Statistical Analysis Plan

PROTOCOL: NIS12501 V1.0 DATED 23 SEP 2021

A RETROSPECTIVE OBSERVATIONAL STUDY OF ADULT PATIENTS WITH EARLY-STAGE HER2-POSITIVE BREAST CANCER, TREATED WITH NERATINIB AS EXTENDED ADJUVANT THERAPY IN THE CONTEXT OF THE EUROPEAN EARLY ACCESS PROGRAM

NEAR

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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The Statistical Analysis Plan (SAP) signature page applies to both SAP text and SAP Templates (output shells or Tables/Listings/Figures [TLFs] shells). Templates must be sent to the customer with the first draft SAP text.

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MODIFICATION HISTORY

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1.0	01MAR2023	Ana Rita Chernyshova	First authorized version.
2.0	22SEP2023	Ana Rita Chernyshova	Updated First Patient In date from 8JUL2023 to 05JUL2023.

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1 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AJCC	American Joint Committee on Cancer
CI	Confidence Interval
CISH	Chromogenic in Situ Hybridization
CNS	Central Nervous System
DDFS	Distant Disease-Free Survival
DTR	Distant Tumor Recurrence
EAP	Early Access Program
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EOB	End of Observation
ENR	Enrolled Set
ER	Estrogen Receptor
FAS	Full Analysis Set
FISH	Fluorescence in Situ Hybridization
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
ICBCR	Invasive Contralateral Breast Cancer Recurrence
ICF	Informed Consent Form
iDFS	Invasive Disease-Free Survival
IHC	Immunohistochemistry

IIBTR	Invasive Ipsilateral Breast Tumor Recurrence
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
pCR	Pathologic Complete Response
PR	Progesterone Receptor
PT	Preferred Term
RIR	Regional Invasive Recurrence
RWS	Real World Solutions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
T-DM1	Trastuzumab Emtansine
TLFs	Tables/Listings/Figures

2 INTRODUCTION

This SAP describes the rules and conventions to be used in the presentation and analysis of patients with early-stage Human Epidermal Growth Factor Receptor-2 positive (HER2+) breast cancer, treated with neratinib as an extended adjuvant therapy in the context of the European Early Access Program (EAP). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 1.0, dated 23 September 2021.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective is to describe the demographic and clinical profiles of patients with early-stage HER2+ breast cancer treated with neratinib as an extended adjuvant therapy as part of the EAP in Europe.

3.2 Secondary Objectives

The secondary objectives are:

- To describe neratinib treatment patterns including time to initiation of neratinib, dosing after trastuzumab-based treatment, treatment dose, treatment duration, permanent and temporary discontinuations, reasons for discontinuations, and concomitant treatments.
- To describe breast cancer treatment history before neratinib initiation, including all neoadjuvant and adjuvant therapies (in terms of agent name, dosage, and duration of use), surgeries and other interventions (type and outcome).
- To describe the frequency of relevant Adverse Events (AEs) in breast cancer patients using neratinib as an extended adjuvant therapy. Relevant AEs are defined as all Serious Adverse Events (SAEs) or AEs leading to dose adaptation or treatment discontinuation, and AEs of interest.

3.3 Exploratory Objectives

The exploratory objectives are:

- To describe the first recurrence patterns.
- To describe invasive disease-free survival (iDFS) in patients with early-stage HER2+ and Hormone Receptor-positive (HR+) breast cancer treated with neratinib as an extended adjuvant therapy, over the study observation period.
- To describe distant disease-free survival (DDFS) in patients with early-stage HER2+ and HR+ breast cancer treated with neratinib as an extended adjuvant therapy, over the study observation period.
- To describe the incidence of central nervous system (CNS) metastasis.
- To describe overall survival (OS) in patients with early-stage HER2+ and HR+ breast cancer treated with neratinib as an extended adjuvant therapy, over the study observation period.

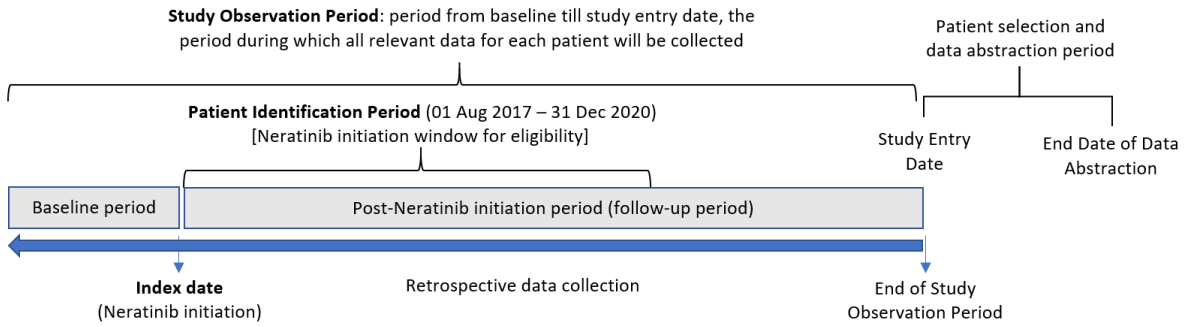
4 STUDY DESIGN

4.1 General Description

This is a European, multi-country, multicenter, retrospective, observational, longitudinal study to describe the demographic characteristics and clinical profiles of patients with HER2+ breast cancer who were treated with neratinib as an extended adjuvant therapy, in the context of the EAP in Europe. The target countries for patient enrollment will include Belgium, Croatia, France, Italy, and Spain.

A pictorial representation of the NEAR study scheme is provided in Figure 1 below.

Figure 1. The NEAR Study Scheme



4.2 Sample Size

Sample size calculation is not applicable, since the study plans to include all eligible breast cancer patients having received neratinib as an extended adjuvant therapy through the EAP in the target European countries. The number of patients is estimated to be up to 200 patients. Using the table below, the precision estimates for a 95% confidence interval (CI) were calculated around proportions ranging from 10% to 50% for a sample size between 150 and 300 patients (see Table 1).

A sample size of 200 patients would allow to assess a category of primary objective (demographic and clinical description of eligible patients) of 10%, 20%, 30%, 40% and 50% of patients with a precision of approximately ± 4.1%, ± 5.5%, ± 6.4%, ± 6.8% and ± 6.9%, respectively.

Based on the feasibility, 120 patients would be enrolled instead of 200 patients originally planned.

A sample size of 120 or 100 patients would allow to assess a category of primary objective (demographic and clinical description of eligible patients) of 10%, 20%, 30%, 40% and 50% of patients with a precision of approximately ± 5.4% or 5.9%, ± 7.2% or 7.9%, ± 8.2% or 9%, ± 8.8% or 9.6% and ± 9% or 9.8%, respectively.

Table 1 Precision estimates for 95% CI around proportions

Precision estimate*	**Proportion**				
Sample size	10%	20%	30%	40%	50%
100 patients	5.9%	7.9%	9%	9.6%	9.8%
120 patients	**5.4%**	**7.2%**	**8.2%**	**8.8%**	**9%**
150 patients	4.8%	6.4%	7.3%	7.8%	8.0%
200 patients	4.1%	5.5%	6.4%	6.8%	6.9%
250 patients	3.7%	4.9%	5.7%	6.1%	6.2%
300 patients	3.4%	4.5%	5.2%	5.5%	5.6%

*Precision estimates for a 95% CI were calculated using statistical analysis system (SAS) version 9.4 or higher (SAS Institute, Cary, NC, USA)

4.3 Patient Selection Criteria

Eligible patients will be selected among those having received at least one dose of neratinib for the treatment of early-stage HER2+ breast cancer in the EAP, between 01 August 2017 and 31 December 2020. Patients (or next of kin/legal representative, if applicable) who provide written informed consent form (ICF) or non-opposition to data collection, as per local regulations, will be enrolled.

4.3.1 Inclusion Criteria

Patients will be eligible for inclusion if they fulfil all the following criteria:

1. Age ≥ 18 years at neratinib treatment initiation.
2. Patient diagnosed with HER+ breast cancer.
3. Having received at least one initial dose of neratinib as an extended adjuvant therapy for the treatment of early-stage HER2+ breast cancer, in the context of the EAP in Europe, and between 01 August 2017 and 31 December 2020.
4. Patients (or next of kin/legal representative, if applicable) who provide written informed consent or non-opposition.

Note: Given the retrospective nature of the study, for deceased or lost to follow-up patients, where a signed informed consent is required, the informed consent may be obtained from a next of kin / legal representative, or an ICF waiver will apply, depending on approval by Ethics Committees and/or local regulations.

4.3.2 Exclusion Criteria

For the purposes of this retrospective data collection, it is desirable that eligibility criteria are the least restrictive possible. Therefore, there are no exclusion criteria for patients in this study.

5 PLANNED ANALYSES

5.1 Interim Analysis

No interim analysis is planned for this study.

5.2 Final Analysis

All planned analyses identified in this SAP will be performed by IQVIA Real World Solutions (RWS) Biostatistics following the final database lock.

6 ANALYSIS SETS

6.1 Enrolled Set [ENR]

The enrolled set (ENR) will contain all enrolled patients.

6.2 Full Analysis Set [FAS]

The full analysis set (FAS) will contain all enrolled patients who fulfilled eligibility criteria.

6.3 HR+ Analysis Set [HRAS]

The HR+ analysis set (HRAS) will contain all HR+ patients from the full analysis set, i.e., who had either Estrogen receptor (ER) positive or Progesterone receptor (PR) positive or both positive at primary breast cancer diagnosis.

7 GENERAL CONSIDERATIONS

7.1 Patient Identification Period

The patient identification period is the eligibility time window for selection of patients who initiated neratinib treatment within the EAP in Europe between 01 August 2017 and 31 December 2020.

7.2 Index Date

The index date is defined as the date of first neratinib initiation through the EAP.

7.3 Baseline Period

Data analyzed for the baseline period will consist of all relevant data available prior to the first dose of neratinib initiation (index date).

7.4 Neratinib Initiation

Data analyzed for the neratinib initiation period will consist of all relevant data collected within +/- 30 days of index date.

7.5 Study Entry Date

The study entry date is defined as the cut-off date until when the eligible patients' data as obtained from medical charts are abstracted for analysis in the study. This date will be the same for all patients and corresponds to the date of first patient in, 05 July 2022.

7.6 Study Observation Period

The overall study observation period extends from baseline period to study entry date.

7.7 Follow-up Period

The follow-up period for each patient extends from index date to end of the study observation period. Patients' data collection will be censored at date of death, or among patients who did not die, at the

end of the study observation period or at the date of last visit, whichever occurs first. Patients will have variable follow-up periods length, depending on their index date and last contact date.

7.8 End of Observation (EOB) Date

The end of observation (EOB) date is defined as the study entry date, date of death or date of last contact, whichever happens first.

7.9 Software Version

All analyses will be conducted using statistical analysis system (SAS)® version 9.4 or higher (SAS Institute, Cary, NC, USA).

7.10 Changes from Protocol

In the eCRF an additional inclusion criterium was considered, i.e., the patient was diagnosed with HER2+ breast cancer. For analysis proposes this additional criterium is considered in the analysis datasets and used in the identification of the FAS.

In the protocol the study entry date was defined as the cut-off date until when the eligible patients' data as obtained from medical charts are abstracted for analysis in the study. Based on a request from Pierre Fabre, the study entry date was assigned in the SAP to the date of first patient in, 05 July 2022, to ensure that all patients have the same cut-off date.

In section 8.2, two additional periods were considered in the time to event analysis, i.e., in protocol the intervals considered were 1, 3, 6, 9 and 12 and for analysis the periods that will be considered are 1, 3, 6, 9, 12, 15 and 18.

The subgroup analysis considered in section 8.4 has been updated from protocol. The nodal status at initial diagnosis and the tumor size at initial diagnosis were removed from the subgroups of interest. The subgroup previous adjuvant or neoadjuvant therapy was defined in the protocol as "Yes/ No" and will be updated to "Neoadjuvant + Post neoadjuvant treatment/ Adjuvant only".

The following subgroups analysis was added: according to EU label status, Concomitant Corrective Antidiarrheal, Concomitant Prophylaxis Antidiarrheal, Initial Dose of Neratinib.
In the protocol the exploratory analysis was planned to be performed only in HR+ patients, it will be analyzed separately for HR+ / HR- patients.

8 STATISTICAL CONSIDERATIONS

8.1 Descriptive Statistics

All data collected for the study will be summarized with appropriate statistics. For continuous variables, the number, mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum will be provided, as well as the associated 95% CI, when appropriate. For categorical variables, the numbers and percentages will be provided, as well as the associated 95% CI, when appropriate. Percentages will be computed among patients with available data.

8.2 Time to Event Analysis

The cumulative incidence of events of interest will be assessed using the Kaplan Meier method and will be presented graphically (Kaplan Meier curve). For Kaplan-Meier, the number of events, number of censored data points, median survival time, Q1 and Q3 survival time and corresponding two-sided 95% CI will be presented. Estimates of the proportion of patients not presenting the event of interest at 3-month intervals (1, 3, 6, 9, 12, 15, 18 months) and the corresponding two-sided 95% CIs will be provided. Censoring rules relative to each event of interest are further detailed in the corresponding analysis sections (see section 13.2).
To determine the potential follow-up time the reverse Kaplan-Meier method will be applied, in this method the events and censors are reversed thus the event of interest (see section 13.2) becomes the censor. For the reverse Kaplan Meier, the number of events, number of censored data points, median follow-up time, Q1 and Q3 follow-up time and corresponding two-sided 95% CI will be presented.

If number of patients is large enough, Cox regression analysis may be performed to adjust for predefined baseline covariates. In this case and for time to Central Nervous System Metastasis, the Fine and Gray model will be used to account for the competing risk of disease recurrences.
Where applicable, the Log rank test will be used to compare time-to-event and survival data between subgroups in an exploratory manner.

8.3 Missing Data

Due to the nature of the study, there will likely be missing data; data may be missing or not recorded in the patient's chart. Generally, missing data will not be imputed, and data will be analyzed and presented as they are recorded in the database. Missingness for all variables will be indicated in descriptive tables. Partial date handling is described in Appendix 1. Listings will present the dates as reported in their original, non-imputed format (i.e., 'UNK' for the missing day, month and/or year).

8.4 Examination of Subgroups

The following subgroups are of interest, based on patient characteristics at neratinib initiation (index date) or primary diagnosis of breast cancer. Analyses of primary, secondary, and exploratory outcomes may be performed for some or all these subgroups, subject to pertinence and the number of patients in each subgroup:

- EU label status: Yes, No
  - Yes, defined as, HR+ patients with initiation of Neratinib <=1 year from trastuzumab-based treatment completion in adjuvant setting (EU Label population)
  - No, otherwise
- Pathologic stage (AJCC classification) at primary breast cancer: Stage I, Stage II+III
  - If missing, derived as in 2
- Residual disease after neoadjuvant treatment (pathologic complete response [pCR]): pCR, No pCR

- Risk: Low risk (Stage I or N- or pCR), High risk (Stage II/III or N+ or no pCR)
  - N-, defined as, the electronic case report form (eCRF) nodal status category of NX or N0
  - N+, defined as N ≥ 1 nodal
- Previous adjuvant or neoadjuvant therapy [(2)]: Neoadjuvant + Post neoadjuvant treatment, Adjuvant only
  - Neoadjuvant + Post neoadjuvant, defined as, at least one neoadjuvant and one adjuvant treatment
  - Adjuvant only, defined as, at least one adjuvant treatment and no neoadjuvant
- Prior trastuzumab-based regimen overall (neoadjuvant or adjuvant): Trastuzumab only, Trastuzumab and Pertuzumab, Trastuzumab emtansine (T-DM1), Other anti HER2
- Prior trastuzumab based regimen the last treatment in adjuvant setting before Neratinib initiation: Trastuzumab only, Trastuzumab and Pertuzumab, Trastuzumab emtansine (T-DM1), Other anti HER2
- Hormone Receptor at Primary Breast Cancer Diagnosis: HR+, HR-
  - HR+, defined as either ER or PR or both are positive
  - HR-, defined as if ER and PR are negative
- Concomitant Corrective Antidiarrheal: Yes, No
- Concomitant Prophylaxis Antidiarrheal: Yes, No
- Initial Dose of Neratinib: <240mg, 240mg, >240mg

Table 2 AJCC staging

Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)	Stage
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1	M0	IB
T1	N1	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

N2 and N3 are not collected in the CRF, this regional lymph node categories will be identified by "≥4" lymph nodes involved.

9 OUTPUT PRESENTATIONS

The TLF shell templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary TLFs to be provided by IQVIA RWS Biostatistics.

10 PATIENT DISPOSITION

All patients with a signed informed consent, non-opposition, or ICF waiver will be accounted in this study. Patient disposition, withdrawals, including inclusion and exclusion criteria will be presented for all enrolled patients.

The following enrolment disposition variables will be described:

- Number and percentage of sites per country. Percentage computed among all active sites.
- Number and percentage of patients enrolled by site and country. Percentage computed among all patients enrolled in each country.

The following patient disposition characteristics will be described:

- Number of enrolled patients (ENR).
- Number and percentage of patients excluded from analysis by eligibility criteria not met. Percentage computed among ENR.
- Number and percentage of patients included in the analysis (FAS). Percentage computed among ENR.
  - Number and percentage of patients that withdrew consent. Percentage computed among FAS.
  - Number and percentage of patients lost to follow-up. Percentage computed among FAS.
  - Number and percentage of patients followed until end of observation period. Percentage computed among FAS.
  - Length of follow-up (months), calculated as:
    - $(EOB - Date\ of\ first\ neratinib\ administration + 1)/30.4$
  - Number and percentage of patients by survival status at study entry. Percentage computed among FAS.
    - If deceased, reason of death and occurrence during neratinib use. Percentage computed among FAS patients deceased at study entry.
  - Number and percentage of patients per analysis subgroup (section 8.4). Percentage computed among FAS.

- Number and percentage of patients included in the HR+ Analysis Set (HRAS). Percentage computed among FAS.

11 PRIMARY OUTCOMES

The primary outcomes will be presented as frequencies and percentages or summary statistics, as appropriate, for the FAS and by subgroups (Section 8.4), subject to pertinence and the number of patients in each subgroup. No statistical testing will be carried out for primary outcomes.

11.1 Demographic Characteristics at Neratinib initiation

To describe the demographic profile of the patients at neratinib initiation, the below demographic characteristics will be analyzed for FAS and by subgroup EU label; Pathologic stage; Residual disease after neoadjuvant treatment; Risk profile; Previous adjuvant or neoadjuvant therapy; Prior transtuzumab-based regimen overall and last treatment; and Hormone Receptor (Section 8.4):

- Age at neratinib initiation (years), calculated as:
  - $(Year\ of\ neratinib\ initiation - Year\ of\ birth)$
- Gender: Female, Male
  - Pregnancy: Yes, No, Unavailable
  - Breastfeeding: Yes, No, Unavailable
  - Menopausal status: Premenopausal, Perimenopausal, Postmenopausal, Surgical/other reason for amenorrhea, Unavailable
- Employment status: Full-time employment, Part-time employment, Student or pupil, Homemaker, Retired, Unemployed, Incapacity to work, Unavailable
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2), calculated as:
  - $Weight\ (kg) / Height\ (m)^2$

- BMI category [1]: Underweight (< 18.5 kg/m^2), Normal weight (18.5 - 24.9 kg/m^2), Pre-obesity (25.0 - 29.9 kg/m^2), Obesity (≥ 30.0 kg/m^2)

Weight changes after neratinib initiation are collected in the CRF, and will be analyzed as follows:

- Weight change from neratinib initiation, calculated as:
  - $(Last\ available\ weight\ at\ neratinib\ stop\ date - Weight\ at\ neratinib\ initiation)$
- Number and percentage of patients by weight change: Weight gain, Weight loss, Weight stable
  - For weight gain and weight loss, the number and percentage of patients by percentage change will be presented: <5%, 5% to 10%, >10%.

The closest measurements to neratinib start and end date, respectively, will be used for the weight change calculation. For patients who might not have completed 1 year of Neratinib treatment the latest record of the weight under neratinib treatment will be considered. If the subject has neratinib ongoing at study end, the latest available measurement will be considered.

11.2 Comorbidities

Relevant comorbidities prior to or ongoing at neratinib initiation are collected in the eCRF. The following variables will be analyzed for all comorbidities (prior to or ongoing at index date) and for comorbidities ongoing at index date, and presented for FAS:

- Number and percentage of patients with at least one relevant comorbidity. Percentage computed among FAS.
- Number of comorbidities per patient
- Comorbidities per patient category: 0, 1, >1.
- Number and percentage of patients with each comorbidity present: Diabetes Type I, Diabetes Type II, Chronic kidney disease, Liver disease, Rheumatoid arthritis, Other chronic inflammatory disease, Heart disease, Heart failure, Arterial hypertension, Stroke, Arrhythmias, History of myocardial infarction, Depression, Lung cancer, Ovarian cancer, Uterine cancer, Colorectal cancer, Gastric cancer, Thyroid cancer, Melanoma, Sarcoma, Liver cancer, ENT

cancer, Acute myeloid leukemia, Previous breast cancer, Other cancer, Skin and subcutaneous tissue disorders, Autoimmune disorder, Gastrointestinal disorders, Other. Percentage computed among FAS.

Specified terms for Other cancer, Skin and subcutaneous tissue disorders, Autoimmune disorder, Gastrointestinal disorders and Other, will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and will be described as number and percentage by System Organ Class (SOC) and Preferred Term (PT).

11.3 Primary Breast Cancer Diagnosis

To describe the clinical profile of the patients, the below characteristics related to the primary breast cancer diagnosis will be presented for FAS and by subgroup EU label; Pathologic stage; Residual disease after neoadjuvant treatment; Risk profile; Previous adjuvant or neoadjuvant therapy and Prior transtuzumab-based regimen overall and last treatment (Section 8.4):

- Age at primary diagnosis of breast cancer, calculated as:
  - $Year\ of\ breast\ cancer\ diagnosis - Year\ of\ birth$
- Age at primary diagnosis of breast cancer category: < 40 years, 40 to 49 years, 50 to 59, 60 to 69, >=70
- HER2 overexpression/amplification testing:
  - Immunohistochemistry (IHC): Yes, No, Unknown
    - If IHC, the result obtained: IHC 3+ (positive), IHC 2+ (equivocal)
  - Fluorescence in situ hybridization (FISH): Yes, No, Unknown
    - If FISH, the result obtained: Positive, Equivocal
  - Chromogenic in situ hybridization (CISH): Yes, No, Unknown
    - If CISH, the result obtained: Amplified, Non-amplified
- HER2 overexpression/amplification testing combination of results: IHC and FISH, IHC and CISH

- Hormone receptor status: ER positive, PR positive, ER negative, and PR negative
  - If ER or PR positive: Receptor expression (%) score, Score unavailable
- Ki-67 protein levels category: Low, Medium, High, Unavailable
  - For each category: Ki-67 protein levels (%), Unavailable
- Primary tumor location: Left Breast, Right Breast
  - For each side the exact location: Upper-outer quadrant, Upper-inner quadrant, Lower-outer quadrant, Lower-inner quadrant, Nipple complex, Axillary tail, Other
- Sentinel lymph node biopsy performed: Yes, No, Unavailable
  - If yes: Positive, Negative
- Primary tumor histology: Infiltrating ductal carcinoma, Infiltrating lobular carcinoma, Invasive carcinoma, Tubular, Other
- Histological grade: G1 Well differentiated, G2 Moderately differentiated, G3 Poorly differentiated, G4 Undifferentiated, Unavailable
- Stage of Breast Cancer: TX, T0, T1, T2, T3, T4, Tis
  - If T1, specified category: T1a, T1b, T1c, Unavailable
  - If T2, specified category: T2a, T2b, Unavailable
- Regional Lymph Nodes (N): NX, N0, N1
- Number of lymph nodes involved: 0, 1-3, ≥ 4
- TNM stage: T0N1M0, T1N0M0...
- Pathologic stage (AJCC classification): I, IIA, IIB, IIIA, IIIB, IIIC

12 SECONDARY OUTCOMES

12.1 Neratinib Treatment Patterns

Neratinib treatment patterns will be described as frequencies and percentages or summary statistics, as appropriate, for FAS and by subgroup EU label; Pathologic stage; Residual disease after neoadjuvant treatment; Risk profile; Previous adjuvant or neoadjuvant therapy and Prior transtuzumab-based regimen overall and last treatment (Section 8.4).

For duration of neratinib treatment calculations, the date of first and last neratinib administration will be taken from the eCRF "Neratinib Treatment" form, variables "Neratinib Initiation date" and "Definitive discontinuation date" respectively. Interruptions, compliance, and dose changes are not considered for duration of neratinib treatment.

Neratinib treatment initiation details:

- Time from breast cancer diagnosis to neratinib initiation (months), calculated as:
  - $(Date\ of\ first\ neratinib\ administration - Date\ of\ diagnosis + 1) / 30.4$
- Time from completion of adjuvant trastuzumab-based therapy to neratinib initiation (months), calculated as:
  - $(Date\ of\ first\ neratinib\ administration - Date\ of\ completion\ of\ adjuvant\ trastuzumab-based\ therapy + 1) / 30.4$
- Performance status scale used at neratinib initiation: ECOG, Karnofsky, Other
  - If ECOG: 0, 1, 2, 3, 4, Unavailable
  - If Karnofsky: 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, Unavailable and 90-100, 70-80, 50-60, 30-40, 10-20, Unavailable
- Performance status computed ECOG score (based on Table 3): 0, 1, 2, 3, 4, Unavailable
- Duration of neratinib treatment (months), calculated as:
  - For discontinued treatment,

    $(Date\ of\ last\ administration - Date\ of\ first\ administration + 1) / 30.4$

- For ongoing treatment, $(EOB\ date - Start\ date + 1)$

- Duration of neratinib treatment (categorized): ≤ 3 months, > 3 months to < 12 months, 12 months, >12 months
- Initial daily dosage (mg)
- Initial daily dose (mg), category: 40mg, 80mg, 120mg, 160mg, 200mg, 240mg, …; and <240mg, 240mg, >240mg

Treatment modifications (dosage changes):

- Number and percentage of patients with at least one neratinib treatment modification. Percentage computed among FAS.
- Number of temporary modifications by patient
- Temporary modifications per patient category: 1, 2, >2. Percentage computed among FAS patients with at least one neratinib treatment modification.
- Number and percentage of patients by reasons reported for all treatment modifications: Worsening condition, Adverse event, Physician's decision, Patient's wish, Other. All dose changes will be captured in the CRF, therefore a patient can contribute to several reasons. Percentage computed among FAS patients with at least one neratinib treatment modification.
- Number and percentage of patients by reason for first treatment modification: Worsening condition, Adverse event, Physician's decision, Patient's wish, Other. All dose changes will be captured in the CRF, therefore a patient can contribute to several reasons.
- Number and percentage of patients by reason for subsequent treatment modifications[(1)]: Worsening condition, Adverse event, Physician's decision, Patient's wish, Other. All dose changes will be captured in the CRF, therefore a patient can contribute to several reasons.
- Dose at first modification (mg)

- Dose at first modification (mg), category: 40mg, 80mg, 120mg, 160mg, 200mg, 240mg; and <240mg, 240mg, >240mg. Percentage computed among FAS patients with at least one neratinib treatment modification.
- Dose at subsequent modifications (mg)[(1)]
- Dose at subsequent modifications (mg) [(1)], category: 40mg, 80mg, 120mg, 160mg, 200mg, 240mg; and <240mg, 240mg, >240mg. Percentage computed among FAS patients with the subsequent neratinib treatment modification.

[(1)]Presented individually for each modification.

- Dose reduction at first modification: Yes, No. Percentage calculated among patients with at least one neratinib treatment modification.
  - Dose reduction[(2)]
  - Dose reduction[(2)] category: 1 tablet, 2 tablets, > 2 tablets. Percentage calculated among patients with a reduction at first modification.
- Dose escalation at first modification*: Yes, No. Percentage calculated among patients with at least one neratinib treatment modification.
  - Dose escalation[(2)]
  - Dose escalation[(2)] category: 1 tablet, 2 tablets, > 2 tablets. Percentage calculated among patients with an escalation at first modification.

[(2)] 1 tablet of neratinib corresponds to 40 mg.

Temporary neratinib treatment discontinuations details:

- Number and percentage of patients with at least one temporary treatment discontinuation. Percentage computed among FAS.
- Number of temporary discontinuations by patient
- Temporary discontinuations per patient category: 1, 2, >2

- Number and percentage of patients by reason for all temporary discontinuations: Worsening condition, Adverse event, Physician's decision, Patient's wish, Other. All temporary discontinuations will be captured in the CRF, therefore a patient can contribute to several reasons. If the same reason was reported several times for the same patient, the patient contributes only once to the reason. Percentage computed among FAS patients with at least one temporary neratinib treatment discontinuation.
- Number and percentage of patients by reason for first temporary discontinuation: Worsening condition, Adverse event, Physician's decision, Patient's wish, Other. All temporary discontinuations will be captured in the CRF, therefore a patient can contribute to several reasons. Percentage computed among FAS patients with at least one temporary neratinib treatment discontinuation.
- Number and percentage of patients by reason for subsequent temporary discontinuations[(1)]: Worsening condition, Adverse event, Physician's decision, Patient's wish, Other. All temporary discontinuations will be captured in the CRF, therefore a patient can contribute to several reasons. Percentage computed among FAS patients with at least one temporary neratinib treatment discontinuation.
- Dose at first re-initiation (mg)
- Dose at first re-initiation (mg) , category: 40mg, 80mg, 120mg, 160mg, 200mg, 240mg; and <240mg, 240mg, >240mg
- Dose at subsequent re-initiations (mg)[(1)]
- Dose at subsequent re-initiations (mg) [(1)], category: 40mg, 80mg, 120mg, 160mg, 200mg, 240mg; and <240mg, 240mg, >240mg

[(1)]Presented individually for each re-initiation.

- Duration of first treatment interruption (days), calculated as:
  - $(End\ date\ of\ the\ first\ neratinib\ treatment - Start\ date\ of\ first\ re-initiation + 1)$

- Duration of subsequent treatment interruptions (days) [(2)], calculated as:
  - $(End\ date\ of\ the\ previous\ neratinib\ treatment - Start\ date\ of\ subsequent\ re-initiation + 1)$

[(2)]Presented individually for each treatment interruption.

Permanent neratinib treatment discontinuation:

- Number and percentage of patients who discontinued the treatment permanently. Percentage computed among FAS.
- Number and percentage of patients by duration of treatment before discontinuation: ≤ 3 months, > 3 months to < 12 months, 12 months and > 12 months. Percentage computed among FAS patients who discontinued neratinib treatment permanently.
- Number and percentage of patients by reason for definitive discontinuation: Disease recurrence, Adverse event, Patient's wish, Physician's decision, Patient death, End of treatment period, Other. Percentage computed among FAS patients who discontinued neratinib treatment permanently.
  - Number and percentage of patients by switch onto another treatment following definitive discontinuation: Yes, No. Percentage computed among FAS patients who discontinued neratinib treatment permanently.

To supplement descriptions of neratinib treatment patterns for FAS, the Kaplan-Meier and reverse Kaplan Meier methods will be used. For Kaplan Meier, the number of events, number of censored data, median survival estimates will be reported along with the 1st and 3rd quartiles, and the corresponding two-sided 95% CI, Estimates of the proportion of patients not presenting the event of interest at 3-month intervals (1, 3, 6, 9, 12, 15, 18 months) and the corresponding two-sided 95% CIs. For the reverse Kaplan Meier, the number of events, number of censored data points, median follow-up time, Q1 and Q3 follow-up time and corresponding two-sided 95% CI will be presented. Kaplan Meier and reverse Kaplan Meier methods will be used for the following outcomes:

- Time from neratinib initiation to first temporary discontinuation (treatment persistence)
- Time from neratinib initiation to permanent treatment discontinuation(1)
- Time from neratinib initiation to first treatment modification

(1) For the analysis of time to permanent discontinuation, death will be considered as an event.

Additionally, the Kaplan-Meier and reverse Kaplan Meier analysis will also be performed for permanent treatment discontinuation by subgroups Concomitant Prophylaxis Antidiarrheal and Initial Dose of Neratinib (section 8.4).

12.1.1 Performance Status Changes

The change in performance status will be analyzed in 3 months intervals from neratinib initiation (from index to month 1, 3, 6, 9, 12) until end of observation date (section 7.8). This analysis will be presented as ECOG scale, if the performance status is collected in the eCRF with the Karnofsky scale, it will be mapped to the corresponding ECOG score [2], using the conversions in Table 3.

Table 3 Performance Scales Conversion Table

ECOG Score	Karnofsky Grade
0	90 to 100
1	70 to 80
2	50 to 60
3	30 to 40
4	10 to 20
5	0

12.2 Concomitant Treatments

Concomitant treatments will be analyzed over the whole follow-up period. For each therapy type of concomitant treatment [Endocrine therapy, Prophylaxis antidiarrheal and Corrective antidiarrheal therapy in response to AE (diarrhea)], the following variables will be presented for FAS:

- Number and percentage of patients with at least one treatment of the therapy type. Percentage computed among FAS.
- Number and percentage of patients by treatment name. Percentage computed among FAS patients with at least one treatment of the concomitant therapy type.
- Duration of treatment (months)*, calculated as:
  - For discontinued treatments, $(End\ date - Start\ date + 1) / 30.4$
  - For ongoing treatments, $(EOB\ date - Start\ date + 1) / 30.4$

*A patient can contribute with multiple treatments for the same therapy type, the duration of treatment will correspond to the total exposure of the patient to the treatment type.

Note: Other specified treatment names will be coded with WHO Drug version B3 March 2021, the reported and coded terms will be presented in a listing.

For concomitant treatment of Corrective therapy in response to other relevant AE, the following variables will be presented:

- Number and percentage of patients with at least one treatment. Percentage computed among FAS.
- Number and percentage of patients by adverse event description. Percentage computed among FAS patients with at least one corrective therapy in response to other relevant AE.
- Number and percentage of patients by treatment name, as ATC 5th level coded with WHO Drug. Percentage computed among FAS patients with at least one corrective therapy in response to other relevant AE.
- Number and percentage of patients with at least one maximum dosage received. Percentage computed among FAS patients with at least one corrective therapy in response to other relevant AE.
- Duration of treatment (days), calculated as:
  - For discontinued treatments, $(End\ date - Start\ date + 1)$

- For ongoing treatments, $(EOB\ date - Start\ date + 1)$

*A patient can contribute with multiple treatments; the duration of treatment will correspond to the total exposure of the patient to the treatment type.

Note: For corrective therapy in response to other relevant AE, the dose, dose unit and frequency, are also collected in the CRF. These details will be presented in a listing.

12.3 Breast Cancer Treatment History

Breast cancer treatment history will be described based on the neoadjuvant and adjuvant therapies, surgeries, and radiotherapy the patient received before neratinib initiation.

12.3.1 Neoadjuvant and Adjuvant Therapy

The following variables will be presented as frequencies and percentages and summary statistics as appropriate, for neoadjuvant therapy (pre-surgery) and adjuvant therapy (post-surgery), separately, for FAS and by subgroup EU label; Pathological stage; Risk profile (section 8.4). For adjuvant therapy analysis will also be performed by subgroup Previous adjuvant or neoadjuvant therapy (section 8.4).

- Number and percentage of patients with at least one therapy. Percentage computed among FAS.
- Number of therapies by patient
- Number and percentage of patients by therapy combinations of any therapy type. Percentage computed among FAS.
- Number and percentage of patients by therapy combination category: Chemotherapy (+/- Endocrine therapy), Chemotherapy + Trastuzumab (+/- Endocrine therapy), Chemotherapy + Trastuzumab + Pertuzumab (+/- Endocrine Therapy), TDM1 (+/- Endocrine therapy) (for adjuvant only) and Other (+/- Endocrine therapy).
- Duration of treatment (months) [(1)], calculated as:
  - $(End\ date - Start\ date + 1)\ /\ 30.4$
- Outcome: pCR, No pCR (for the neoadjuvant therapy overall)

- Number and percentage of patients by neoadjuvant/adjuvant therapies received. Percentage computed among FAS.
- For each therapy type (Chemotherapy, Endocrine Therapy, Anti-HER2, Immunotherapy, Other):
  - Number and percentage of patients by therapy name. Percentage computed among FAS with each treatment type.
  - Number and percentage of patients by therapy combination. Percentage computed among FAS with each treatment type.
  - Duration of treatment (months)[(1)], defined as:
    - $(End\ date - Start\ date + 1) / 30.4$
  - Number and percentages of patients who stopped the treatment as initially planned: Yes, No
    - If no, the reason: Toxicity, Worsening condition, No response/ Partial response, Physician's decision, Patient's wish, Other
  - Outcome: pCR, No pCR (in neoadjuvant therapy only)

[(1)]A patient can contribute with multiple therapies, the duration of treatment will correspond to the total exposure of the patient to the treatment type.

Additionally, for anti-HER2, the therapy combinations will also be presented.
In the adjuvant setting, for anti-HER2, the number and percentage of patients by Prior trastuzumab-based regimen (last treatment) will be presented.

Note: Immunotherapy names and other specified therapy names will be coded with WHO Drug version B3 March 2021, the reported and coded terms will be presented in a listing and the preferred term will be presented in the respective table.

12.3.2 Radiotherapy and Surgery

The type of surgery and its outcome will be presented as frequencies and percentages. The time from surgery to neratinib initiation will be presented and calculated as:

- $(Date\ of\ first\ neratinib\ administration - Date\ of\ surgery + 1) / 30.4$

Additionally, the patients with radiotherapy before/after surgery will be described.

12.4 Adverse Events

In this study relevant AEs that occurred between index date and 30 days after Neratinib discontinuation, study entry date or death, whichever occurs first, are collected in the eCRF and will be analyzed. Relevant AEs are defined as all SAEs, AEs leading to dose adaptation or treatment discontinuation, and AEs of interest.

The following are AEs of interest:

- Occurrence of diarrhea
- Gastro-intestinal disorder
- Hepatic disorders
- Cardiac disorders
- Pulmonary disorders
- Pancreatitis
- Reproductive and developmental disorders

SAEs will be identified as those reported as “Serious” on the Adverse Events page of the eCRF, AEs leading to treatment dose change (increase/decrease) or permanent discontinuation of neratinib will be identified from the action taken in the AE details page of the eCRF.

Adverse Events (AEs) will be coded using MedDRA version 24.1.

See Appendix 1 for handling of partial dates for AEs.

12.4.1 Relevant AEs

Relevant AEs will be summarized as number and percentage of subjects experiencing the event and number of events reported. The analysis of all relevant AEs recorded in the eCRF will be presented by the following variables for FAS and by subgroup EU label; Prior trastuzumab-based regimen overall and last treatment:

- Any relevant AE
- Any AEs of special interest
  - by interest type: Occurrence of diarrhea, Gastro-intestinal disorder, Pulmonary disorder, Reproductive and developmental disorder, Hepatic disorder, Cardiac disorder, Pancreatitis
- Any SAEs
  - by SAE type: Death, Life threatening, Hospitalization due to AE – initial or prolonged, Congenital diseases/abnormalities, Disability/ incapacity and Other clinically significant conditions
- By Severity: Grade 1, 2, 3, 4 and 5
- By Action taken: None, Treatment dose increased, Treatment dose decreased, Treatment discontinued, Corrective treatment
- By Outcome: Recovered, Recovered with sequelae, Recovering, Not recovered, Death, Unknown
  - By Causal relationship to neratinib treatment: Reasonable possibility, Not reasonable possibility

If number of patients is large enough, the following analyses will be performed :

- Relevant AEs by SOC and PT for each Severity grade
- Relevant AEs by SOC and PT for each Severity grade by subgroup Prior trastuzumab-based regimen subgroup
- Relevant AEs by SOC and PT for each Severity grade, for patients with treatment discontinuation reason “Patient wish”

12.4.2 Occurrence of Diarrhea

The occurrence of diarrhea is an AE of particular interest, thus, the following variables will be summarized as number and percentage of subjects experiencing the event and number of events reported for FAS and by subgroup EU label; Prior trastuzumab-based regimen overall and last

treatment; Concomitant Corrective Antidiarrheal Treatment and Concomitant Prophylaxis Antidiarrheal Treatment (section 8.4):

- Any Occurrence of Diarrhea AE
- Any Occurrence of Diarrhea SAEs
  - by SAE type: Death, Life threatening, Hospitalization due to AE – initial or prolonged, Congenital diseases/abnormalities, Disability/ incapacity and Other clinically significant conditions
- By Severity: Grade 1, 2, 3, 4 and 5
- Occurrence of diarrhea episodes by Severity: Grade 1, 2, 3, 4 and 5
- By Action taken: None, Treatment dose increased, Treatment dose decreased, Treatment discontinued, Corrective treatment
- By Outcome: Recovered, Recovered with sequelae, Recovering, Not recovered, Death, Unknown
- By Causal relationship to neratinib treatment: Reasonable possibility, Not reasonable possibility

13 EXPLORATORY OUTCOMES

The exploratory outcomes described in this section will be analysed for HRAS.

13.1 First Recurrence

The patterns of the first recurrence after neratinib initiation will be described based on frequencies and percentages of the following variables for HRAS by EU label and for FAS by Hormone receptor (section 8.4):

- Number and percentage of patients with a first recurrence. Percentage computed among HRAS.
- Number and percentage of patients by type of the recurrence: Invasive ipsilateral breast tumor recurrence (IIBTR), Invasive contralateral breast cancer recurrence (ICBCR), Regional invasive recurrence (RIR), Distant tumor recurrence (DTR) – or metastasis, Second breast cancer. Percentage computed among HRAS.
  - Number and percentage of patients by site of recurrence. Percentage computed among HRAS with the type of recurrence:
    - IIBTR, ICBCR and RIR: Breast, Chest, Axillary lymph node(s), Skin, Nipple complex, Other
    - DTR or metastasis: Bone, Skin, Non-regional lymph node(s), Lung, Liver, CNS, Pleura, Adrenal glands, Ovary(ies), Left breast, Right breast, Other
  - If second breast cancer, the type: HR+, Triple negative, Other
- Number and percentage of patients with treatment administered for first recurrence
- Number of treatments by patient
- Treatment name: Trastuzumab, Pertuzumab, T-DM1, T-deruxtecan, Lapatinib, Tucatinib, Other
- Treatment duration (months), calculated as:
  - For discontinued treatment, $(End\ date - Start\ date + 1) / 30.4$
  - For ongoing treatment, $(EOB\ date - Start\ date + 1)$

13.2 Time to Event Analysis

All time to event outcomes described in the subsections below will be summarized using the Kaplan-Meier method as described in section 8.2, for FAS and by subgroup EU label; Previous adjuvant or neoadjuvant therapy; Residual disease after neoadjuvant treatment; Prior trastuzumab-based regimen overall; and Prior trastuzumab-based regimen last treatment. (section 8.4)

Patients for whom the event did not occur or who are lost to follow-up, will be censored at the last recorded date that the patient is known to be alive. For patients alive at end of study will be considered the date of study entry, for patients who withdraw consent will be considered the date of consent withdrawal, for patients lost to follow-up will be considered the date of last contact, as collected in the eCRF.

13.2.1 Invasive Disease-Free Survival

iDFS is defined as the time, in months, from neratinib treatment initiation (index date) to the first occurrence of an iDFS event. The iDFS events include:

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

Table 4 Event and time details for iDFS

Event	Type	Events and censoring dates
Invasive disease recurrence	Uncensored	Date of first recurrence
Death (all causes)	Uncensored	Date of death
Loss to follow-up	Censored	Date of EOB (section 7.8)
Withdraw consent	Censored	Date of EOB (section 7.8)
No event	Censored	Date of EOB (section 7.8)

iDFS in months, will be calculated as follows:

- For patients who have an event:
  - $(Date\ of\ event - Index\ date + 1)/30.4$
- For patients who do not have an event (censored):
  - $(Last\ available\ date - Index\ date + 1)/30.4$

All recurrences and respective dates will be identified from the "First Breast Cancer Recurrence" page of the eCRF. Death and corresponding date will be identified from the "Survival Status" page of the of the eCRF.

13.2.2 Distant Disease-Free Survival

DDFS is defined as the time, in months, from neratinib treatment initiation (Index date) to the first distant tumor recurrence or death from any cause.

Table 5 Event and time details for DDFS

Event	Type	Events and censoring dates
Distant tumor recurrence	Uncensored	Date of first recurrence
Death (all causes)	Uncensored	Date of death
Loss to follow-up	Censored	Date of EOB (section 7.8)
Withdraw consent	Censored	Date of EOB (section 7.8)
No event	Censored	Date of EOB (section 7.8)

DDFS in months, will be calculated as follows:

- For patients who have an event:
  - $(Date\ of\ event - Index\ date + 1)/30.4$
- For patients who do not have an event (censored):
  - $(Last\ available\ date - Index\ date + 1)/30.4$

DDFS and respective date will be identified from the "First Breast Cancer Recurrence" page of the eCRF.

13.2.3 Time to Central Nervous System Metastasis

Time to CNS metastasis (either isolated or concurrent with other metastatic sites) is defined as the time, in months, from neratinib initiation (index date) to CNS metastasis as first distant recurrence.

Table 6 Event and time details for CNS metastasis

Event	Type	Events and censoring dates
CNS metastasis	Uncensored	Date of first recurrence
Death (all causes)	Censored	Date of death
Loss to follow-up	Censored	Date of EOB (section 7.8)
Withdraw consent	Censored	Date of EOB (section 7.8)
No event	Censored	Date of EOB (section 7.8)

Time to CNS metastasis in months, will be calculated as follows:

- For patients who have an event:
  - $(Date\ of\ event - Index\ date + 1)/30.4$
- For patients who do not have an event (censored):
  - $(Last\ available\ date - Index\ date + 1)/30.4$

CNS metastasis as first distant recurrence and respective date will be identified from the "First Breast Cancer Recurrence" page of the eCRF.

13.2.4 Overall Survival

OS is defined as the time, in months, from neratinib initiation date (index date) until the date of death (due to any cause).

Table 7 Event and time details for CNS metastasis

Event	Type	Events and censoring dates
Death (all causes)	Uncensored	Date of death
Loss to follow-up	Censored	Date of EOB (section 7.8)
Withdraw consent	Censored	Date of EOB (section 7.8)
No event	Censored	Date of EOB (section 7.8)

OS in months, will be calculated as follows:

- For patients who have an event:
  - $(Date\ of\ death - Index\ date + 1)/30.4$
- For patients who do not have an event (censored):
  - $(Last\ date\ known\ to\ be\ alive - Index\ date + 1)/30.4$

Death and corresponding date will be identified from the "Survival Status" page of the of the eCRF.

14 REFERENCES

[1] "World Health Organization," [Online]. Available: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. [Accessed 02 December 2021].

[2] M. Oken, R. Creech, D. Tormey, J. Horton, T. Davis, E. McFadden and P. Carbone, "Toxicity and response criteria of the Eastern Cooperative Oncology Group," *Am J Clin Oncol,* vol. 5, no. 6, pp. 649-55, 1982.

Appendix 1. Partial Date Conventions

No imputation of missing data will be performed; missing data will not be replaced in this study, unless specified and for the following dates (Table 8). Imputed dates will not be presented in the listings.

Table 8 Missing data imputation rules

Variable	Rule
General rule for partial dates	If the day of event is missing and month and year are available: the day will be imputed to the first day of the month, in case of a start date, and to the last day of the month, in case of an end date. Unless such imputation is illogical. If the day and month are missing, the date will not be imputed.
Date of abstraction	Will not be imputed
Date of informed consent/ non-opposition	Will not be imputed
Date of primary diagnosis of Breast Cancer	General rule for partial dates applies.
Date of pregnancy	Will not be imputed
Start date (Pre-/Post-surgery neoadjuvant therapy)	Will not be imputed.
End date (Pre-/Post-surgery neoadjuvant therapy)	Will not be imputed.
Date of surgery	Will not be imputed.
Date of radiotherapy	Will not be imputed.
Date of weight measurement	General rule for partial dates applies.
Date of performance status assessment (follow-up)	Will not be imputed.
Neratinib initiation date	General rule for partial dates applies.

Variable	**Rule**
Neratinib definitive discontinuation Date	General rule for partial dates applies.
Treatment modification date	Will not be imputed.
Treatment temporary discontinuation date	Will not be imputed.
Treatment date of re-initiation	Will not be imputed.
Concomitant treatment start date	General rule for partial dates applies.
Concomitant treatment end date	General rule for partial dates applies.
Start date of AE	General rule for partial dates applies.
Date of death	General rule for partial dates applies.
Admission date (Hospitalization due to AE)	Will not be imputed.
Discharge date (Hospitalization due to AE)	Will not be imputed.
Date of recurrence (AE recurrence)	Will not be imputed.
Date of recovery (AE outcome)	Will not be imputed.
Date of first breast cancer recurrence	General rule for partial dates applies.
Treatment start date (Breast cancer recurrence)	General rule for partial dates applies.
Treatment end date (Breast cancer recurrence)	General rule for partial dates applies.
Date of last contact	General rule for partial dates applies.
Date of consent withdrawn	Will not be imputed.