 (32.5)	94 (6.7)	33 (24.1)	22 (34.4)	35 (27.1)
Grade 3	561 (39.8)	23 (1.6)	42 (30.7)	17 (26.6)	20 (15.5)
Grade 4	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cumulative duration of any grade per patient (days)					
Median (Min, Max)	59 (1, 523)	6 (1,570)	14 (1, 400)	28 (1,369)	31 (1,373)
Cumulative duration of grade 2 or higher per patient (days)					
Median (Min, Max)	10 (1, 450)	3 (1,340)	5 (1,400)	6 (1,117)	3 (1, 302)
Cumulative duration of grade 3 or higher per patient (days)					
Median (Min, Max)	5 (1, 139)	2 (1, 23)	3 (1, 17)	2 (1, 110)	3 (1, 45)
Action taken					
Discontinuation due to AE – n (%)	388 (27.6)	76 (5.4)	56 (40.9)	11 (17.2)	15 (11.6)
Discontinuation due to diarrhoea – n (%)	237 (16.8)	3 (0.2)	28 (20.4)	7 (10.9)	2 (1.6)

Hepatotoxicity

AEs indicative of potential cases of hepatotoxicity were retrieved using MedDRA SMQs for Biliary Disorders and Hepatic Disorders. Hepatic laboratory parameters were also analysed. The incidence of AEs indicative of potential cases of hepatotoxicity (broad search) was 12.3% in the Monotherapy Breast Cancer Safety Analysis Set. The incidence was 12.4% (≥ grade 3: 1.8%) for the neratinib arm compared to 6.6% (≥ grade 3: 0.6%) for the placebo arm, in study 3004. The incidence of SAEs indicative of potential cases of hepatotoxicity (broad search) was 0.5% (9 cases) in the Monotherapy Breast Cancer Safety Analysis Set. There were 4 (0.3%) hepatotoxicity SAEs in the neratinib arm compared to 2 (0.1%) in the placebo arm of study 3004. All but one of the nine SAEs in the neratinib patients were laboratory abnormalities: elevations of AST or ALT (up to 20x ULN). The one exception was ascites in a patient with terminal disease. The investigator considered the eight hepatotoxicity SAEs that were laboratory abnormalities to be related to study drug.

Transaminase elevations of all categories were more common for the neratinib arm of study 3004 compared to placebo:

Table 34 Incidence of LFT abnormalities (study 3004)

Category	Neratinib N=1408	Placebo N=1408

	n (%)	n (%)
AST or ALT >3x ULN	74 (5.3)	20 (1.4)
AST or ALT >5x ULN	24 (1.7)	9 (0.6)
AST or ALT >10x ULN	10 (0.7)	2 (0.1)
AST or ALT >20x ULN	3 (0.2)	1 (0.1)
Total bilirubin >2x ULN	7 (0.5)	10 (0.7)
ALP >1.5x ULN	145 (10.3)	162 (11.5)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN = upper limit of normal

The Program-Wide Safety Analysis Set (healthy volunteers excluded) was analysed for Hy's Law cases (ALT or AST ≥3x ULN, total bilirubin ≥2x ULN, without substantially elevated ALP). Six cases that met the Hy's law criteria have been reviewed by an external consultant; it is agreed and alternative aetiologies are considered likely in all cases.

Cardiac toxicities

SMQs of cardiac arrhythmia, cardiac failure, ischaemic heart disease and Torsade de Pointes/QT prolongation were used to retrieve potential cardiac toxicity AEs. In Study 3004, cardiac toxicity was reported for 148 (10.5%) patients in the neratinib group and 182 (12.9%) in the placebo group; events ≥ grade 3 were reported for 21 (1.5%) and 7 (0.5%) respectively. This included an excess of 6 syncope reports which general occurred in association with gastrointestinal events. SAEs were reported for 6 (0.4%) and 5 (0.4%) patients respectively. The PTs of ejection fraction decreased and left ventricular dysfunction were of comparable incidence for neratinib and placebo. Regarding Torsade de Pointes/QT prolongation SMQ (broad), the incidences were 4.7% and 7.3% in the neratinib and placebo arms respectively. Left ventricular ejection fraction (LVEF) was measured at least 3-monthly during study 3004; the mean reduction from baseline to minimum post-baseline was comparable between treatment arms.

Patients with unstable angina, congestive heart failure (New York Heart Association class II, III, or IV) (including individuals who used digitalis, beta-blockers, or calcium channel blockers specifically for congestive heart failure), ventricular arrhythmia requiring medical therapy, or with a history of myocardial infarction within 12 months were excluded from study 3004. In addition, LVEF had to be within institutional range of normal.

Dermatological toxicities

In study 3004, AEs in the Skin and Subcutaneous Tissue Disorders SOC were reported for 36.9% patients in the neratinib group (1.1% grade 3) vs. 22.3% in the placebo group (0.4% grade 3). The commonest PTs were rash (15.0% vs 7.1%) and dry skin (9.0% vs 2.3%). The incidence of palmar-plantar erythrodysaesthesia (PPE) syndrome was 1.8% vs 0.2%. There were no reports of serious cutaneous adverse reactions (SCARs) across the Program-Wide Safety Analysis Set. The applicant also conducted a search for nail disorder PTs (sponsor-derived search). In study 3004, TEAEs in this category were reported for 8.0% patients in the neratinib group (0.6% grade 3) vs. 1.8% in the placebo group (0% grade 3). Although the majority of events were less than grade 3, and there were few SAEs, dermatological toxicity, including nail disorders, can have an impact on quality of life.

Laboratory findings

Haematology

There were 44 (3.1%) reports of anaemia in the neratinib arm of study 3004 of which 4 (0.3%) were ≥ grade 3, compared to 16 (1.1%) reports in the placebo arm of which 1 (0.1%) were ≥ grade 3. The median % change from baseline to minimum post-baseline for haemoglobin was -5.93% for neratinib vs -3.10% for placebo. The incidence of leukopenia or neutropenia was 3.1% for neratinib vs 2.3% for placebo. The median % change from baseline to minimum post-baseline was also comparable for leucocyte subclasses between neratinib and placebo. The incidence of thrombocytopenia was 0.9% for neratinib vs 0.4% for placebo. The median % change from baseline to minimum post-baseline was also comparable for platelet count between neratinib and placebo.

The incidences of haematological toxicities were low, with a slight imbalance between neratinib and placebo. Cases were generally grade 1 or 2. It is possible that the increased incidence of anaemia for neratinib vs. placebo is secondary to diarrhoea.

Clinical chemistry

Changes in albumin, sodium, potassium, calcium, phosphate, magnesium, LDH, bilirubin and ALP were comparable for patients treated with neratinib and patients treated with placebo in Study 3004. Median percent change from baseline to maximum post-baseline values for ALT was 45. 5% for patients treated with neratinib monotherapy compared to a 25.0% increase for patients treated with placebo. This reflects the hepatotoxic effect of neratinib (see *Adverse events of special interest* section).

For renal parameters, median percent change from baseline to maximum post-baseline values for creatinine was higher, with an increase of 14.3% for patients treated with neratinib monotherapy compared to 8.1% increase for patients treated with placebo in Study 3004. This reflects the increased incidence of renal impairment for neratinib, mainly due to diarrhoea-related dehydration. The incidence of the PT Blood creatinine increased' was 1% in the neratinib arm of study 3004 compared to 0.3% for placebo.

Vital signs

There were no ≥ grade 3 AEs of *Blood pressure increased* for patients on neratinib in the Monotherapy Breast Cancer Safety Analysis Set. Regarding *Hypertension*, there were 4 (0.2%) ≥ grade 3 AEs in the Monotherapy Breast Cancer Safety Analysis Set, compared to 6 AEs in the placebo arm of study 3004. The median % increase in systolic BP from baseline to maximum post-baseline was 5.4% for neratinib vs 7.8% for placebo in study 3004. For diastolic BP the respective median % increases were 5.9% and 7.9%. The median % decrease in heart rate from baseline to minimum post-baseline was 8.1% for neratinib vs 9.4% for placebo in study 3004. The respective median % increases from baseline to maximum post-baseline were 7.2% and 9.7%. There is no evidence that neratinib causes hypertension, tachycardia or bradycardia.

Safety in special populations

Elderly

The overall incidence of TEAES leading to discontinuation of study treatment was higher in patients 65 years and older compared to younger patients, primarily due to discontinuation of study treatment due to GI disorders (≥65 years, 26.8%; <65 years, 16.1%), including diarrhoea (≥65 years, 24.4%; <65 years, 13.1%). The percentage of older patients who had an AE in the MedDRA SMQ for acute renal failure was increased compared to younger patients. This was largely due to TEAEs related to

laboratory abnormalities. There were 2 reports (1.0%) of renal failure acute in patients ≥ 65 years compared to 3 reports (0.2%) in patients < 65 years. There were 2 reports (1.0%) of renal failure in patients ≥ 65 years compared to 3 reports (0.2%) in patients < 65 years. Older patients are at increased risk of complications of diarrhoea, including renal impairment.

The applicant has provided a table of AE's per age group for the Monotherapy Breast Cancer Safety Analysis Set:

Table 35 Treatment-emergent adverse events per age group (monotherapy breast cancer safety analysis set)

Adverse Events	Age <65 N=1501	Age 65-74 N=176	Age 75-84 N=32	Age 85+ N=1	Total N=1710
Total AEs – n (%)	1476 (98.3)	172 (97.7)	32 (100.0)	0	1680 (98.2)
Serious AEs – Total – n (%)	143 (9.5)	26 (14.8)	4 (12.5)	0	173 (10.1)
- Fatal	13 (0.9)	1 (0.6)	0	0	14 (0.8)
- Hospitalization/prolong existing hospitalization	118 (7.9)	24 (13.6)	3 (9.4)	0	145 (8.5)
- Life-threatening	5 (0.3)	0	0	0	5 (0.3)
- Disability/incapacity	2 (0.1)	0	0	0	2 (0.1)
- Other (medically significant)	28 (1.9)	4 (2.3)	2 (6.3)	0	34 (2.0)
AE leading to drop-out – n (%)[a]	336 (22.4)	71 (40.3)	13 (40.6)	0	420 (24.6)
Psychiatric disorders (SOC) – n (%)	138 (9.2)	12 (6.8)	2 (6.3)	0	152 (8.9)

Adverse Events	Age <65 N=1501	Age 65-74 N=176	Age 75-84 N=32	Age 85+ N=1	Total N=1710
Nervous system disorders (SOC) –n (%)	513 (34.2)	36 (20.5)	7 (21.9)	0	556 (32.5)
Accidents and injuries (SMQ) - n (%)	65 (4.3)	4 (2.3)	0	0	69 (4.0)
Cardiac disorders (SOC) - n (%)	73 (4.9)	11 (6.3)	3 (9.4)	0	87 (5.1)
Vascular disorders (SOC)– n (%)	126 (8.4)	13 (7.4)	3 (9.4)	0	142 (8.3)
Cerebrovascular disorders (SMQ) – n(%)	6 (0.4)	0	0	0	6 (0.4)
Infections and infestations (SOC) – n (%)	518 (34.5)	53 (30.1)	4 (12.5)	0	575 (33.6)
Anticholinergic syndrome (SMQ) – n (%)	320 (21.3)	32 (18.2)	6 (18.8)	0	358 (20.9)
Quality of life decreased – n (%)[b]	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	167 (11.1)	17 (9.7)	5 (15.6)	0	189 (11.1)
Acute renal failure (SMQ) – n (%)	24 (1.6)	7 (4.0)	8 (25.0)	0	39 (2.3)

Adverse events were coded using MedDRA 17.0; Grade was based on CTCAE V3.0 or above. SOC=System Organ Class; SMQ=MedDRA 17.0 Standardized MedDRA Query.
[a]Study 201 does not have information on discontinuation from treatment, therefore discontinuation from study is used.
[b]Quality of life decreased is based on the single PT of "Quality of life decreased".

Race

In study 3004, the frequency of TEAEs in the *Skin and Subcutaneous Tissue Disorders* SOC in Asian patients treated with neratinib was higher than in White patients (56.4% vs. 34.5%) but comparable in placebo patients (24.9% vs. 22.8%). In the neratinib group, rash was reported by 29.4% of Asian patients compared to 13.5% of White patients, and palmar-plantar erythrodysaesthesia (PPE) syndrome was reported by 9.9% of Asian patients compared to 1.0% of White patients. The frequencies of ≥ grade 3 AEs and SAEs were similar between Asian and White patients.

Renal impairment

No patients with severe renal impairment (CrCl ≤ 30 mL/min) were enrolled. In patients with mild or moderate renal impairment compared with normal renal function, AEs and SAEs were reported at the same frequency in the Nerlynx and placebo groups. Discontinuations were higher in the mild renal impairment patients (37.0% vs. 6.6%, Nerlynx vs. placebo, respectively) compared to patients with normal renal function (24.5% vs. 5.2%) due to diarrhoea and dehydration. The population PK analysis suggest that mild and moderate renal impairment have a limited effect on the PK. Patients with renal impairment would need careful monitoring during episodes of diarrhoea due to the risks associated with dehydration and electrolyte imbalance.

Hepatic impairment

The Monotherapy Breast Cancer Safety Analysis Set included limited number of patients with hepatic impairment. Patients with Child-Pugh Class C hepatic impairment were excluded. In a hepatic impairment study of non-oncology patients with severe pre-existing hepatic impairment (Child-Pugh C), the clearance of neratinib was decreased by 36% and exposure to neratinib increased by about 3-

fold as compared to healthy volunteers. Treatment of patients with Child Pugh C hepatic impairment is not recommended.

Pregnancy and breastfeeding

There is no experience with neratinib in pregnant or lactating women. There were no effects on mating or the ability of animals to get pregnant, but embryo-fetal lethality and fetal morphologic anomalies (e.g., domed head, dilation of brain ventricles, misshapen anterior fontanelles, and enlarged anterior and/or posterior fontanelles) were observed. No cases of exposure to neratinib during pregnancy were reported. The applicant has agreed to conduct an oral contraception drug-drug interactions study.

Immunological events

There were 18 AEs (1.1%) reported for the SOC *Immune system disorders* in the Monotherapy Breast Cancer Safety Analysis Set. In study 3004, there were 14 AEs (1.0%) for neratinib vs 18 AEs (1.3%) for placebo. There was one SAE from this SOC in the Monotherapy Breast Cancer Safety Analysis Set, a report of food allergy for a patient on placebo. This was also the only ≥ grade 3 AE reported in the SOC. There is no evidence that neratinib causes serious immunological events.

Safety related to drug-drug interactions and other interactions

The proportion of patients who reported at least 1 SAE was higher in patients who received concomitant CYP inhibitors (18.5%) compared with those who did not (9.0%). The overall incidence of ≥ Grade 3 AEs was 60.5% in patients who received concomitant CYP inhibitors vs. 47.2% for those who did not. Concomitant use of cytochrome P450 inhibitors may increase neratinib exposure and therefore increase the risk of toxicity. However, use was also associated with an increase incidence of AEs in the placebo group for those PTs commonly associated with neratinib use e.g. diarrhoea (48.6% vs 33.9%), rash (10.4% vs 6.7%). Therefore, no firm conclusions can be drawn.

The overall incidence of SAEs was higher in patients who received concomitant PPI (18.6%) compared with those who did not (8.3%), primarily due to serious GI disorders. Patients exposed to PPIs and neratinib had an incidence of 43.5% for Grade 3 or Grade 4 diarrhoea while the overall reported rate was 37.1%. PPIs use may be associated with an increased incidence of more severe diarrhoea due to a reduced absorption of neratinib from the GI tract. However, PPIs can also cause GI ADRs commonly, including diarrhoea. It is noted that patients in the placebo arm of study 3004 who took PPIs also reported more AEs in the GI class including diarrhoea (42.2% vs 34.2%).

Digoxin is a P-gp substrate. Neratinib has been shown to inhibit P-gp, and increase digoxin AUC by 32%. A case of digoxin toxicity in study 201 may have been due to a DDI.

Loperamide is recommended for diarrhoeal prophylaxis. Loperamide is a substrate of P-gp, and therefore exposure to loperamide may be increased when used concomitantly with neratinib. However, this interaction is unlikely to be clinically relevant.

Tamoxifen is expected to be used by around 25% of the target population. CYP3A4 and CYP2D6 are involved in the metabolism of tamoxifen. However, neratinib has not been shown to induce or inhibit CYP2D6 or CYP3A4. Therefore, PK interactions are not foreseen. Nausea, fatigue and rash are very common ADRs for tamoxifen. Therefore, some additive toxicity is possible when used concomitantly with neratinib. The adverse event profile of patients who received concomitant hormonal therapy was similar to that of patients who did not receive concomitant hormonal therapy (regardless of tumour hormone receptor status).

Aromatase inhibitors are expected to be used by around 25% of the target population. Anastrozole inhibits CYP3A4 *in vitro*, but is thought unlikely to cause clinically significant interactions based on clinical data. Rash, asthenia and nausea are very common ADRs for anastrozole. Therefore, some additive toxicity is possible when used concomitantly with neratinib.

Discontinuation due to adverse events

Table 36 Treatment-emergent Adverse Events Leading to Treatment Discontinuation in >2 Neratinib Monotherapy Patients by Preferred Term (Monotherapy Breast Cancer Safety Analysis Set)

	Study 3004		Study 3003	Study 201	Study 6201	All Neratinib Monotherapy
Preferred Term	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib N=116 n (%)	Neratinib N=136 n (%)	Neratinib N=50 n (%)	N=1710 n (%)
Diarrhoea	3 (0.2)	237 (16.8)	2 (1.7)	- (-)	8 (16.0)	247 (14.4)
Vomiting	2 (0.1)	54 (3.8)	1 (0.9)	- (-)	3 (6.0)	58 (3.4)
Nausea	4 (0.3)	39 (2.8)	0	- (-)	3 (6.0)	42 (2.5)
Fatigue	9 (0.6)	25 (1.8)	0	- (-)	4 (8.0)	29 (1.7)
Abdominal pain	2 (0.1)	21 (1.5)	0	- (-)	1 (2.0)	22 (1.3)
Alanine aminotransferase increased	1 (0.1)	17 (1.2)	0	- (-)	1 (2.0)	18 (1.1)
Aspartate aminotransferase increased	1 (0.1)	12 (0.9)	0	- (-)	1 (2.0)	13 (0.8)
Ejection fraction decreased	5 (0.4)	13 (0.9)	0	- (-)	0	13 (0.8)
Decreased appetite	0	9 (0.6)	0	- (-)	1 (2.0)	10 (0.6)
Rash	2 (0.1)	8 (0.6)	0	- (-)	1 (2.0)	9 (0.5)
Abdominal pain upper	0	8 (0.6)	0	- (-)	0	8 (0.5)
Asthenia	1 (0.1)	5 (0.4)	0	- (-)	2 (4.0)	7 (0.4)
Dizziness	2 (0.1)	5 (0.4)	0	- (-)	0	5 (0.3)
Weight decreased	0	4 (0.3)	0	- (-)	1 (2.0)	5 (0.3)
Dyspepsia	0	4 (0.3)	0	- (-)	0	4 (0.2)
Pulmonary embolism	1 (0.1)	3 (0.2)	1 (0.9)	- (-)	0	4 (0.2)
Dehydration	0	3 (0.2)	0	- (-)	0	3 (0.2)
Dyspnoea	1 (0.1)	2 (0.1)	0	- (-)	1 (2.0)	3 (0.2)
Headache	2 (0.1)	3 (0.2)	0	- (-)	0	3 (0.2)
Renal Failure	0	3 (0.2)	0	- (-)	0	3 (0.2)

Note: Adverse events were coded using MedDRA V17.0.
Note: This table is based on action taken from the AE CRF. The AE CRF for Study 201 did not have "discontinue treatment" as an option taken for an AE.
Abbreviations: AE=adverse event; CRF=case report form.

During study 3004, the incidence of AEs leading to treatment discontinuation was 27.6% for neratinib vs 5.4% for placebo. Gastrointestinal AEs were the commonest AEs leading to treatment discontinuation from the neratinib arm. For diarrhoea, the discontinuations rates were 16.8% for neratinib vs 0.2% for placebo. Study 6201 included a similar population to study 3004, and employed anti-diarrhoeal prophylaxis. In the loperamide cohort, 20.4% discontinued due to diarrhoea. This is increased compared to the neratinib arm of study 3004.

Adverse events leading to dose reductions

In the Monotherapy Breast Cancer Safety Analysis Set, 502 (29.4%) patients who received neratinib monotherapy had at least 1 dose reduction due to an AE. In study 3004, 440 (31.3%) of patients in the neratinib arm had at least one dose reduction due to an AE, compared to 35 (2.5%) in the placebo arm. In the Anti-Diarrhoea Prophylaxis Safety Analysis Set, 25 out of 159 (15.7%) patients treated with neratinib monotherapy had at least one dose reduction due to an AE.

Gastrointestinal disorders was the commonest SOC for AEs leading to dose reductions, for the monotherapy breast cancer safety analysis set, in particular diarrhoea. In study 3004, an AE of diarrhoea led to dose reductions for 26.4% of patients in the neratinib arm compared to 0.6% in the placebo arm. The next commonest AE leading to dose reduction was nausea (2.8% of patients in the neratinib arm).

Gastrointestinal AEs were the commonest AEs leading to treatment discontinuation from the neratinib arm of study 3004, particularly diarrhoea. Study 6201 included a similar population to study 3004, and employed loperamide prophylaxis. The rate of discontinuations due to diarrhoea is similar for both studies. The pattern was similar for dose reductions.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

A total of 1710 patients with breast cancer have been exposed to neratinib monotherapy at the proposed dose of 240 mg daily, 1408 from study 3004. This includes 793 patients exposed for ≥ 6 to <12 months and 251 patients exposed for ≥12 months, of which the majority were from pivotal placebo-controlled study 3004. The exposure, including long-term exposure, is adequate to support this application which concerns a maximum treatment duration of one year, in the early breast cancer adjuvant setting. In the pivotal study (3004), the placebo exposure is adequate to allow a meaningful comparison.

The most common AEs were gastrointestinal (GI). These were reported more commonly for neratinib compared to placebo: diarrhoea (95%; ≥ Grade 3: 40%), nausea (43%), vomiting (26%) and abdominal pain (24%). There was a marked difference in the incidence of diarrhoea, including the incidence of ≥ grade 3 diarrhoea, between the neratinib and placebo arms of study 3004. Nausea, vomiting, abdominal pain and decreased appetite were also more commonly reported in the neratinib arm compared to placebo. Non-GI AEs that were common and more frequent in the neratinib arm compared to placebo were fatigue (27%), rash (15%) and muscle spasms (11%). The pattern of AEs is similar to that observed for other EGFR tyrosine kinase inhibitors except that diarrhoea is reported more commonly; the reported incidence is around 65% for lapatinib, another inhibitor of HER2.

Gastrointestinal toxicity (diarrhoea and stomatitis) is included as an important identified risk in the RMP and the Applicant proposed to submit the final results of the ongoing study 6201.

Reported SAEs were predominantly gastrointestinal, particularly diarrhoea (1.6%) and vomiting (0.9%). Dehydration in association with diarrhoea was also notable. In the neratinib arm of study 3004 there were 4 cases of renal failure/acute renal failure associated with diarrhoea.

The incidence of diarrhoea was highest during the first month of treatment. The median time to onset was 2 days and the median cumulative duration was 59 days. This would be expected to have an impact on quality of life. In study 3004, prophylactic loperamide was not mandated, although investigators ensured that subjects had loperamide available when starting neratinib.

An ongoing open-label single arm study (6201) has characterised the incidence and severity of diarrhoea on neratinib plus intensive loperamide prophylaxis, in a similar population to study 3004 (n=137). The incidence of diarrhoea (any severity) was reduced for the loperamide cohort compared to the neratinib arm pivotal study (3004): 77.4% vs 95.4%, respectively. Regarding grade 3 or higher diarrhoea, the respective incidences are 30.7% and 39.9% for studies 6201 and 3004. The use of prophylactic loperamide also appears to reduce the cumulative duration of diarrhoea. The incidence of constipation is significantly increased for the loperamide cohort compared to the neratinib arm of study 3004: 56% versus 8%. In the loperamide cohort, 28 patients (20.4%) discontinued due to diarrhoea.

Transaminase elevations of all categories were more common for the neratinib arm of study 3004 compared to placebo. The Program-Wide Safety Analysis Set (healthy volunteers excluded) was analysed for Hy's Law cases (ALT or AST ≥3x ULN, total bilirubin ≥2x ULN, without substantially elevated ALP). Six cases that met the Hy's law criteria have been reviewed by an external consultant, and it is agreed that alternative aetiologies are likely in all cases.

There was no evidence of cardiac toxicity, including reduced LVEF, cardiac failure or QT prolongation. However, given the known class effect for HER2 blockade, and the exclusion of subjects with cardiac disease from the clinical development programme, cardiac toxicity is included in the RMP as an important potential risk.

Rash and dry skin were very common and nail disorders were common. Although no serious cutaneous adverse reactions are reported, dermatological toxicity can have an impact on quality of life.

No additional concerns were raised on assessment of laboratory findings.

Older patients were more likely to discontinue neratinib treatment due to diarrhoea. The incidence of acute renal failure was also increased in this population. Older patients are at increased risk of complications of diarrhoea, including renal impairment, and should be carefully monitored. Rash and PPE syndrome were reported more commonly by Asian patients compared to White patients. Patients with mild renal impairment were more likely to discontinue treatment due to diarrhoea and dehydration, and should be carefully monitored if diarrhoea develops.

Concomitant CYP inhibitor use was associated with an increased incidence of serious and severe AEs. However, this effect was also seen to some extent in the placebo arm, and may be associated with underlying medical conditions as well as increased exposure. A similar pattern was observed for concomitant PPI use, relating to GI AEs. Loperamide, tamoxifen and aromatase inhibitors are expected to be used concomitantly with neratinib; clinically relevant PK interactions are not expected, but some additive toxicity is possible, particularly nausea, rash and fatigue.

During study 3004, the incidence of AEs leading to treatment discontinuation was 28% for neratinib vs 5% for placebo. For diarrhoea, the discontinuations rates were 17% for neratinib vs 0.2% for placebo. Therefore, diarrhoea is the main cause of the marked difference in treatment discontinuation for neratinib compared to placebo. In routine clinical practice, there may be an even greater rate of treatment discontinuations due to diarrhoea, leading to a reduction in benefit.

To determine which events were adverse drug reactions (ADRs), all AEs from patients treated with 240 mg neratinib in Studies 3144A2-3004-WW, 3144A2-3003-WW, 3144A2-201-WW, and PUMA-NER-6201 were reviewed. AEs were identified for additional review as ADRs if the event occurred in ≥2% of patients in the neratinib group and if it also occurred at a higher incidence in the neratinib group compared with the placebo group, and the absolute difference was ≥2%.

The applicant applied ADR assessment criteria based on the CIOMS Working Groups III and V (CIOMS 1999), and medical judgment to determine which terms were ADRs.

In addition to the assessment of individual AE terms (preferred terms [PTs]), SMQs (Version 17.0, 2014) were used to assess the incidence of diarrhoea, hepatotoxicity, cardiac toxicity (cardiac failure - left ventricular ejection fraction decreased), and pulmonary toxicity (interstitial lung disease [ILD]). Sponsor-defined search terms were used to assess the incidence of stomatitis, and dermatologic toxicities (rash and nail disorders). Pulmonary toxicity (interstitial lung disease) has been included as an important potential risk and hepatotoxicity as an important identified risk in the RMP.

Neratinib's side effect profile is well characterized and is based on the large number of patients treated in the neratinib program (> 3000 patients), including randomized data from study 3004. This provides robust monotherapy experience from which considerable understanding of the risks can be ascertained. Diarrhoea is the primary AE observed with neratinib treatment and is the most common AE leading to discontinuation. In study 3004, where no anti-diarrhoeal prophylaxis was used, 95.4% of patients experienced diarrhoea, 39.8% experienced grade 3 diarrhoea, and 16.8% discontinued due diarrhoea.

Additional expert consultations

The SAG Oncology was asked to provide their view on the following issues:

2. Is the risk of gastrointestinal toxicity, which is ameliorated to some extent by loperamide (with unknown effect on quality of life), acceptable in the proposed patient population?

The SAG agreed that the role of loperamide is not well understood in view of the conflicting results in the studies submitted. Trial 6201, which was specifically designed to answer the toxicity handling question, is still in progress and early data from the trial as presented at the meeting show a significant number of patients still having clinically relevant grades of diarrhoea. Further prospective research needs to be conducted to establish optimal anti-diarrhoeal prophylaxis and treatment regimens.

The acceptability of gastrointestinal (and other, e.g., fatigue) toxicity can only be assessed in the context of the observed benefits. As the SAG views were split about the observed benefits (see answer to question No. 1), the SAG views also diverged in terms of acceptability of the observed toxicity.

The observed toxicity was acceptable according to one view, because it mainly occurred in the first cycles, it was transient, and if unacceptable could be managed with treatment interruptions or discontinuation. The tolerability of toxicity is highly dependent on individual tolerance and the tradeoff between toxicity and decreasing the likelihood of invasive cancer recurrence is highly dependent on individual patient preferences and physicians' attitudes about additional treatment to follow adjuvant trastuzumab-based therapy in case of higher-risk disease.

According to another view, due to the limitations of the study, the many remaining uncertainties (including the shape of the KM curve of the neratinib arm around the 2 year mark), and the unlikely existence of an effect on overall survival or other true clinical endpoints, the efficacy cannot be

considered convincingly demonstrated. Taking the non-negligible toxicity into account (gastrointestinal toxicity; fatigue), the balance of risks and benefits cannot be considered positive for any clearly defined patient population. Thus, according to this view, the observed toxicity cannot be considered acceptable.

2.6.2. Conclusions on the clinical safety

Although gastrointestinal toxicities are a class effect of EGFR TKIs, the very high incidence of diarrhoea is a particular safety concern of neratinib treatment. Diarrhoea can affect quality of life, but can also lead to complications including dehydration and renal failure, particularly in older patients. Based on available data from study 6201, it is uncertain at this time whether the diarrhoea can be adequately managed by anti-diarrhoeal prophylaxis.

2.7. Risk Management Plan

Safety concerns

Table 37 Summary of the Safety Concerns

Important identified risks	• Gastrointestinal toxicity (diarrhoea and stomatitis [a]) • Hepatotoxicity • Drug-drug interaction (inhibitors and inducers of CYP3A4, PPIs, H2-receptor antagonists, antacids, and P-gp transporters)
Important potential risks	• Cardiotoxicity (LVEF decreased) • Pulmonary toxicity (interstitial lung disease) • Reproductive and developmental toxicity
Missing information	• Use in patients with significantly impaired hepatic function (Child-Pugh class C) • Use in patients with severe renal impairment • Use in patients with clinically significant or uncontrolled cardiac disease, including congestive heart failure (NYHA functional classification of ≥2), angina requiring treatment, myocardial infarction within the past 12 months, or ventricular arrhythmia requiring treatment or intervention

Abbreviations: CYP = cytochrome P450; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; P-gp = P-glycoprotein; PPI = proton-pump inhibitor.

a. Includes mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering

Pharmacovigilance Plan

Table 38 Ongoing and planned studies in the PhV development plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PUMA-NER-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 (Open-label interventional, category 3)	To characterise the incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer treated with neratinib and intensive loperamide prophylaxis with/without anti-inflammatory treatment (budesonide), and with/without a bile acid sequestrant (colestipol)	Gastrointestinal toxicity (diarrhoea)	Ongoing	Interim: February 2016 Interim 2: March 2017 Interim 3: December 2017 Final: Q3 2019

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 39 Summary of risk minimisation measures

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Gastrointestinal toxicity – Diarrhoea and stomatitis	For the optimal management of diarrhoea, prophylactic treatment with loperamide is recommended. Guidance on management of diarrhoea is provided (SmPC Sections 4.2 and 4.4). Further information on diarrhoea is also provided in SmPC Section 4.8. Stomatitis adverse reactions are listed in SmPC Section 4.8.	None
Hepatotoxicity	Posology in patients with hepatic impairment is described in SmPC Section 4.2 Special warnings and precautions for use in case of hepatic impairment are described in SmPC Section 4.4. Liver-associated adverse reactions are listed and described in SmPC Section 4.8.	None
Drug-drug interactions (strong inhibitors and inducers of CYP3A4, PPIs, H2-receptor antagonists, antacids, and P-gp transporters)	Drug-drug interactions and recommendations for concomitant drug use are described in SmPC Sections 4.2, 4.4 and 4.5.	None
Important potential risks		
Cardiotoxicity – LVEF decreased	Special warnings regarding left ventricular function are provided in SmPC Section 4.4.	None
Pulmonary toxicity – Interstitial lung disease	None	None

PRAC Outcome

The day 150 Joint Assessment Report on the RMP part of Nerlynx was fully endorsed by the PRAC without any changes proposed to the list of outstanding issues.

Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Not applicable.

2.9. New Active Substance

The applicant compared the structure of neratinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers neratinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union. However, in light of the negative recommendation, new active substance status is not applicable at this stage.

2.10. Product information

In light of the negative recommendation a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Nerlynx as a single agent is intended for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy).

3.1.2. Available therapies and unmet medical need

In the extended adjuvant setting, following one year of trastuzumab therapy, endocrine therapy is standard treatment for HRc+ disease. There is no standard treatment for HRc- disease. The annual hazard of recurrence peaks in the second year after diagnosis but remains at 2%–5% in years 5–20. 25% of HER2+ early breast cancer patients suffer a recurrence or die within 10 years of initiation of adjuvant therapy. Mortality from breast cancer is 23.1/100 000 in Europe. There is an unmet need for additional therapies to further reduce the risk of recurrence and prolong survival.

3.1.3. Main clinical studies

This application is supported by data from a single pivotal study. Study 3144A2-3004-WW was a multicentre, randomized, double-blind, placebo-controlled trial of neratinib in women with early stage HER2+ breast cancer. The primary objective of this study was to compare iDFS of women with early-stage HER2+ breast cancer who received neratinib or placebo, following trastuzumab in the adjuvant setting. The eligibility criteria defined a HER2+ early breast cancer population who had received loco-regional surgery ± radiotherapy, as well as standard of care chemotherapy and trastuzumab. Following a protocol amendment, patients who were node negative or had received the last dose of trastuzumab ≥ 1 year previously were excluded. A total of 2840 patients were randomized, 1420 to each treatment arm of which 1408 were dosed in each arm.

3.2. Favourable effects

At 24 months from randomisation (12 months after stopping study drug) the Kaplan-Meier point estimate for iDFS was 94.2% for the neratinib arm compared to 91.9% for the placebo arm, a difference of 2.3%. This difference could be accepted as representing a clinically relevant benefit. The hazard ratio was 0.66 (0.49, 0.90), p=0.004 1-sided (p=0.008 2-sided).

The pre-specified sensitivity analyses in the amended ITT population (node positive, completion of trastuzumab ≤ 1 year) and centrally-tested HER2-positive population were consistent with the primary ITT analysis: hazard ratios were 0.65 (95% CI: 0.46, 0.92) and 0.51 (95% CI, 0.33-0.78) respectively. A sensitivity analysis including all events up to 2 years and 28 days leads to a very similar result to the primary analysis: hazard ratio 0.67 (95% CI: 0.50, 0.91).

In exploratory analyses, neratinib appeared to have more activity in patients with HRc -positive disease. In this sub-group, the HR is 0.49 (95% CI: 0.31, 0.75) whereas in the HRc negative sub-group the HR is 0.93 (95% CI: 0.60, 1.43). The outcomes for the secondary endpoints of DFS-DCIS, DDFS and TTDR were in line with the primary endpoint, but statistically significance was only reached for DFS-DCIS. However, the robustness of such analyses cannot be confirmed.

The final 5-year analysis was provided. The Kaplan-Meier point estimate for iDFS was 90.2% for the neratinib arm compared to 87.7% for the placebo arm, a difference of 2.5%. The hazard ratio was 0.73 (0.57, 0.92), p=0.004 1-sided (0.008 2-sided).

At an oral explanation, the Applicant presented additional subgroup analyses in support of the amended indication, restricted to patients at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy). The estimated absolute iDFS treatment differences were 3.1% (95% CI: 0.3, 5.8) and 3.7% (95% CI: 0.4, 7.0) at the 2-year and 5-year analysis timepoints, respectively.

There is no supportive efficacy data in the adjuvant setting. However, data from two uncontrolled studies (studies 3144A1-201-WW/B1891012 and 3144A2-3003-WW/ B1891003) provide some evidence of the activity of neratinib in the advanced breast cancer setting, in terms of objective response, in both HRc positive and HRc negative disease.

3.3. Uncertainties and limitations about favourable effects

For the clinically relevant endpoint of DDFS, statistical significance was not achieved.

Only one of the secondary endpoints (DFS-DCIS) achieved statistical significance and the overall statistical significance for the primary endpoint was not statistically compelling. The lack of a high level of internal consistency raises concerns in a single pivotal trial. Considering also the lack of long term follow-up, the high level of censoring and possible bias, there are doubts about the magnitude of a true effect.

At an oral explanation, the Applicant presented additional subgroup analyses in support of the indication restricted in patients at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy). This partially addresses the concerns regarding the external validity of the pivotal study. Although the absolute benefit in this subgroup is increased relative to the ITT population, as would be expected in a higher risk population, the 95% confidence intervals remain wide. Therefore, the uncertainty remains regarding the magnitude of the iDFS benefit.

The long-term efficacy in terms of iDFS is uncertain. The primary analysis was conducted at 2 years (one year after stopping treatment). A 5-year analysis has also been conducted. This was based on incomplete data, since only about 75% of patients were re-consented. Sensitivity analyses provide some reassurance that the missing data is unlikely to affect the study conclusions. However, bias cannot be completely excluded. The effect of neratinib on OS is unknown. There is currently no evidence that the difference in iDFS will translate to a survival benefit or that a detriment in terms of OS can be excluded.

3.4. Unfavourable effects

The most common AEs in study 3004 were gastrointestinal (GI). These were reported more commonly for neratinib compared to placebo: diarrhoea (93.6%; ≥ Grade 3: 36.9%), nausea (42.5%), fatigue (27.3%), vomiting (26.8%) ,abdominal pain (22.7%), rash (15.4%), decreased appetite (13.7%), abdominal pain upper (13.2%), stomatitis (11.2%) and muscle spasms (10.0%).

The key unfavourable effect for neratinib is diarrhoea. The incidence of diarrhoea was highest during the first month of treatment. The median time to onset was 2 days and the median cumulative duration was 59 days. Whether the diarrhoea can be adequately managed by anti-diarrhoeal prophylaxis has not been established so far.

Reported SAEs were predominantly gastrointestinal, particularly diarrhoea (1.6%) and vomiting (0.9%). Dehydration in association with diarrhoea was also notable. In the neratinib arm of study 3004 there were 4 cases of renal failure/acute renal failure associated with diarrhoea.

Older patients were more likely to discontinue neratinib treatment due to diarrhoea. The incidence of acute renal failure was also increased in this population.

3.5. Uncertainties and limitations about unfavourable effects

Based on available data from study 6201, it is uncertain at this time whether the diarrhoea can be adequately managed by anti-diarrhoeal prophylaxis.

3.6. Effects Table

Table 40 Effects Table for Nerlynx based on data from study 3004 (data cut-off: 01/03/2017 for 5-year analysis)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
2-year iDFS (primary analysis)	K-M Estimate 24 Month Point estimate	%	94.2	91.9	HR 0.66 (95% CI: 0.49, 0.90); 2-sided p=0.008	
5-year iDFS	K-M Estimate 60 Month Point estimate	%	90.2	87.7	HR 0.73 (95% CI: 0.57, 0.92); 2-sided p=0.008	
Unfavourable Effects						
Diarrhoea	Incidence all grades	%	95.4	35.4	Uncertain whether the diarrhoea can be adequately managed	
Diarrhoea	Incidence ≥ Grade 3	%	39.9	1.6		
Nausea	Incidence all grades	%	43.0	21.5		
Vomiting	Incidence all grades	%	26.2	8.0		
Abdominal pain	Incidence all grades	%	15.1	6.8		
Rash	Incidence all grades	%	15.0	7.1		
AST or ALT	Incidence >3x ULN	%	5.3	1.4		

Abbreviations: iDFS = invasive disease free survival; K-M = Kaplan-Meier; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Over the past few years, the rate of recurrence of HER2 positive early breast cancer has fallen. Therefore, it is not surprising that the estimated 2-year iDFS in the placebo arm of study 3004 was almost 92%, detracting from the medical need for a new treatment. It is acknowledged that the relative and absolute improvements in iDFS in the adjuvant breast cancer setting have been

incremental and cumulative. In this context, the estimated treatment difference of 2.3%, although rather small in absolute terms, could be accepted as representing a clinically relevant benefit.

However, the hazard ratio upper bound is 0.90, and the 2-sided P value is 0.008. Therefore, the estimate is associated with considerable uncertainty. Furthermore, the 95% confidence intervals for the estimated absolute treatment difference include a range of values that would not be considered clinically meaningful.

There is currently no evidence that the difference in iDFS will translate to a survival benefit.

There was a lack of strong support from clinically relevant secondary endpoints including distant disease-free survival.

In addition, the efficacy estimate may be subject to bias due to the high rate of treatment discontinuation, and incomplete re-consent for longer term follow-up. In conclusion, there are doubts whether clinical efficacy has been demonstrated.

The Applicant has highlighted subgroups, in particular hormone receptor-positive patients, for which the absolute treatment difference (and hazard ratio) was more favourable. However, the isolation of the measured effect to hormone receptor-positive patients lacks a clear explanation, contributing to uncertainty and precluding an indication limited to this subset.

The lack of supportive evidence of a clinically useful anti-tumour effect from confirmatory studies in the neoadjuvant or metastatic breast cancer is a concern.

Over 95% of patients in the pivotal study reported diarrhoea on neratinib, most commonly during the first month. The median cumulative duration was 59 days. More than 39% reported diarrhoea of ≥grade 3 severity. More than 16% discontinued neratinib due to diarrhoea. In most cases, diarrhoea was manageable using anti-diarrheal medication, dose hold, dose reduction or discontinuation. It is uncertain at this time whether the diarrhoea can be adequately managed by anti-diarrhoeal prophylaxis.

3.7.2. Balance of benefits and risks

The estimates of iDFS benefit, although rather small in absolute terms, could be accepted as representing a clinically relevant benefit. However, these estimates are associated with considerable uncertainty, based on the evidence from a single pivotal trial, which is not convincing due to uncompelling statistical significance and methodological weaknesses. Thus efficacy has not been demonstrated.

Neratinib causes significant gastrointestinal toxicity, particularly diarrhoea which can be severe, leads to a high rate of discontinuation, and may affect quality of life. The extent to which these effects may be ameliorated by anti-diarrhoeal prophylaxis is unclear at this time. In the absence of established efficacy, the toxicity cannot be considered acceptable.

For these reasons, it is considered that the benefits of Nerlynx do not outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Nerlynx is negative.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Nerlynx as a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer at high risk of recurrence (node positive and within 1 year of completion of prior adjuvant trastuzumab based therapy), the CHMP considers by majority decision that that the efficacy and safety of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

Grounds for refusal

Whereas

1. For the primary endpoint of invasive disease-free survival (iDFS) in the intention-to-treat (ITT) population, the 2-year and 5-year point estimates for absolute difference (2.3-2.5%) are rather small, but could be accepted as representing a clinically relevant benefit. However, the point estimates for the hazard ratios are imprecise as demonstrated by wide 95% confidence intervals including values close to unity. Importantly, the 5-year efficacy estimate may be subject to bias due to incomplete re-consent for longer term follow-up. There was a lack of strong support from clinically relevant secondary endpoints including distant disease-free survival. Furthermore, there is internal inconsistency in the outcomes, as the isolation of the measured effect to hormone receptor positive patients lacks a clear rationale, contributing to uncertainty. Therefore, for a number of reasons there is considerable uncertainty in the magnitude of the treatment effect demonstrated by this single pivotal trial. Given these uncertainties, the lack of supportive evidence of a clinically useful anti-tumour effect from confirmatory studies in the neoadjuvant or metastatic breast cancer settings is notable. A proposal to restrict the indication to patients at high risk of recurrence has some rationale from the benefit / risk perspective but the evidence of efficacy in such a population was not more compelling than in the full ITT population.
2. Neratinib causes significant gastrointestinal toxicity. Diarrhoea affects most patients, is severe in a high proportion, and can be expected to affect quality of life. Based on available data from study 6201, it is uncertain at this time whether the diarrhoea can be adequately managed by prophylactic anti-diarrhoeals. The very high rate of early discontinuations from this trial despite intensive loperamide prophylaxis is of concern. It is also unclear to what extent diarrhoea may improve over time for the individual patient who decides to remain on treatment after experiencing severe diarrhoea. In routine clinical practice, there may be an even greater rate of treatment discontinuations due to diarrhoea, leading to a reduction in efficacy. In the presence of a robustly demonstrated important clinical benefit the side effect profile might be considered acceptable, but is of major concern in the context of the deficiencies in the demonstration of efficacy.

3. A clinically relevant benefit on iDFS has not been established with an acceptable degree of certainty and the gastrointestinal toxicity is substantial. For these reasons, it is considered that the benefits of Nerlynx do not outweigh the risks.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Divergent position to the majority recommendation is appended to this report.

5. Re-examination of the CHMP opinion of 22 February 2018

Following the CHMP conclusion that Nerlynx was not approvable based on the efficacy and safety grounds outlined above, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented detailed grounds for re-examination in writing and at an oral explanation.

A summary of the applicant's grounds for re-examination is presented below.

Clinical ground 1:

The applicant argued that the absolute iDFS benefit seen in Study 3004 with neratinib is well within the range of iDFS benefits seen with other drugs that are currently approved for adjuvant use in early stage breast cancer in Europe. More specifically, neratinib's magnitude of benefit appears to be similar to that which was achieved with the endocrine agents (anastrozole, letrozole, exemestane) that are widely used in the adjuvant treatment of early stage hormone receptor positive breast cancer in Europe.

Table 41 Summary of Clinical Studies in Breast Cancer Supporting Marketing Authorization

Docetaxel	TAX316	5.4% at 2 years 5.8% at 5 years	0.80 (0.68, 0.93)	0.0043	96
	GEICAM 9805	4.8%	0.68 (0.49, 0.93)	0.01	77
Anastrozole	ATAC	1.6% at 2 years 2.7% at 5 years	0.87 (0.78, 0.97)	0.0127	68
	ABCSG-8	NR	0.67 (0.49, 0.92)	0.014	24
Letrozole	BIG 1-98	1.7% at 2 years 2.6% at 5 years	0.81 (0.70, 0.93)	0.003	26
	MA-17 (ext adj)	1.9%	0.62 (0.49, 0.78)	0.00003	28
Exemestane	IES	3.1%	0.76 (0.67, 0.88)	0.00015	52
Trastuzumab	NCCTG N9831/NSABP B-31	7.2% at 2 years 13% at 5 years	0.48 (0.39, 0.59)	<0.0001	24
	BCIRG 006 AC->D	5.8%	0.61 (0.49, 0.77)	<0.0001	36
	BCIRG 006 DCarbH	4.5%	0.67 (0.54, 0.83)	0.0003	36
	BO16348 (HERA)	7.6%	0.54 (0.44, 0.67)	<0.0001	>12

The results of the adjuvant trastuzumab trials as well as other adjuvant trials including Study 3004 demonstrate that HER2+, hormone receptor positive disease has a different clinical course than HER2+ hormone receptor negative disease with regard to risk of recurrence. HER2+, hormone receptor

positive patients tend to be at a long term continuous risk of recurrence, whereas hormone receptor negative disease tends to have the highest risk of recurrence closest to the completion of adjuvant trastuzumab.

In study 3004, patients were allowed to enrol in the trial up to two years after the completion of treatment with adjuvant trastuzumab. During the review of the MAA, the Rapporteurs stated that in clinical practice neratinib would likely be sequenced immediately after adjuvant trastuzumab treatment which brought up concerns regarding the external validity of the trial. Therefore, it was agreed that the indication should be limited to the patients who are within 1 year of completing trastuzumab. The Applicant performed a quartile analysis of the efficacy from Study 3004 (hazard ratio and absolute iDFS benefit) based on time from discontinuation from trastuzumab treatment.

Table 42 Hazard ratios invasive disease free survival, 5-year analysis Per time from last trastuzumab to randomization, ITT, hormone receptor +/-

	Quartile 1 HR	Quartile 2 HR	Quartile 3 HR	Quartile 4 HR
ITT	0.85	0.49	0.72	1.02
HRc+	0.73	0.50	0.55	0.65
HRc-	1.01	0.45	0.95	1.91

The secondary endpoints of distant disease free survival (DDFS) and time to distant recurrence (TTDR) are based on the number of distant recurrence events. Distant recurrences tend to occur over the long term and hence with more time there are more distant recurrences. It is interesting to note as more time occurs and more distant recurrences occur, the DDFS and TTDR endpoints come closer to statistical significance (2 year results DDFS p=0.094, TTDR p=0.087; 5 year results DDFS p=0.032, TTDR p=0.039). This may suggest that with more time and more distant recurrence events, these two secondary endpoints may become statistically significant at a later date.

The Applicant proposed a restriction of the applied indication to the HRc+ population and claimed that a clinically meaningful improvement is clearly demonstrated in this subgroup. The applicant considered this subgroup, as ascertained as a stratification factor, to be an appropriate, robust subgroup to propose as the indication population.

Table 43 HRc positive tumours

Endpoint	Estimated event-free survival rate at 2 years (%)[a]			
	Neratinib n=670	Placebo n=664	Hazard ratio (95% CI)[b]	P-value[c]
Primary endpoint				
Invasive disease-free survival (iDFS)	95.3	90.8	0.49 (0.30, 0.78)	0.002
Secondary endpoint				
Disease-free survival including ductal carcinoma *in situ* (DFS-DCIS)	95.3	90.0	0.45 (0.28, 0.71)	<0.001
Distant disease-free survival (DDFS)	96.1	92.9	0.53 (0.31, 0.88)	0.015
Time to distant recurrence (TTDR)	96.3	93.3	0.53 (0.30, 0.89)	0.017

a Event-free rates for all endpoints
b Unstratified Cox proportional hazards model.
c P-value is descriptive. Unstratified 2-sided log-rank test form all endpoints, except for CNS recurrence for which Gray's method was used.

Table 44 HRc negative tumours

Endpoint	Estimated event-free survival rate - 2 years (%)[a]			
	Neratinib n=482	Placebo n=481	Hazard ratio (95% CI)[b]	P-value[c]
Primary endpoint				
Invasive disease-free survival (iDFS)	91.7	91.1	0.83 (0.52, 1.31)	0.419
Secondary endpoint				
Disease-free survival including ductal carcinoma *in situ* (DFS-DCIS)	91.7	90.8	0.80 (0.50, 1.27)	0.354
Distant disease-free survival (DDFS)	93.9	93.2	1.04 (0.61, 1.78)	0.879
Time to distant recurrence (TTDR)	93.9	93.5	1.00 (0.58, 1.72)	0.996

a Event-free rates for all endpoints
b Unstratified Cox proportional hazards model.
c P-value is descriptive. Unstratified 2-sided log-rank test form all endpoints, except for CNS recurrence for which Gray's method was used.

The Applicant considers that the enhanced neratinib treatment benefit observed in hormone receptor positive patients in Study 3004 can be explained by:

1) the difference in the risk recurrence profile of HR positive patients compared to HR negative patients and (see comment above)

2) the mechanism of action of neratinib on inhibiting the cross talk between the oestrogen receptor (ER) and with HER2 and EGFR.

Endocrine therapies which solely block ER have limited effectiveness in tumours with HER2 signalling. Conversely, blockade of amplified or overexpressed HER2 with HER2 inhibitors induces ER expression, which serves as an adaptive mechanism for tumor survival.

Breast tumour cell lines with acquired endocrine resistance and treated with neratinib were shown to result in increased ER-mediated gene transcription and increased ER occupancy to ER target genes and oestrogen response elements (Johnston and Martin 2011). This transcriptional rewiring and subsequent re-sensitization of ER function following HER2 signaling blockade by neratinib, represents an adaptive tumor response and based on the ER-HER2 crosstalk, it would be predicted that that inhibition of both HER2 and ER pathways would enhance anti-tumor activity in hormone receptor-positive/HER2-positive breast cancers. These preclinical results suggest that the simultaneous blockade of ER and HER2 signaling pathways in hormone receptor-positive/HER2-positive breast tumors results in enhanced and sustained anti-tumor activity and that combined blockade with neratinib may re-sensitize ER+ pathways to endocrine therapy. The results from these preclinical studies with neratinib in HR positive HER2 positive cells further suggests that the effect of neratinib in HR positive, HER2 positive patients that was seen in Study 3004 could have been anticipated.

The Applicant referred to three exploratory studies supportive evidence of a clinically useful anti-tumour effect in the neoadjuvant or metastatic breast cancer.

Table 45 Observed Response Rate and Progression-Free Survival for HR-positive and HR-negative Patients in Studies 201 and 3003

	ORR (95% CI)				Median PFS, months (95% CI)	
	HR-positive		HR-negative		HR-positive	HR-negative
Monotherapy	N		N			
Study 201						
No prior trastuzumab	36	61% (43%–77%)	32	59% (41%–76%)	9.2 (5.4–14.5)	9.2 (5.5–25.7)
Prior trastuzumab	26	23% (9%–44%)	38	37% (22%–54%)	3.7 (1.7–5.5)	5.4 (3.5–9.0)
Study 3003	52	23% (13, 37)	63	32% (21, 45)	4.1 (2.3, 5.6)	5.6 (4.2, 8.9)

Table 46 Results from a Phase 2, Randomized, Open-label, Standard Neoadjuvant Chemotherapy + Neratinib or Trastuzumab in High-risk Locally Advanced Breast Cancer (I-SPY2)

Parameter	Estimated pCR rate, % (95% CI)	
	Neratinib + standard neoadjuvant chemotherapy [a]	Trastuzumab + standard neoadjuvant chemotherapy [a]
All HER2-positive patients	39 (28-51) n=65	23 (8-38) n=22
HER2-positive / HR-positive	30 (18-44)	17 (3-32)
HER2-positive / HR-negative	56 (37-73)	33 (11-54)

pCR=pathological complete response; PI=probability intervals.
[a] Standard neoadjuvant chemotherapy = paclitaxel followed by doxorubicin + cyclophosphamide.

There were a larger number of earlier censored patients in the neratinib arm than the placebo arm. Non-reconsent led to censuring of 347 (neritanib) versus 268 (placebo) individuals (see table below). The time interval with the largest difference was established in the first 3 months interval: total censoring 80 versus 25. Otherwise differences were small but tended towards more censoring in the neritanib arm.

Table 47 Event and Censoring Count by Time for Neratinib Group (5 Year)

	Baseline	M3	M6	M9	M12	M15	M18	M21	M24	M30	M36	M42	M48	M54	M60
Number at risk	1420	1337	1316	1296	1272	1250	1225	1194	1106	978	965	949	938	920	885
Patients with events in the interval	0	3	4	10	11	9	10	8	18	16	6	7	4	4	6
Patients with events cumulatively	0	3	7	17	28	37	47	55	73	89	95	102	106	110	116
Patients censored in the interval	0	80	17	10	13	13	15	23	70	112	7	9	7	14	29
Patients censored cumulatively	0	80	97	107	120	133	148	171	241	353	360	369	376	390	419
Patients censored due to non-reconsent to 5 year follow-up in the interval	0	75	16	10	13	12	15	22	68	108	5	1	1	1	0
Patients censored due to non-reconsent to 5 year follow-up cumulatively	0	75	91	101	114	126	141	163	231	339	344	345	346	347	347
Patients censored due to loss to follow-up in the interval	0	0	0	0	0	1	0	1	2	2	2	7	6	13	29
Patients censored due to loss to follow-up cumulatively	0	0	0	0	0	1	1	2	4	6	8	15	21	34	63

Table 48 Event and Censoring Placebo Group

	Baseline	M3	M6	M9	M12	M15	M18	M21	M24	M30	M36	M42	M48	M54	M60
Number at risk	1420	1386	1354	1330	1298	1277	1248	1217	1142	1029	1011	991	978	958	927
Patients with events in the interval	0	9	22	16	15	15	17	11	8	10	7	8	4	13	3
Patients with events cumulatively	0	9	31	47	62	77	94	105	113	123	130	138	142	155	158
Patients censored in the interval	0	25	10	8	17	6	12	20	67	103	11	12	9	7	28
Patients censored cumulatively	0	25	35	43	60	66	78	98	165	268	279	291	300	307	335
Patients censored due to non-reconsent to 5 year follow-up in the interval	0	25	8	8	16	4	12	19	64	100	10	2	0	0	0
Patients censored due to non-reconsent to 5 year follow-up cumulatively	0	25	33	41	57	61	73	92	156	256	266	268	268	268	268
Patients censored due to loss to follow-up in the interval	0	0	1	0	0	0	0	0	3	1	1	10	9	7	28
Patients censored due to loss to follow-up cumulatively	0	0	1	1	1	1	1	1	4	5	6	16	25	32	60

The 5-year analysis relied on re-consenting all patients, because after Amendment 9 (October 2011) follow-up was truncated from 5 years to 2 years. Approximately 75% of patients re-consented to Part B (5-year follow-up). Baseline demographic and disease characteristics of the re-consented patients were comparable between treatment arms, and comparable to the ITT population. Median follow-up time was comparable between the treatment arms. The 2-year iDFS HR was comparable for patients who did or did not re-consent for part B. Tipping point analysis showed that in order to lose statistical significance, there would need to be 35/419 events in the neratinib patients who did not re-consent, compared to 18/335 events in the placebo arm. Simulations based on assuming all non-consenting patients would behave like placebo patients on average gave hazard ratios very similar to those seen in the primary 5-year analysis (0.75 compared to 0.73).

Clinical ground 2:

In Study 3004, the AEs associated with neratinib were generally transient and manageable with conventional therapy. In addition to diarrhoea and other gastrointestinal AEs, other commonly reported treatment emergent adverse events (TEAEs) included fatigue, dermatologic toxicities, and hepatotoxicity; less than 2% of these events were severe or required treatment discontinuation, and <0.5% were serious. AST and ALT elevation were mostly Grade 1 or Grade 2 elevations, and generally occurred early in the course of treatment. Live aminotransferase (AT) elevations were reversible either spontaneously without dose change, with dose reduction or with dose discontinuation. Of the patients with higher order AT elevations, none met the definition of a drug-induced liver injury (DILI). There were no fatal TEAEs reported during treatment or within 28 days after the last dose of IP. The frequency of cardiac-associated TEAEs, SAEs, and TEAEs leading to discontinuation was not higher in the neratinib arm compared to the placebo arm; there were no fatal cardiac events. There was no evidence of neratinib-induced hematopoietic, pulmonary or cardiac toxicity and no evidence of increased risk for second malignancy. Data from Study 6201 demonstrate that anti-diarrhoeal prophylaxis helps decrease the incidence and severity of diarrhoea and reduces the duration of the severe diarrhoea episodes. The addition of budesonide or colestipol to the loperamide antidiarrhoeal

prophylaxis regimen appears to further reduce the incidence and severity of neratinib related diarrhoea and appears to improve the tolerability of Nerlynx with less patients discontinuing Nerlynx treatment. Data from the post approval setting in the United States demonstrate that use of improved and proactive diarrhoea management techniques for both physicians and patients and the introduction of a comprehensive education and support program results in reduced diarrhoea rates. The implementation of the support program reduced discontinuation rate due to diarrhoea to 7% (from 17% in the confirmatory study).

Clinical ground 3:

Study 3004 achieved its primary endpoint. Extended adjuvant therapy with neratinib provides a clinically meaningful and statistically significant reduction in risk of disease recurrence. The magnitude of the benefit seen in Study 3004 is in line with other drugs that are currently approved in Europe for the adjuvant treatment of early stage breast cancer and a single pivotal trial has typically been used as the basis for the approval of cancer drugs in Europe. Additionally, patients within pre-stratified sub-groups (including node positive and HR positive breast cancer) had an observed benefit that was substantially increased relative to the ITT population. Other than diarrhoea, Nerlynx is associated with a low incidence of severe or serious adverse events and, with a safety database of over 3000 cancer patients (early stage and metastatic), there is no evidence for irreversible or cumulative toxicity associated with neratinib, with some patients receiving neratinib for more than 5 years. Diarrhoea is the most frequently reported adverse event in the neratinib arm of Study 3004 with an overall incidence of 95.4% and 39.8% of patients experiencing at least one episode of grade 3 diarrhoea. Once diarrhoea occurs it can be managed with antidiarrhoeal agents and/or reducing or temporarily holding the dose of neratinib. Using these diarrhoea management techniques, 95-97% of the patients with diarrhoea due to neratinib achieved resolution of their diarrhoea. All treatment related adverse events, including diarrhoea, in the neratinib arm of Study 3004 were reversible after discontinuation of neratinib. Neratinib is also not associated with cumulative or irreversible toxicity such as cardiac toxicity as seen with other agents in the adjuvant setting. No safety issues of major concern have emerged to negate the demonstrated benefit. In the proposed restricted indication of the HRc+ population, a clinically meaningful improvement is clearly demonstrated. Overall, the benefit/risk profile of neratinib is favourable and whilst it is recognized that extended adjuvant treatment with Nerlynx may not be appropriate for every patient, it is considered an appropriate treatment option on a case by case basis, especially in the HRc+ population.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and justifications presented by the applicant.

Concerning clinical ground 1:

Although the outcomes for the secondary endpoints of DFS-DCIS, DDFS, TTDR and CNS recurrence favoured neratinib, only DFS-DCIS achieved statistically significance. For the more clinically relevant endpoint of DDFS, statistical significance was not achieved. However, the study was not powered to demonstrate efficacy on this endpoint at the 0.05 level, and results are trending in the same direction as the primary endpoint.

In the provided analysis by the Applicant, there are no apparent systematic differences between the consenting and non-consenting groups in terms of censoring and baseline characteristics. This supports the reliability of the statistically significant effect at year 5. Acknowledging the limitations of the robustness of the 5 year result due to a reduced reconsenting, the CHMP agreed that it is unlikely

that a dramatically different outcome for the two groups would have occurred even if all patients were included in the 5 year follow-up. This was considered even more evident for the restricted indication of HRc positive population since the event rate is low and so few additional events would be expected. It is reasonable to conclude that the missing data, due to early drop-outs and incomplete follow-up, are unlikely to have affected the study conclusions.

Neratinib activity differs substantially depending on hormone receptor status. The HRc negative patient subgroup does not appear to benefit from neratinib, although a benefit in the HRc negative patient subgroup is not excluded. The applicant attributes this finding to dual inhibition of the ER-HER2 cross talk, supported by non-clinical and clinical data. However, an alternative explanation for the findings is that due to the pattern of earlier recurrences in HRc negative patients, those recruited into the study were a lower risk sub-group compared to the recruited HRc positive patients.

The supportive studies reported (201, 3003 and I-SPY2) provide sufficient evidence of anti-tumour activity. The higher pCR rate in HRc negative tumours in I-SPY2 is a replication of other neo-adjuvant studies with neratinib and other agents, and is thus expected and again underlines the biological difference related to hormone receptor expression.

The single pivotal 3144A2-3004-WW was overall positive at 2 years. For reasons that are not fully clear, but may be due to the differential relapse patterns in HRc+ and HRc- disease, efficacy appears almost exclusively confined to the HR+ subgroup, where outcomes are statistically compelling, and this seems to be the driver for the statistically significant results in the full population. Efficacy cannot be considered demonstrated in the HRc- subgroup. This further supports the restricted indication to HRc+. The absolute effect estimate in the HRc positive subpopulation, with a difference in iDFS at 2 years of 4.5%, is considered clinically relevant and statistically significant with a HR of 0.49 (95% CI, 0.30-0.78, p=0.002), and is supported by data on Distant disease-free survival at 2 years showing a HR of 0.5 (p=0.015). This is expected to translate in a substantial clinical benefit for the HRc+ population. Although there are some uncertainties on the magnitude of effect at five years of follow-up due to the study conduct, data are indicative of a maintained benefit in the HRc+ population, since the size of the effect is such that even in a worst case scenario it will remain clinically compelling. Therefore the statistically and clinically significant efficacy results in this subgroup supports a positive benefit-risk balance in the restricted indication.

Concerning clinical ground 2:

Gastrointestinal toxicities are a class effect of EGFR TKIs, but the very high incidence of diarrhoea is a particular safety concern of neratinib treatment. However, this side effect is reversible on discontinuation. Data indicate a limited effect of loperamide, and a possible beneficial effect of colestipol. However, the apparent effect of combining loperamide with colestipol could considerably reduce the diarrhoea problem. The applicant has commited to further investigate optimal diarrhoea management post approval (see RMP). In the absence of other major concerns the safety profile is considered acceptable.

Concerning clinical ground 3:

During the Oral Explanation, the majority of the CHMP acknowledged the positive and significant efficacy in the HRc+ subgroup, and it was considered that, even with the missing data or bias of censoring, this effect is considered robust and clinically meaningful and despite the concerns on the GI toxicity, the Benefit-Risk is positive in this subpopulation. In conclusion, in the proposed restricted indication of HRc+ patients, a clinically relevant benefit on iDFS can be considered established with an acceptable degree of certainty. The gastrointestinal toxicity, although substantial, is expected in this class and is potentially manageable. Planned activities by the Applicant aim to improve the management of diarrhoea (see RMP). No other safety issues of major concern have been identified to

negate the demonstrated benefit in this subgroup. It can be concluded that the benefits of Nerlynx outweigh the risks in the HRc+ population.

5.1. Risk Management Plan

Safety concerns

Important identified risks	• Gastrointestinal toxicity (diarrhoea and stomatitis [a]) • Hepatotoxicity
Important potential risks	• Cardiotoxicity (LVEF decreased) • Pulmonary toxicity (interstitial lung disease) • Reproductive and developmental toxicity

a. Includes mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering
LVEF = left ventricular ejection fraction;

Changes made to the list of safety concerns during the re-exanimation phase, were the result of the implementation of the new RMP template revision 2.

Pharmacovigilance plan

Study/activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
PUMA-NER-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 (Open-label interventional, category 3)	To characterise the incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer treated with neratinib and intensive loperamide prophylaxis with/without anti-inflammatory treatment (budesonide), and with/without a bile acid sequestrant (colestipol)	Gastrointestinal toxicity (diarrhoea)	Ongoing	Interim: February 2016 Interim 2: March 2017 Interim 3: December 2017 Interim 4: December 2018 Final: Q1 2021

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PUMA-NER-6202 A Randomized Study to Characterize the Incidence and Severity of Diarrhoea in Patients With Early stage HER2+ Breast Cancer Treated With Neratinib and Intensive Loperamide Prophylaxis Versus Neratinib and Intensive Loperamide Prophylaxis Plus a Bile Acid Sequestrant in the First Month of Treatment (Randomized interventional, category 3)	To characterise the incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer treated with Nerlynx and intensive loperamide prophylaxis with/without a bile acid sequestrant	Gastrointestinal toxicity (diarrhoea)	Planned	• Protocol: Q1 2019 • Interim 1: Q3 2020 • Final: Q4 2021
PUMA-NER-7201 Safety of Neratinib Among Breast Cancer Patients (Observational, category 3)	Characterise the incidence and duration of diarrhoea in a real world setting. Describe patient characteristics, incidence rates and duration of diarrhoea. Describe use of loperamide and other concomitant antidiarrhoeal medication. Describe adherence to neratinib therapy. Assess the impact of neratinib therapy on patient self-reported, health related quality of life and their ability to perform their activities of daily living. Further assess and characterize adverse events hepatic, cardiac (LVEF decreased), pulmonary (interstitial lung disease), reproductive and developmental toxicity.	Gastrointestinal toxicity (diarrhoea) Hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (interstitial lung disease), reproductive and developmental toxicity.	Planned	• Protocol: Q1 2019 • Interim 1: Q2 2020 • Interim 2: Q4 2021 • Final: Q4 2023

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PUMA-NER-7202 Evaluate the availability, interpretability, and impact of Nerlynx educational materials for health care professionals and patients (Survey, category 3)	To evaluate the availability, interpretability, and impact of Nerlynx Educational Materials	Gastrointestinal toxicity (diarrhoea)	Planned	• Protocol: Q1 2019 • Interim 1: Q1 2020 • Final: Q4 2021

The conclusion of the re-examination procedure lead to the inclusion of 3 additional post-authorisation safety studies to the pharmacovigilance plan which already contained PASS "PUMAR-NER-6201". PUMA-NER-6201 is investigating prophylactic treatment for diarrhoea.

The 3 new studies PUMA-NER-6202, PUMA-NER-7201 and PUMA-NER-7202 have been added to the pharmacovigilance plan in order to address GI toxicity (diarrhoea), the main safety concern for Nerlynx.

PUMA-NER-7201 will also look at other safety concerns (Hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (interstitial lung disease), reproductive and developmental toxicity).

PUMA-NER-7202 will look at the effectiveness of the educational materials which have been introduced to minimise the risk of diarrhoea.

Risk minimisation measures

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Gastrointestinal toxicity – Diarrhoea and stomatitis	• For the optimal management of diarrhoea, prophylactic treatment with anti-diarrhoeal medication is recommended. Guidance on management of diarrhoea is provided (SmPC Sections 4.2 and 4.4). Further information on diarrhoea is also provided in SmPC Section 4.8. • Stomatitis adverse reactions are listed in SmPC Section 4.8.	• Provide patients and health care professionals with educational resources to help minimize diarrhoea events (see Annex 6).

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	• Posology in patients with hepatic impairment is described in SmPC Section 4.2 • Special warnings and precautions for use in case of hepatic impairment are described in SmPC Section 4.4. • Liver-associated adverse reactions are listed and described in SmPC Section 4.8.	• None
Important potential risks		
Cardiotoxicity – LVEF decreased	• Special warnings regarding left ventricular function are provided in SmPC Section 4.4.	• None
Pulmonary toxicity – Interstitial lung disease	• None	• None
Reproductive and developmental toxicity	• A special warning that neratinib may cause foetal harm when administered to pregnant women is included in SmPC Section 4.4. Recommendation not to use Nerlynx during pregnancy and further recommendations regarding pregnancy, contraception and breastfeeding are provided in Section 4.6. • Preclinical safety data regarding reproductive toxicity are described in SmPC Section 5.3	• None

Educational materials for health care professionals and patients have been requested to help minimise GI toxicity (diarrhoea). Effectiveness of this additional risk minimisation measure will be assessed with PASS PUMA-NER-7202.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.9 could be acceptable if the applicant implements the changes to the RMP with the following details:

- to adjust due dates of the post-authorisation safety studies milestones in the Pharmacovigilance plan

A revised RMP should be submitted at the first regulatory opportunity in the post-authorisation phase.

5.2. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17.07.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

5.3. Product information

5.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

5.3.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nerlynx (neratinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.

6.1.2. Available therapies and unmet medical need

In the extended adjuvant setting, following one year of trastuzumab therapy, endocrine therapy is standard treatment for HRc+ disease. There is no standard treatment for HRc- disease. The annual hazard of recurrence peaks in the second year after diagnosis but remains at 2%–5% in years 5–20. 25% of HER2+ early breast cancer patients suffer a recurrence or die within 10 years of initiation of adjuvant therapy. Mortality from breast cancer is 23.1/100 000 in Europe. There is an unmet need for additional therapies to further reduce the risk of recurrence and prolong survival.

6.1.3. Main clinical studies

This application is supported by data from a single pivotal study. Study 3144A2-3004-WW was a multicentre, randomized, double-blind, placebo-controlled trial of neratinib in women with early stage HER2+ breast cancer. The primary objective of this study was to compare iDFS of women with early-stage HER2+ breast cancer who received neratinib or placebo, following trastuzumab in the adjuvant setting. Eligible patients were randomized in a 1:1 ratio to treatment with either neratinib 240 mg or placebo daily for a period of 1 year. The study consisted of 3 parts: (A) follow-up period of 2 years post randomization to provide data for the primary analysis (iDFS); (B) extended follow-up for 2-5 years based on medical records upon re-consent; (C) long-term follow-up of overall survival (OS).

The eligibility criteria defined a HER2+ early breast cancer population who had received loco-regional surgery ± radiotherapy, as well as standard of care chemotherapy and trastuzumab. Following a protocol amendment, patients who were node negative or had received the last dose of trastuzumab ≥ 1 year previously were excluded. Hormone receptor status was a stratification factor.

The primary endpoint of iDFS was agreed with CHMP. The chosen secondary endpoints of DFS including ductal carcinoma in situ (DFS-DCIS), distant disease-free survival (DDFS), time to distant recurrence (TTDR), incidence of CNS recurrence and overall survival were appropriate. The collection of quality of life data was incomplete.

A total of 2840 patients were randomized, 1420 to each treatment arm of which 1408 were dosed in each arm. The primary analysis was conducted in the ITT population.

6.2. Favourable effects

In the primary analysis of iDFS at 2 years, there was a 34% reduction in the risk of disease recurrence or death in neratinib-treated patients relative to placebo-treated patients (stratified HR 0.66; 95% CI 0.49–0.90; two-sided p=0.008). The 2-year iDFS rate was 94.2% and 91.9% in the neratinib- versus placebo-treated patients. The 5-year analysis showed a difference for iDFS of 2.5% with HR of 0.73 (95% CI 0.57-0.92; two-sided p=0.008).

In subgroup analyses neratinib reduced the 2-year risk of recurrence or death by 51% relative to placebo in hormone receptor (HR)-positive women (n=1,631, HR 0.49; 95% CI, 0.31–0.75; p<0.001), whereas 2-year iDFS rates were not different in HR-negative women (n=1.209, HR 0.93; 95% CI, 0.60–1.43; p=0.365). In women who completed trastuzumab treatment within 1 year of randomisation, neratinib reduced the risk of recurrence or death by 37% relative to placebo (n=2,297, HR 0.63; 95% CI, 0.45–0.88; p=0.003), but iDFS was not different in women who completed trastuzumab therapy more than 1 year prior to randomisation (n=543, HR 0.92; 95% CI, 0.37–2.23; p=0.430). In women who completed trastuzumab treatment within 1 year of randomisation, and were HRc+ the iDFS difference in 2 years was 4.5% (HR 0.49; 95% CI, 0.30-0.78; 2-sided p=0.002), while for the HRc- was 0.1% (HR 0.83; 95%CI, 0.52-1.31).

At five years post baseline the iDFS estimates for HRc positive tumours were 85.7 vs. 90.8 %, HR 0.58, p= 0.002; for HRc negative tumours: 87.6 vs. 88.2 %, HR 0.89, p=0.5.

6.3. Uncertainties and limitations about favourable effects

The study was originally planned with 5-year follow up for iDFS, but with the primary endpoint at 1 year after end of 1 year of neratinib or placebo therapy. However, for commercial reasons, follow-up was truncated at two years of follow-up. Subsequently patients were reconsented for further follow-up to year five post baseline, where outcomes were captured retrospectively. Approximately 75% of patients were reconsented; furthermore, there was differential reconsent in the respective arms with more patients in the Nerlynx arm refusing reconsent. While sensitivity analyses, including a tipping point analysis, indicate that loss of efficacy over placebo at five years is unlikely, there is considerable uncertainty about the 5 year efficacy estimates.

The efficacy underlying the primary outcome is almost entirely isolated to the HRc+ subgroup, whereas any potential efficacy in the HRc- subgroup appears transient. This finding was unanticipated and is not explained by pharmacological mechanism. HRc+ and HRc- cancer is recognised as two different disease entities, with different patterns of recurrence. In particular, HRc- disease tends to recur earlier. This may indicate that the window of opportunity to provide benefit through prolonged adjuvant therapy is larger in HRc+ disease, and that the difference in efficacy depending on subgroup status is due to the timing of adjuvant therapy with Nerlynx.

6.4. Unfavourable effects

The most common AEs in study 3004 were gastrointestinal (GI). These were reported more commonly for neratinib compared to placebo: diarrhoea (93.6%; ≥ Grade 3: 36.9%), nausea (42.5%), fatigue (27.3%), vomiting (26.8%) ,abdominal pain (22.7%), rash (15.4%), decreased appetite (13.7%), abdominal pain upper (13.2%), stomatitis (11.2%) and muscle spasms (10.0%).

The key unfavourable effect for neratinib is diarrhoea, which is a class effect. The incidence of diarrhoea was highest during the first month of treatment. The median time to onset was 2 days and the median cumulative duration was 59 days. Whether the diarrhoea can be adequately managed by anti-diarrhoeal prophylaxis has not been established so far.

Reported SAEs were predominantly gastrointestinal, particularly diarrhoea (1.6%) and vomiting (0.9%). Dehydration in association with diarrhoea was also notable. In the neratinib arm of study 3004 there were 4 cases of renal failure/acute renal failure associated with diarrhoea.

Older patients were more likely to discontinue neratinib treatment due to diarrhoea. The incidence of acute renal failure was also increased in this population.

6.5. Uncertainties and limitations about unfavourable effects

Based on available data from study 6201, it is currently uncertain what is the best strategy to ensure that diarrhoea is adequately managed, and what is the optimal strategy for anti-diarrhoeal prophylaxis.The applicant has committed to further study appropriate strategies for anti-diarrhoeal management (see RMP). Once identified, this would contribute to the favourable use of neratinib in clinical practice. In the meantime, relevant measures are agreed to help mitigate this risk (see RMP and PI).

6.6. Effects Table

Table 49 Effects Table for Nerlynx based on data from study 3004 (data cut-off: 01/03/2017 for 5-year analysis)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
2 Year iDFS HRc+, ≤ 1 year since trastuzumab treatment	K-M Estimate 24 Month Point estimate	%	95.3	90.8	HR 0.49 (95% CI: 0.30, 0.78); 2-sided p=0.002
5 Year iDFS HRc+, ≤ 1 year since trastuzumab treatment	K-M Estimate 60 Month Point estimate	%	90.8	85.7	HR 0.58 (95% CI: 0.41, 0.82); 2-sided p=0.002
2 Year dDFS HRc+, ≤ 1 year since trastuzumab treatment	K-M Estimate 24 Month Point estimate	%	96.1	92.9	HR 0.53 (95% CI: 0.31, 0.88); 2-sided p=0.015
Unfavourable Effects (TEAEs)					
Diarrhoea	Incidence all grades	%	95.4	35.4	Optimal strategy for anti-diarrhoeal prophylaxis not yet identified
Diarrhoea	Incidence ≥ Grade 3	%	39.9	1.6	
Nausea	Incidence ⩾ Grade 3	%	1.8	0.1	
Vomiting	Incidence ⩾ Grade 3	%	3.3	0.4	
Abdominal pain	Incidence ⩾ Grade 3	%	1.7	0.2	
AST or ALT	Incidence >3x ULN	%	5.3	1.4	

Abbreviations: iDFS = invasive disease free survival; K-M = Kaplan-Meier; d-DFS = Distant disease-free survival; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; TEAE = treatment emergent adverse event

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The single pivotal 3144A2-3004-WW was overall positive at 2 years. For reasons that are not fully clear, but may be due to the differential relapse patterns in HRc+ and HRc- disease, this effect is almost exclusively confined to the HR+ subgroup, where outcomes are statistically compelling. The results in HRc- tumours are, in addition, coherent with what has been observed for the trastuzumab (2 years versus 1 year of trastuzumab) therapy adjuvant trial, showing a transient effect on recurrence

rates with some remaining effect at 2 years but no effect at 5 years for prolonged trastuzumab treatment (Goldhirsch et al 2013). Therefore, efficacy has been demonstrated in the HRc+ subgroup, but not in the HRc- subgroup.

The absolute effect estimate in the HRc positive subpopulation, with a difference in iDFS at 2 years of 4.5%, is considered clinically relevant, and is supported by data on Distant disease-free survival at 2 years showing a HR of 0.5 (p=0.015). Contrariwise, it is not considered that efficacy has been demonstrated in the HRc-negative subgroup, with a difference in iDFS at 2 years of 0.6%.

Three year data have been required in general in the setting of adjuvant treatment of breast cancer. The robustness of the data for the 2 year is acknolewdged, but due to the study conduct after the 2 year phase (see above), the extent of benefit at five years remains uncertain; however, maintained benefit is expected, especially in the restricted HRc+ population with a larger effect size. The limited tolerability of Nerlynx due to diarrhoea, frequently leading to treatment discontinuation, is recognized as an important limitation on clinical utility. However, this side effect is reversible on discontinuation and further studies to identify appropriate strategies for anti-diarrhoeal management are underway (see RMP). Furthermore, no safety issues of major concern to negate the demonstrated benefit have emerged. At present, from a patient and clinical perspective, as long as benefits, risks, and uncertainties are clearly understood, it is considered that meaningful treatment decisions can be made and that treatment with neratinib can be a good option for some patients. Consequently, while it is recognized that adjuvant treatment with Nerlynx may not be appropriate for every patient, it is considered a reasonable treatment option on a case by case basis, as extended adjuvant therapy for HER2+, HRc+ early breast cancer (see PI). The clinical utility is expected to improve with optimisation of anti-diarrhoeal management.

6.7.2. Balance of benefits and risks

The magnitude of benefit on iDFS in HER2+ HRc+ patients is statistically significant and clinically relevant and, therefore, outweighs the risks; primarily treatment-induced diarrhoea whose management is expected to be improved in light of the ongoing and planned studies.

6.8. Conclusions

The overall B/R of Nerlynx is positive for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.

Divergent position is appended to this report.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Nerlynx in the following indication:

“Nerlynx is indicated for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.”

was favourable and that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation.

Divergent position to the majority recommendation is appended to this report.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Nerlynx in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Nerlynx is marketed, all healthcare professionals who are expected to prescribe/dispense Nerlynx, as well as all patients/carers who are expected to use Nerlynx, have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

The physician educational material should contain:

o The Summary of Product Characteristics

- Guide for healthcare professionals
- Patient educational material

➢ **The Guide for healthcare professionals** shall contain the following key elements:

- Name of the product, active substance and approved indication of the product
- Relevant information on the safety concern “Gastroinstestinal toxicity (diarrhea)” (e.g. seriousness, severity, frequency, time to onset, duration, reversibility of the AE as applicable)
- Details of the population at higher risk for the safety concern
- Key message to convey in patients counselling on how to prevent and minimise Gastrointestinal toxicity through appropriate monitoring and management:
    - prophylactic treatment with antidiarrheal medicinal product
    - dietary changes
    - dose modification (with guideline to adjust doses)/ discontinuation of treatment
- The importance of handing over the educational material to the patients/carers at the end of counselling
- Remarks on the importance of reporting ADRs

➢ **The patient educational material:**

The patient information pack should contain:

- Patient information leaflet
- A patient/carer treatment guide
- “My Treatment Journal”

The Patient/carer guide shall contain the following key messages (in lay language)

- Name of the product, active substance and approved indication of the product
- Relevant information of Gastrointestinal toxicity (diarrhea) (e.g. signs and symptoms to be detailed (seriousness, severity, frequency, time to onset, duration, risks and consequences))
- Key messages on how to prevent and minimise GI toxicity through appropriate monitoring (with reference to treatment journal) and management:
    - prophylactic treatment with antidiarrheal medicinal product
    - dietary changes
    - when to alert HCP and the importance of it for further treatment adjustment
- Remark on importance of reading the PIL
- Remarks on the importance of reporting ADRs

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that neratinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union

8. Appendices

1. Divergent position to the majority recommendation for the initial opinion

2. Divergent position to the majority recommendation for the re-examination

APPENDIX 1

DIVERGENT POSITION DATED 22 February 2018

Nerlynx EMEA/H/C/004030/0000

The undersigned member of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Nerlynx.

The reasons for divergent opinion were as follows:

For the primary endpoint, iDFS, at 2 years from randomization, the Kaplan-Meier point estimate for iDFS was 94.2% for the neratinib arm compared to 91.9% for the placebo arm, a difference of 2.3%. The hazard ratio was 0.66 (0.49, 0.90), p=0.008.

Further, according to an interim 5-year analysis, the Kaplan-Meier point estimate for iDFS was 90.2% for the neratinib arm compared to 87.7% for the placebo arm, a difference of 2.5%. The hazard ratio was 0.73 (0.57, 0.92), p=0.008.

The conduct of the study, necessitating re-consent for further follow-up confers some uncertainty on data post 2 year due to missing data. However, given the sensitivity analyses presented, the five year data are considered sufficiently robust; further, they are consistent with the 2-year findings.

The statistical strength of this efficacy demonstration is in line with what is generally accepted for single pivotal trials in oncology. Furthermore, the magnitude of the effect is such that would generally not be dismissed as clinically meaningless in an adjuvant setting.

The limited tolerability of Nerlynx due to diarrhea, frequently leading to treatment discontinuation, is recognized as an important limitation on clinical utility. However, this side effect is reversible on discontinuation. Furthermore, no safety issues of major concern to negate the demonstrated benefit have emerged. Consequently, while it is recognized that adjuvant treatment with Nerlynx may not be appropriate for every patient, it is considered a reasonable treatment option on a case by case basis.

Therefore, I consider the B/R of Nerlynx positive.

CHMP Member expressing a divergent position:

Kristina Dunder

APPENDIX 2

DIVERGENT POSITION DATED 28 June 2018

Nerlynx EMEA/H/C/004030/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Nerlynx indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.

The reason for divergent opinion was the following:

- Although the single pivotal trial submitted in support of the application achieves nominal statistical significance, it falls short of the expectations to be exceptionally compelling and with precise estimates of the treatment effect as described in the points to consider document on applications with one pivotal study (CPMP/EWP/2330/99). For the primary endpoint of invasive disease-free survival (iDFS) in the intention-to-treat population, the 2-year and 5-year point estimates for hazard ratio (0.66-0.73) and absolute difference (2.3-2.5%) are modest in absolute terms in particular if maintained in the long term. However, the effect size is uncertain due to incomplete re-consent for longer term follow-up, and hence the potential for important bias in the estimated treatment effect.

  In addition, the company's claim that there is substantially greater efficacy in the HR+ patients is not accepted. The data on the ER/HER cross-talk presented during the re-examination to support a possible mechanistic explanation for efficacy selectively in HR+ patients appeared plausible, but must be considered hypothesis-generating. Also, the transient effect in the complement subgroup of HR- patients has not been fully explained.

  Therefore, for a number of reasons, it is considered that therapeutic efficacy is not adequately established.

- Neratinib causes significant gastrointestinal toxicity. Diarrhoea affects most patients, is severe in a high proportion, and can be expected to affect quality of life. Based on available data from study 6201, it is uncertain at this time whether the diarrhoea can be adequately managed by prophylactic anti-diarrhoeals. The high rate of early discontinuations from this trial despite intensive loperamide prophylaxis is of concern. It is also unclear to what extent diarrhoea may improve over time for the individual patient who decides to remain on treatment after experiencing severe diarrhoea and there is no evidence for tolerability after rechallenge when experiencing Grade 3 diarrhoea. In the presence of a robustly demonstrated benefit, the emerging side effect profile would not be a blocking issue; however, in the context the deficiencies in the efficacy demonstration, the adverse effect profile of neratinib is a matter of important concern.

- A benefit on iDFS has not been established with an acceptable degree of certainty and the gastrointestinal toxicity, albeit reversible on discontinuation, is substantial. For these reasons, it is considered that the benefits of Nerlynx are not established to outweigh the risks.

CHMP Members expressing a divergent position:

Alar Irs, Alexandre Moreau, Bruno Sepodes, Daniela Melchiorri, Emilia Mavrokordatou, Greg Markey, Peter Kiely, Johann Lodewijk Hillege, Tomas Boran, Robert James Hemmings, Romaldas Maciulaitis