HISTORY OF CHANGES

VERSIONS

Date	Version N°	Reason for change
22/09/2021	1.0	Not applicable

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

Version 1.0

Date: 22 September 2021

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Protocol number	NIS12501

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CNS	Central Nervous System
CRO	Contract Research Organization
DDFS	Distant Disease-Free Survival
DFS	Disease-Free Survival
EAP	Early Access Program
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ER	Estrogen Receptor
EU	European Union
GVP	Good Pharmacovigilance Practice
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
iDFS	Invasive Disease-Free Survival
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
pCR	Pathologic Complete Response
PgR	Progesterone Receptor
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
T-DM1	Trastuzumab Emtansine
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor/Node/Metastasis

1 SYNOPSIS

STUDY TITLE	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.
SPONSOR	Pierre Fabre Médicament
STUDY RATIONALE	Neratinib (Nerlynx®), an orally available, irreversible tyrosine kinase inhibitor (TKI), was approved by the Food and Drug Administration (FDA) in 2017 and in the European Union (EU) in 2018. Neratinib is indicated for the extended adjuvant therapy of adult patients with early-stage Hormone Receptor-positive (HR+) and Human Epidermal Growth Factor Receptor 2 (HER2)-overexpressed/amplified breast cancer, who completed prior adjuvant trastuzumab-based therapy less than one year ago in Europe. The efficacy of neratinib has been demonstrated in a phase III randomized controlled clinical trial (ExteNET) for adult patients with early-stage HER2-positive breast cancer who completed prior adjuvant trastuzumab therapy. Current clinical practice in some countries has recently evolved and may involve the use of two additional HER2-directed agents (pertuzumab[1] with trastuzumab or trastuzumab emtansine[2]) prior to receiving extended adjuvant therapy with neratinib, which differs from the patient population in ExteNET. The precise implications of this therapeutic strategy remain to be defined. Therefore, the real-world clinical data in patients treated with neratinib as an extended adjuvant therapy are necessary to put these results into context. Therefore, there is a need to document the clinical profile of these patients, and the effectiveness of neratinib as an extended adjuvant therapy in a real-world setting. This real-world, multicenter, observational retrospective study will describe the demographics and clinical profile of patients with early-stage HER2-positive breast cancer in Europe, who have been treated with neratinib as an extended adjuvant therapy, as part of an Early Access Program (EAP). Data on the safety profile of neratinib based on real-world use will also be described.
STUDY OBJECTIVES	**Primary objective:** 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. **Secondary objectives:** 1. 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. 2. 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). 3. To describe the frequency of relevant Adverse Events (AEs) in patients with breast cancer using neratinib as an extended adjuvant therapy. Relevant AEs are defined as all Serious AEs (SAEs) or AEs leading to dose adaptation or treatment discontinuation, and AEs of interest.

	Exploratory objectives: 1. To describe the first recurrence patterns 2. To describe invasive disease-free survival (iDFS) in patients with early-stage HER2+ and HR+ breast cancer, treated with neratinib as an extended adjuvant therapy, over the study observation period 3. 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. 4. To describe the incidence of central nervous system (CNS) metastasis 5. To describe overall survival (OS) in patients with early-stage HER2+ HR+ breast cancer, treated with neratinib as an extended adjuvant therapy, over the study observation period.
STUDY OUTCOMES	**Primary outcome:** Demographics and clinical profile of patients with early-stage HER2+ breast cancer, for the full analysis set and by subgroup(s) of interest, will be described if the number of patients allow it. The following baseline data will be collected at study entry: 1. Patient demographic and clinical characteristics: • Age (year of birth), gender, weight, height, body mass index (BMI) at neratinib initiation • Performance status using the Eastern Cooperative Oncology Group (ECOG), Karnofsky or any other scoring system at primary diagnosis of breast cancer and at neratinib initiation • Employment status at neratinib initiation • Date of primary diagnosis of breast cancer • Menopausal status at primary diagnosis of breast cancer • Primary tumor location at primary diagnosis of breast cancer • Histology of primary diagnosis of breast cancer: grade and subtype • Breast cancer stage at the time of primary diagnosis, using the Tumor/Node/Metastasis (TNM) classification system (I, II, III) • Pathological Stage (American Joint Committee on Cancer classification) at the time of primary diagnosis • Relevant comorbidities at neratinib initiation • Tumor biology at primary diagnosis ▪ HR status (estrogen receptor [ER] and progesterone receptor [PgR] status) ▪ HER2 overexpression/amplification ▪ Ki-67 (if available) ▪ Grading **Secondary outcomes:** 1. Neratinib treatment patterns will be described, including time to initiation after a trastuzumab based treatment, treatment dose, treatment duration, permanent and temporary discontinuation and reasons for treatment discontinuation or switch at the end of neratinib treatment as an extended adjuvant therapy for early-stage HER2+ breast cancer. All relevant information up to the end of the study observation period (study entry date) will be collected. Additionally, treatment persistence, median time to permanent discontinuation and median time to first dosage modification will also be evaluated using Kaplan-Meier's method.

	2. Treatment history for breast cancer before neratinib initiation will be described. The following data will be collected: • Prior anti-cancer drugs/therapies/procedures for breast cancer: type, medication name, start date and stop date • Type of surgeries and date • Radiotherapy after surgery (Yes/No): date and area • Prior neoadjuvant and/or adjuvant anti HER2-directed therapy(ies) (including trastuzumab): type, start date and stop date • Outcome of neoadjuvant treatment (if applicable): pathologic complete response (pCR) or no pCR • Concomitant endocrine therapy 3. Frequency of relevant AEs during treatment with neratinib as an extended adjuvant therapy will be determined. Relevant AEs will be defined as all SAEs or AEs leading to dose adaptation or treatment discontinuation, and AEs of interest. The following are some AEs of interest: occurrence of diarrhea (onset/resolution dates, maximum grade, actions taken), gastro-intestinal toxicity (nausea, vomiting, abdominal pain, constipation), hepatic disorders, cardiac disorders, pulmonary disorders, pancreatitis, and reproductive and developmental disorders. All relevant AE data will be extracted from medical records and mapped into the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred term (PT). **Exploratory outcomes:** Effectiveness will be evaluated only on HR+ patients based on the following outcomes, up to the end of the study observation period (study entry date): 1. Characterization of the first recurrence patterns (location, distribution, size, timing) 2. iDFS, defined as the time from neratinib treatment initiation to: a. First ipsilateral invasive breast cancer recurrence b. First locoregional invasive breast cancer recurrence c. First contralateral invasive breast cancer recurrence d. First distant tumor recurrence e. Death attributable to any cause. 3. DDFS, defined as the time from neratinib treatment initiation to the first distant tumor recurrence or death from any cause. 4. Cumulative incidence of CNS metastasis (either isolated or concurrent with other metastatic sites), defined as the time from neratinib initiation to CNS recurrence as first distant recurrence to other metastatic sites) 5. OS, defined as the time between neratinib treatment initiation (for early breast cancer) and death (due to any cause)
STUDY DESIGN	Multi-country, multicenter, retrospective, observational, longitudinal study
STUDY POPULATION	The study population will include approximately up to 200 patients having received neratinib as an extended adjuvant therapy in the context of the EAP in Europe, and residing in one of the five target countries: Belgium, Croatia, France, Italy and Spain.

INCLUSION AND EXCLUSION CRITERIA	**Patients will be eligible for inclusion if they fulfill <u>ALL</u> of the following criteria**: • Age ≥ 18 years at neratinib treatment initiation • Having received at least one initial dose of neratinib as an extended adjuvant therapy of early-stage HER2+ breast cancer, in the context of the EAP in Europe, and between August 01, 2017 and December 31, 2020 • 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 subjects, where a signed informed consent is required, the informed consent may be obtained from a next of kin / legal representative, or an informed consent form (ICF) waiver will apply, depending on approval by Ethics Committees and/or local regulations. Eligibility for treatment with neratinib was assessed at the time of early access drug supply provision. For the purposes of this retrospective data collection, it is desirable that eligibility criteria are the least restrictive possible. Therefore, there are <u>no exclusion criteria</u> for patients in this study.
SAMPLE SIZE	Up to 200 patients.
STATISTICS	**Analysis of primary and secondary outcomes** Summary statistics will be used depending on the nature of the variables, and the number of available and missing data will be specified for each variable. Categorical variables will be presented as frequencies and proportions, and continuous data will be expressed as median, mean, standard deviation, range, and quartiles (Q1 and Q3). The 95% Confidence Intervals (CI) will be presented upon relevance to the analysis. To supplement descriptions of neratinib treatment patterns, Kaplan-Meier estimates for treatment persistence, median time to permanent treatment discontinuation, and median time to first treatment modification will also be provided. **Analysis of exploratory outcomes** iDFS, DDFS, cumulative incidence of CNS metastasis and OS will be evaluated using Kaplan-Meier's method. Time will be expressed in months. Median survival estimates will be reported along with the 1st and 3rd quartiles, and the corresponding 95% CI. Kaplan-Meier estimates will be presented with a summary of associated statistics (number of events, number of censored data / median, Q1 and Q3 survival time / estimate rates of patients not presenting the event of interest at 1, 3, 6, 9 ,12 months) including the corresponding two-sided 95% CIs. Cox regression analysis may be performed to adjust for predefined baseline covariates, which will be detailed in a statistical analysis plan (SAP). For OS, 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.

2 BACKGROUND AND RATIONALE

Background

Breast cancer is the most common type of cancer and the leading cause of cancer mortality in women worldwide. It was estimated that, in 2020, 2.261.419 new cases of breast cancer were diagnosed, and 684,996 deaths were reported due to the disease[3]. Approximately 15% to 25% of breast cancer tumors are Human Epidermal growth factor Receptor-2-positive (HER2+). Breast cancers with high levels of HER2 are usually more aggressive, with an increased risk of recurrence, reduced survival rates compared to other types of cancer and inadequate treatment response in the metastatic setting[4-6]. Nevertheless, treatments targeted towards HER2 can be very effective.

For instance, trastuzumab (Herceptin®)[7] is a monoclonal antibody that specifically binds to the HER2 receptor and induces its internalization and downregulation, thus resulting in inhibition[8]. Trastuzumab is the standard of care for most patients with early-stage HER2+ breast cancer. One year of trastuzumab in the adjuvant setting offers significant benefit in terms of disease-free survival (DFS) and overall survival (OS) in women with early-stage HER2-positive breast cancer[9,10]. However, breast cancer recurs in 15-24% of patients after a median of 8-11 years[11]. Extending the duration of trastuzumab therapy to 2 years did not provide significant DFS benefit in patients with early-stage HER2-positive breast cancer, compared to one year of treatment[12].

Alternative therapeutic strategies have been recently approved.

Pertuzumab (Perjeta®)[1] is a humanized monoclonal antibody that binds to a different epitope of the HER2 extracellular domain than trastuzumab. The APHINITY trial results showed a significant improvement in the rates of invasive-disease-free survival (iDFS) in patients with HER2+ breast cancer, when pertuzumab was added to adjuvant trastuzumab and chemotherapy[13].

Trastuzumab emtansine (T-DM1, Kadcyla®)[2] is an antibody–drug conjugate of trastuzumab and the cytotoxic agent, emtansine (DM1). Results of the KATHERINE trial showed that the risk of invasive breast cancer recurrence or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone, in HER2+ early breast cancer patients who had residual invasive disease after completion of neoadjuvant therapy[14].

Trastuzumab-based therapy includes treatment with trastuzumab combined with chemotherapy, with or without pertuzumab, or treatment with T-DM1.

Neratinib (Nerlynx®), an orally available, irreversible tyrosine kinase inhibitor (TKI), was approved by the Food and Drug Administration (FDA) in 2017 and in the European Union (EU) in 2018. In the EU, Neratinib's approved indication is for extended adjuvant therapy of adult patients with early-stage Hormone Receptor-positive (HR+) HER2-overexpressed/amplified breast cancer and who completed prior adjuvant trastuzumab-based therapy less than one year ago. The recommended dose of neratinib is 240 mg (six 40 mg tablets) taken orally once daily, continuously for one year[15]. Comparatively, the FDA approved indication applies to a broader profile of patients, where neratinib as a single agent is approved for the extended adjuvant

therapy of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy. Nothing is specified in terms of HR status or the length of prior adjuvant trastuzumab-based therapy.

Certain patients may have received neratinib as per the FDA indication, as part of the EAP in Europe.

Results of the ExteNET trial showed that patients with early-stage HER2+ breast cancer receiving one year of extended adjuvant therapy with oral neratinib (within a year of standard of care adjuvant trastuzumab), had significant improvement in the 2-year iDFS rate compared to placebo (93.9% versus 91.3%, respectively; hazard ratio, 0.67; 95% Confidence Interval (CI), 0.50–0.91; p = 0.0017)[16]. A 5-year follow-up reported similar results (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008)[17]. Furthermore, greater improvement in iDFS was observed in HER2+ patients with HR+ breast cancer [16-18].

An Early access program (EAP) was initiated in Europe in 2017, providing access to neratinib to individual patients following specific criteria outside of a clinical trial. This program is currently ongoing in certain European countries, awaiting product reimbursement. This study will provide real-world data to characterize the profile of patients treated with neratinib, their previous medical history, the conditions for using neratinib and its profile in terms of safety and effectiveness as an extended adjuvant therapy. The profile of patients may be more diverse compared to those enrolled in the ExteNET trial.

Rationale

The efficacy of neratinib has been demonstrated in a phase III randomized controlled clinical trial (ExteNET) for adult patients with early-stage HER2-positive breast cancer who completed prior adjuvant trastuzumab therapy[16,17]. Current clinical practice in some countries may involve the use of two additional HER2-directed agents (pertuzumab[1] and trastuzumab emtansine[2]), prior to receiving extended adjuvant therapy with neratinib, which differs from the patient population in ExteNET. The precise implications of this therapeutic strategy on the findings from the ExteNET trial are not known. Therefore, there is a need to document the clinical profile of such patients, and the effectiveness of neratinib as an extended adjuvant therapy in a real-world setting across multiple countries.

This real-world, multicenter, observational retrospective study will describe the demographics, medical history, and clinical profile of patients with early-stage HER2+ breast cancer treated with neratinib as an extended adjuvant therapy in the context of the EAP in Europe. Data on the safety profile of neratinib based on real-world use will also be described.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

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.

The primary objective will be analyzed for the full analysis set and for predefined subgroup(s) of interest (section 4.3.4), if patient numbers allow it.

3.2 SECONDARY OBJECTIVES

Secondary objectives will be analyzed for the full analysis set and for predefined subgroup(s) of interest (section 4.3.4), if patient numbers allow it.

1. 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.
2. 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).
3. 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 AEs (SAEs) or AEs leading to dose adaptation or treatment discontinuation, and AEs of interest.

   The following are some AEs of interest: occurrence of diarrhea (onset/resolution dates, maximum grade, actions taken), gastro-intestinal toxicity (nausea, vomiting, abdominal pain, constipation), hepatic disorders, cardiac disorders, pulmonary disorders, pancreatitis, and reproductive and developmental disorders.

3.3 EXPLORATORY OBJECTIVES

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

4 RESEARCH METHODS

4.1 STUDY DESIGN

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. Eligible patients will be selected among those having received at least one dose of neratinib in this EAP, between August 01, 2017 and December 31, 2020 (the patient identification period). The decision to prescribe neratinib was taken prior to and independent of the proposal to select a patient into this study and all data will be retrospectively collected from the patients' medical charts.

The definitions of terms used to describe various phases of this study are as below:

Patient Identification Period: Time period eligibility for selection of patients who initiated neratinib treatment within the EAP in Europe, from August 01, 2017 until December 31, 2020.

Study Entry Date: The cut-off date until when the eligible patients' data as obtained from medical charts are abstracted for analysis in the study.

Index Date: The index date is defined as the date of neratinib initiation

Baseline Period: All relevant data available prior to the first dose of neratinib initiation (index date)

Follow-up period: The period starting from neratinib initiation within the EAP in Europe (index date) until data cut-off date (end of the study observation period). Patients will be censored at date of death, or among patients who did not die, the data cut-off date (end of the study observation period) or date of last visit, whichever occurs first. Patients will have variable follow-up time periods, depending on their index dates and last contact dates.

A study completion follow-up will be performed for all enrolled patients for whichever of the following cases that come first:

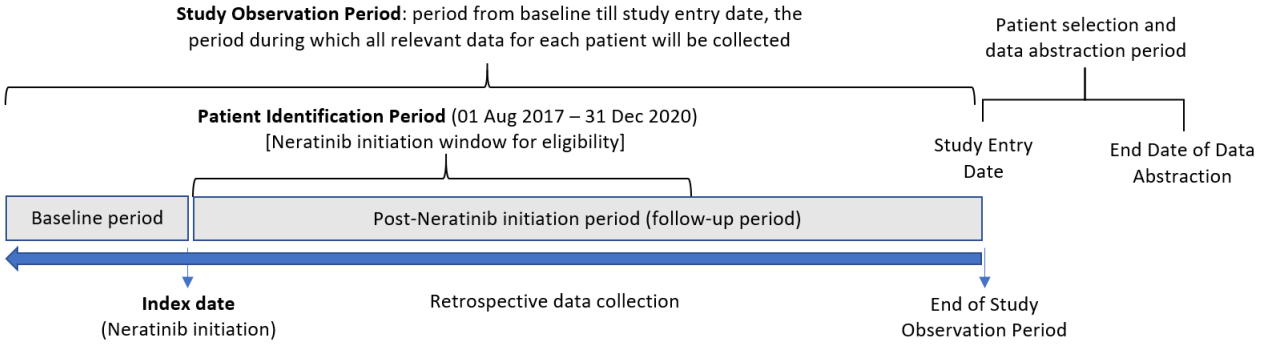
a. At the end of the study observation period
b. Upon study withdrawal
c. After attempts to trace patients lost to follow-up
d. Deceased patients

Study Observation Period: The overall study observation period includes the period from baseline till study entry date, and all available data for each patient will be collected until the end of the observation period

Data Abstraction Period: Time period from study entry date to end date of data abstraction of all eligible patients.

A schematic representation of the study timeline is provided in Figure 1 below.
The target countries for patient enrollment will include Belgium, Croatia, France, Italy, and Spain. Adult patients (≥ 18 years) with HER2+ breast cancer who had at least one dose of neratinib treatment in the context of the EAP in Europe will be invited to participate in this observational study. Patients (or next of kin/legal representative, if applicable) who provide written informed consent or non-opposition to data collection, as per local regulations, will be enrolled. Patients will also be enrolled in countries where an informed consent form (ICF) waiver has been approved by Ethics Committees and/or local regulations.

Figure 1: A pictorial representation of the NEAR study scheme



4.2 POPULATIONS

4.2.1 Study population

The study population will include all patients with early-stage HER2+ breast cancer having received at least one dose of neratinib as an extended adjuvant therapy in the context of the EAP in Europe between August 01, 2017 and December 31, 2020.

4.2.1.1 Inclusion criteria

Patients will be eligible for inclusion if they fulfill ALL of the following criteria:

- Age ≥ 18 years at neratinib treatment initiation
- 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 August 01, 2017 and December 31, 2020
- 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 subjects, 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.

4.2.1.2 Exclusion criteria

Eligibility for treatment with neratinib was assessed at the time of early access drug supply provision. 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.

4.2.2 Patient selection and follow-up

4.2.2.1 Study centers

The target countries for study participation will include Belgium, Croatia, France, Italy, and Spain. Only study centers where treating physicians have treated at least one patient with neratinib as an

extended adjuvant therapy for early stage HER2+ breast cancer in the context of the European EAP between August 01, 2017 and December 31, 2020 (41 centers) will be approached to participate in this study. All centers from the list will be invited to participate in the feasibility phase. All responses, whether positive or negative, will be tracked and recorded by IQVIA.

4.2.2.2 Patient selection

- Study initiation, patient selection, and data abstraction are planned to start in 2022
- All patients ≥ 18 years old who received at least one initial dose of neratinib as part of the EAP in Europe, between August 01, 2017 and December 31, 2020, will be invited to participate in this observational study
- After verification of the eligibility criteria, the investigator or qualified designee will inform the patient (or his/her next of kin or legal representative, in the case of deceased patients) about:
  - The study objectives
  - The possibility of refusing to participate or terminating his/her participation in the study, without any prejudice to the relationship with the investigator and the patient's medical care
  - Processing of personal data that will be collected during this study and the rights of access, opposition, and rectification to this data.

The patient (or his/her next of kin or legal representative, in the case of deceased patients) will be provided with a written or electronic information sheet about the study prior to data abstraction from patient records. If the patient (or his/her legal representative or next of kin) agrees to participate, he/she (or his/her next of kin or legal representative) will be asked to provide their written informed consent or non-opposition to study participation to the investigator (depending on local regulations), which will be documented in the patient's medical file. Wherever applicable, an ICF waiver will be obtained, depending on approval by Ethics Committees and/or local regulations. The patient (or his/her next of kin/legal representative) may, at any time, object to the use of the patient's data, in the context of research.

In the singular case of France, it is permissible to merely obtain a non-opposition in order to enrol a patient in observational studies. In order to do this, it is sufficient to inform potential subjects (or their next-of-kin/legal representative) about the study by post. Thus, participating centres will be able to send patient information sheets via registered post with an acknowledgement of receipt. Patients will have 4 weeks to oppose data collection following reception of the letter. Even if no formal opposition is received, their data may be collected for the study. Patients will also be informed that they may oppose data collection at any time during the study without any repercussions on their ongoing care. In the case of opposition to the collection of their data at any point during the study, their case would be considered as withdrawn.

The investigator will document, in the patient's medical file, the patient's (or the next-of-kin's/ legal representative's) informed consent, refusal, non-opposition or opposition to study participation, before data abstraction is performed.

Since there are no anticipated benefits or detriments to taking part in this study, patients refusing to participate will be treated identically to those enrolled in the study, as per the current standard of care.

A screening log will be maintained at each center for all eligible patients, where sex, age category and survival status (dead/alive/lost to follow-up) will be collected. The reason(s) for refusal to participate will be recorded for those who declined to participate in the study.

Data that will be collected upon study inclusion are detailed in section 4.3 below.

4.2.2.3 Patient follow-up

- Initiation of neratinib treatment as an extended adjuvant therapy within the European EAP is the index date for each eligible patient.
- The maximum follow-up duration is until the end of the study observation period (study entry date), up to which all available data will be collected.
- Data will be extracted from existing medical records by the investigator or qualified designee as per standard clinical practice, from baseline till study entry date, death, study withdrawal, or loss to follow-up.
- Data for each patient will be recorded by the investigator or qualified designee in electronic case report forms (eCRF). Following study inclusion, data will be abstracted from the medical charts until study entry date as detailed in section 4.3, and summarized in the data collection schedule (Table 1).

Table 1: Data collection schedule for eligible patients in the NEAR study

The eligible patients' data from baseline until the end of the study observation period will be collected during data abstraction period (from study entry date to end date of data abstraction).

Data	Baseline Period	Start of Neratinib Treatment	Treatment Phase	End of Treatment (EOT)	Available Tumor / Survival assessment post EOT
Treatment history before neratinib initiation (section 4.3.1)	X				
Patient characteristics at primary diagnosis of breast cancer/neratinib initiation (section 4.3.1)		X			
Neratinib treatment details (section 4.3.2)		X	X	X	
Concomitant treatments with neratinib (section 4.3.2)		X	X	X	
Adverse Events* (section 4.3.2)		X	X	X	
Breast cancer recurrence / Survival status until the end of the study observation period				X	X
Reasons for neratinib discontinuation					X

** For the safety outcomes, only relevant AEs, that occurred during neratinib use (until the end of the study observation period) (section 4.3.2) will be assessed.*

4.3 STUDY OUTCOMES

The outcomes of this retrospective, observational study is purely descriptive. They aim to summarize the characteristics of patients receiving neratinib in the context of the EAP in Europe, and to describe the use of neratinib in real-life, as well as the associated adverse effects of this medication.

4.3.1 Primary outcome

Demographics and clinical profile of patients with early-stage HER2+ breast cancer will be described, for the full analysis set and by subgroup(s) of interest, if the number of patients allow, (see section 4.3.4). The following baseline data will be collected at study entry:

1. Patient demographic and clinical characteristics at neratinib initiation, unless stated otherwise:
    - Age (year of birth), gender, weight, height, body mass index (BMI)
    - Performance status using the Eastern Cooperative Oncology Group (ECOG), Karnofsky or any other scoring system at primary diagnosis of breast cancer and at neratinib initiation
    - Employment status
    - Date of primary diagnosis of breast cancer
    - Menopausal status at primary diagnosis of breast cancer
    - Location of the primary tumor at primary diagnosis of breast cancer
    - Histology of primary diagnosis of breast cancer
        - Histological grade (Grade 1, Grade 2, Grade 3)
        - Histological subtype (Ductal, Lobular, Other etc.)
    - Breast Cancer stage at the time of primary diagnosis, using the Tumor/Node/Metastasis (TNM) classification system (I, II, III)[19]
    - Pathological Stage (American Joint Committee on Cancer classification) at the time of primary diagnosis
    - Relevant comorbidities at neratinib initiation, including, but not limited to the following:
        - Renal disease
        - Liver disease
        - Gastro-intestinal disorders
        - Cardiovascular conditions
        - Skin and subcutaneous tissue disorders
        - Diabetes (Type I or II)
    - Tumor biology
        - HR status (estrogen receptor [ER] and progesterone receptor [PgR] status)
        - HER2 overexpression/amplification
        - Ki-67 (if available)
        - Grading

4.3.2 Secondary outcomes

1. Neratinib treatment patterns will be described, including time to initiation after a trastuzumab based treatment, treatment dose, treatment duration, permanent and temporary discontinuation and reasons for treatment discontinuation or switch at the end of neratinib treatment as an extended adjuvant therapy for early-stage HER2+ breast cancer. All relevant information up to the end of the study observation period will be collected. Additionally, treatment

persistence, median time to permanent discontinuation and median time to first dosage modification will also be evaluated via Kaplan-Meier estimates.

The following data will be collected to describe treatment patterns during neratinib use as an extended adjuvant therapy:

- End date of preceding trastuzumab treatment
- Initial dosage, Start and end date (if applicable)
- Dosage modifications (if applicable): dates, new dosage, reason for modification
- Neratinib discontinuation: date and reason for permanent or temporary discontinuation, duration of temporary discontinuation, subsequent treatment after discontinuation
- Subsequent treatment(s) upon disease recurrence or treatment discontinuation
- Concomitant endocrine therapy (for HR+ patients): type, start date, stop date
- Others concomitant treatment (if any): type, start date, stop date
- Corrective treatment for relevant AEs

2. Treatment history for breast cancer before neratinib initiation will be described. The following data will be collected:
    - Prior anti-cancer drugs/therapies/procedures for breast cancer: type, medication name, start date and stop date
    - Type of surgeries and date
    - Radiotherapy after surgery (Yes/No): date and area
    - Prior neoadjuvant and/or adjuvant anti HER2-directed therapy(ies) (including trastuzumab): type, start date and stop date
    - Outcome of neoadjuvant/ treatment (if applicable): pathologic complete response (pCR) or no pCR
    - Concomitant endocrine therapy

3. Frequency of relevant AEs during treatment with neratinib as an extended adjuvant therapy will be determined. Relevant AEs will be defined as all SAEs or AEs leading to dose adaptation or treatment discontinuation, and AEs of interest.

    The following are some AEs of interest: occurrence of diarrhea (onset/resolution dates, maximum grade, actions taken), gastro-intestinal toxicity (nausea, vomiting, abdominal pain, constipation), hepatic disorders, cardiac disorders, pulmonary disorders, pancreatitis, and reproductive and developmental disorders.

    All relevant AE data will be extracted from medical records and mapped into the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred term (PT).

4.3.3 Exploratory outcomes

Effectiveness will be evaluated only on HR+ patients based on the following outcomes, until the end of study observation period:

1. Characterization of first recurrence patterns (location, distribution, size, date)
2. iDFS, defined as the time from neratinib treatment initiation to:
    a. First ipsilateral invasive breast cancer recurrence
    b. First regional invasive breast cancer recurrence
    c. First contralateral invasive breast cancer recurrence
    d. First distant tumor recurrence
    e. Death attributable to any cause.
3. DDFS, defined as the time from neratinib treatment initiation to the first distant tumor recurrence or death from any cause.
4. Incidence of CNS metastasis (either isolated or concurrent with other metastatic sites), defined as the time from neratinib initiation to CNS recurrence as first distant recurrence.
5. OS, defined as the time between neratinib treatment initiation (for early breast cancer) and death (due to any cause)

The following key data items will be collected for the **first three** clinical exploratory outcomes:

1. Recurrences after neratinib initiation: date of documented recurrence and site of recurrence, including size and distribution.
    a. Invasive ipsilateral breast tumor recurrence
    b. Invasive contralateral breast cancer
    c. Local/regional invasive recurrence
    d. Appearance / Occurrence of metastasis /Distant recurrence, including CNS metastasis
2. Date of death and cause of death (related to this cancer, non-breast cancer related, related to another cancer, related to neratinib, other, unknown)
3. Date of last patient visit during follow-up (if applicable)

4.3.4 Subgroups of interest

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 of these subgroups, subject to pertinence and the number of patients in each subgroup.

1. Nodal status at initial diagnosis (0, 1-3, ≥ 4), Tumor size at initial diagnosis (T1, T2, ≥ T3), Stage I vs Stage II+III
    a. Low risk (Stage I and N- or pCR) vs high risk (Stage II/III or N+ or no pCR)
2. Previous adjuvant or neoadjuvant therapy (Yes/No)
3. Residual disease after neoadjuvant treatment (no pCR)
4. Prior trastuzumab-based regimen (trastuzumab only/ trastuzumab and pertuzumab/ T-DM1)

4.4 DATA SOURCES

Data for each patient will be collected from the date of neratinib treatment initiation up to the end of the study observation period (or date of death, study withdrawal, or lost-to-follow-up, if these come

first). Patients lost to follow-up will be censored at the date of their last available medical record. A data collection schedule is provided in Table 1. Data at following timepoints during the Study Observation Period will be collected: (a) at baseline; (b) at the index date; (c) 1 month, 2 months, 3 months, 6 months, 12 months after the index date; and (d) at any additional tumor assessment visits

The source of collected data will include all elements that constitute a reliable source of patient-level information and are available at the center. This includes inpatient medical charts (e.g., consultation notes, discharge summaries, laboratory test results, recorded prescription data and any other documentation of communication with other health care providers). The center investigator will be responsible for ensuring that all the required data is collected and entered into an eCRF. The data will be anonymized during the entry into the eCRF by using an algorithm which generates a patient number without any indication of the patient. This anonymization will be maintained in the database used for statistical analysis.

Key data items that will be collected are listed in section 4.3, Study outcomes.

4.5 STUDY 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.

We estimate the number of patients to be up to 200 patients. Using the table below, the precision estimates for a 95% confidence interval were calculated around proportions ranging from 10% to 50% for a sample size between 150 and 500 patients (see Table 2).

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.

Table 2. Precision estimates for a 95% confidence intervals around proportions

Precision estimate*	Proportion				
Sample size	10%	20%	30%	40%	50%
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%
350 patients	3.1%	4.2%	4.8%	5.1%	5.2%
400 patients	2.9%	3.9%	4.5%	4.8%	4.9%
450 patients	2.8%	3.7%	4.2%	4.5%	4.6%
500 patients	2.6%	3.5%	4.0%	4.3%	4.4%

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

4.6 DATA MANAGEMENT

A data management plan will be created before the start of data collection and will describe all functions, processes, and specifications for data collection, cleaning and validation to ensure that the data are as clean and accurate as possible when presented for analysis. Data collection and validation procedures will be detailed in the appropriate operational documents.

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented. Data quality control (QC) will be performed remotely and at the center level, where permissible according to local regulations, by qualified designated personnel under professional secrecy.

All medical data will be confidential. Pierre Fabre, as the Sponsor of the study and data controller, is responsible for the processing of personal data in accordance with the provisions of Regulation 2016/679/EU of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of such data (GDPR), the data collected being for research purposes in the field of health, the legal basis of the processing being the legitimate interest of the data controller.

Data from patient medical records will be entered by the investigator or delegated data entry specialists in the eCRF. Data entered in the eCRF will be sent to a central database via a secure transfer. The qualified designee for data entry must ensure that:

- Data entry is performed in a timely manner
- Data entry is complete and accurate
- All eCRF data are verifiable in the source documentation
- Data queries are resolved and documented by authorized study staff
- All eCRFs are approved with an electronic signature (changes to data previously submitted will require a new electronic signature to acknowledge/approve the changes).

Data entered into the eCRF will be reviewed for consistency by using both automated logical checks (issuing in automatic queries generated by the system) and manual review (issuing in manual checks into the eCRF). For each detected inconsistency, a case report form specific query will be generated (automatic or manual) and the investigator or data entry specialist will be responsible to correct or update any information that is incorrect or incomplete. An audit trail within the system will track all changes made to the data.

All data collected within the eCRF will be approved and electronically signed and dated by the investigator or designee. This approval will acknowledge the investigator's review and acceptance of the data as being complete and accurate.

At study end and before the final statistical analysis, the eCRF and other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

Quality assurance department representatives from Pierre Fabre and/or Contract Research Organization (CRO) may visit a study center to conduct quality assurance audit and ensure the study is conducted in compliance with protocol, Standard Operating Procedures and all applicable legal requirements (section 4.8).

4.7 DATA ANALYSIS

4.7.1 General considerations

All statistical analyses will be performed by using statistical analysis system (SAS)® version 9.4 or higher (SAS Institute, Cary, NC, USA). A detailed Statistical Analysis Plan (SAP) will be validated by the Sponsor before the database lock. Should there be any major changes in the planned analyses, an amendment to the SAP will be made prior to database lock. Deviations from the SAP after database lock will be outlined in the clinical study report and/or statistical analysis report.

Study outcomes will be analyzed for the full analysis set (comprising of all patients enrolled in the study), and also by country and other predefined subgroups of interest (see section 4.3.4), which will be detailed in the SAP. Where possible, and if allowed by the number of patients, a descriptive analysis of the outcomes across various subgroups will also be performed in an exploratory manner.

4.7.2 Analysis of primary and secondary outcomes

Appropriate summary statistics will be used depending on the nature of the variables, and the number of available and missing data will be specified for each variable. Categorical variables will be presented as frequencies and proportions, and continuous data will be expressed as median, mean, standard deviation, range, and quartiles (Q1 and Q3). The 95% CI will be presented upon relevance to the analysis.

In order to supplement descriptions of neratinib treatment patterns, Kaplan-Meier estimates for treatment persistence, median time to permanent treatment discontinuation, and median time to first treatment modification will also be provided.

4.7.3 Analysis of exploratory outcomes

Time-to-event data (iDFS, DDFS and OS) and cumulative incidence of CNS metastasis will be evaluated using Kaplan-Meier's method and time will be expressed in months. Median survival estimates will be reported along with the 1st and 3rd quartiles, and the corresponding 95% CI. For the description, Kaplan-Meier estimates will be presented with a summary of associated statistics (number of events, number of censored data / median, Q1 and Q3 survival time / estimate rates of patients not presenting the event of interest at 1, 3, 6, 9 ,12 months) including the corresponding two-sided 95% confidence intervals.

Range of follow-up will be provided using Reverse Kaplan-Meier method.

Cox regression analysis may be performed to adjust for predefined baseline covariates, which will be detailed in the SAP.

For OS, 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.

4.7.4 Missing data

In general, missing data will not be imputed (except for dates) and the data will be analyzed according to the complete case approach. Proportion of missing data will be provided for all variables during descriptive analyses.

4.8 QUALITY CONTROL

After formal agreement of participation, centers will be trained in the protocol's procedures by a designated Clinical Research Associate. The frequency of subsequent contacts (monitoring on center visits, phone or e-mail) with the centers will be decided with the Sponsor and will be adapted if specific difficulties are identified during the training. A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented. Data QC will be performed remotely and at the center level, where permissible according to local regulations, by qualified designated personnel under professional secrecy.

Taking into account the context of the COVID-19 pandemic, no additional sanitary restrictions will be necessary other than the measures already set up at participating centers to ensure patient safety.

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of national authorities, and local health authorities as applicable, the Sponsor and representatives, and the IRB/IEC for each study center. The investigator will permit authorized representatives of the Sponsor, the respective national or local health authorities, and auditors to inspect facilities and records relevant to this study.

The Sponsor or representative CRO is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the Sponsor or representative CRO applicable SOPs, completeness, accuracy and consistency of the data, and adherence to the Good Pharmacovigilance Practice (GVP): Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (EMA/873138/2011Rev 2), ICH GCP (ICH E6) and local regulations on the conduct of clinical research. Source data to be reviewed during this study will include but will not be restricted to: patient medical files, patient questionnaires (if applicable), patient's original laboratory test, histology, and pathology reports. All key data must be recorded in the patient hospital notes.

During and/or after completion of the study, quality assurance auditor(s) named by the Sponsor or the regulatory authorities may wish to perform on-center audits. The investigator will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

The Sponsor representatives are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that patient confidentiality is respected.

The investigator agrees to cooperate with the monitors to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

4.9 STUDY MANAGEMENT

Pierre Fabre is the Sponsor of the study. The Sponsor will be responsible, among others, for:

- Initiating, managing, and financing the study
- Selecting the qualified Principal Investigators
- Providing necessary information to the study centers to allow them to successfully conduct the study
- Obtaining the investigator agreement from all participating study centers
- Ensuring that the required regulatory approvals / favorable opinions are received
- Ensuring that any modifications required by the ethics committee or regulatory authority are implemented
- Performing and documenting root cause analysis and implementing appropriate corrective and preventive actions if non-compliance significantly affects or has the potential to significantly affect subject protection or reliability of clinical study results
- Ensuring that study procedures comply with applicable regulation for data protection.

4.10 LIMITATIONS OF THE RESEARCH METHODS

The biggest strength of this study is that it will be able to yield data on the utilization of neratinib and its effectiveness in real-life conditions of use and in the current treatment landscape, and in a more varied profile of patients (for example, those with more advanced disease or with certain comorbidities) than those who were evaluated as part of the pivotal ExteNET trial.

However, an observational and retrospective study comes with its limitations which are as follows:

1. Selection bias: Patients (or their next of kin/legal representative) who refuse to participate may limit the representativeness of the study results. Confounding can occur due to unobservable characteristics of patients. Even though a screening log would be established to record the details of patients who received neratinib as part of the EAP in Europe, irrespective of study inclusion status, it would only record patient demographic characteristics. Investigators will be asked to prospectively enroll consecutive patients who meet the eligibility criteria.
2. Retrospective design: since all data in the study will be extracted from past medical records, investigators will have no control over how the data was recorded and managed prior to the study. Furthermore, this retrospective design implies limited control over the exposure (neratinib treatment), covariates and potential confounders.
3. Attrition bias: Patients lost to follow-up and patients who withdraw their consent will be the main source of attrition bias in this observational study. This can threaten sample representativeness if too many patients are lost to follow-up or if they differ from those who are continuing follow-up. Should the proportion of patients lost to follow-up be non-negligible, the target precision will not be reached. To minimize any risks and potential impact, efforts will be undertaken to collect the data from the lost-to-follow-up patient's most recent visit. Baseline characteristics of patients lost-to-follow-up/withdrawn and those who completed the study may be compared, to evaluate representativeness.
4. Missing data: Depending on physician practices, some data might not be systematically measured or available (such as data on AEs). Missing data can bias the descriptions if it is not completely random. Even in cases where missing data is truly random, a potential impact on the precision of

the estimates cannot be overlooked. Remote Monitoring procedures will be implemented, wherein it will be ensured that the eCRFs have been comprehensively filled. Sensitivity analyses may be carried out, where applicable, to estimate the impact of missing data on the study's outcomes. Furthermore, if a non-negligible proportion of missing data is observed for a certain parameter, groups of patients with and without missing data may be compared.

5. Heterogeneity between study centers: since this is an observational study of real-life neratinib use in the context of a European EAP, prescription modalities and patient follow-up schedules can vary widely based on standard practices in each country and/or investigating center. This could lead to an over or under-reporting of certain data (such as AEs). Where deemed appropriate subgroup analyses by country could be performed for certain outcomes or variables of interest.

Further details on how biases in the study design are to be addressed will be elaborated in the SAP.

5 PROTECTION OF HUMAN SUBJECTS AND LOCAL REGULATORY ASPECTS

The study will be conducted in accordance with the ethical principles of the declaration of Helsinki and the General Data Protection Regulation (UE 2016/679) and other local regulatory requirements. The need to submit the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent will be considered in accordance with local law. Any amendments to the study protocol, as well as the associated ICF will be submitted to the appropriate IRB/IEC for approval prior to implementation, according to the requirement of each IRB/IEC.

This observational study does not involve any changes in the local care standards of the patients participating in the study, does not compromise their physical or psychological integrity and does not require any special follow-up visits for these patients. Each patient will be fully informed before enrollment in the study and start of data abstraction, and their written consent or verbal non-opposition will be taken, as per the local regulations of each target country. Wherever applicable, an ICF waiver will be obtained, depending on approval by Ethics Committees and/or local regulations.

Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. In case of sub-contracting, it is the responsibility of the service provider concerned to ensure that computerized processing is in conformity with the applicable national regulations regarding the protection of personal data and, if necessary, carry out any formality with the supervisory authorities and transmit the declaration date to Sponsor.

The investigator must ensure that patient confidentiality is maintained. It is required that the investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the institutional ethics committees' direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. Access to the patient's medical file is to be granted under the supervision and responsibility of the principal investigator or their center personnel. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to their study-related records without violating the confidentiality of the patient. The study will be registered on ClinicalTrials.gov and will be in national registries where applicable.

6 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a retrospective, observational, longitudinal study. As this is a study based on secondary use of data from the EAP, it will not be necessary to collect and transmit the AEs/adverse reactions data to Pierre Fabre Pharmacovigilance team. The system of Pharmacovigilance data collection from the EAP is already put in place prospectively. Therefore, safety data are already recorded in the Pierre Fabre Pharmacovigilance safety database, reported, and analyzed.

According to the study objectives, data on relevant AEs will be collected and analyzed. Relevant AEs will be defined as all SAEs or AEs leading to dose adaptation or treatment discontinuation, and AEs of interest. The following are some AEs of interest: occurrence of diarrhea (onset/resolution dates, maximum grade, actions taken), gastro-intestinal toxicity (nausea, vomiting, abdominal pain, constipation), hepatic disorders, cardiac disorders, pulmonary disorders, pancreatitis, and reproductive and developmental disorders.

7 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data will be analyzed and presented in a final report which will be submitted to the Sponsor. This final report will help in the preparation of one or more publications.

Any written or oral communication of the research results will receive prior consent of the Sponsor and, if necessary, of any committee formed for the research. All publications will follow the International Committee of Medical Journal Editors (ICMJE, 2010) guidelines. In addition, communication in appropriate scientific meetings will be considered.

8 REGULATORY CONSIDERATIONS

8.1 CONFIDENTIALITY

The subject matter and aim of the Study, all information, data relating to the Study or any product studied provided to ..... and/or their collaborators during the term of this agreement and all results of the Study (hereinafter collectively called the "Information") will be maintained confidential for an unlimited time period by ..... and/or their collaborators.

In addition, all Information shall not be used by ..... for any other purpose than the one described in this Agreement.

The above obligations shall, however, not apply to:

- Information which at the time of disclosure to ..... is part of the public knowledge,
- Information, which, after disclosure, becomes part of the public knowledge through no fault of .....,

- Information which ..... can establish by competent proof was in its possession prior to disclosure hereunder and was not acquired from PFM, directly or indirectly under a secrecy obligation,
- Information which is subsequently obtained lawfully from a third party without any secrecy obligation and was not acquired by such third party from PFM, directly or indirectly under a secrecy obligation.

No publication or communication relating to the Study or the results thereof, in written or oral form, shall be made by ..... and/or their collaborators, without PFM's prior written consent.

8.2 OWNERSHIP OF RESULTS

The results of the Study shall be owned exclusively by PIERRE FABRE MEDICAMENT's and PIERRE FABRE MEDICAMENT and/or any designee shall have free use of the same in France and worldwide.

Such ownership shall apply to any data, patentable or non-patentable inventions, know-how and any invention resulting from the Study.

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