Study protocol ML29844

OUTCOMES OF THE SPANISH COHORT OF EARLY ACCESS TO PERTUZUMAB AND TRASTUZUMAB EMTANSINE

KNOWHER STUDY

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2 List of abbreviations

Term	Definition
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AEMPS	Spanish medicines agency
AESI	Adverse events of special interest
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CU	Compassionate use
CRF	Case report/record form
CSR	Clinical study report
DOR	Duration of response
EAP	Early access programs
ECOG PS	Eastern cooperative oncology group performance status
eCRF	Electronic case report form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Estrogen receptors
EU	European Union
GPP	Good pharmacoepidemiology practices
HER	Human epidermal growth factor receptor
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	Intravenous
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall survival
PAS	Post-authorization study
PFS	Progression-free survival
PgR	Progesterone receptors
PR	Partial response
REC	Research ethics committee
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics

T-DM1	Trastuzumab emtansine
TTNT	Time to next treatment
ULN	Upper limit of normal

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4 Abstract

Title: OUTCOMES OF THE SPANISH COHORT OF EARLY ACCESS TO PERTUZUMAB AND TRASTUZUMAB EMTANSINE

Version: 2.0. **Date:** October 2016

Rationale and background: Currently, four targeted anti-HER2 agents are available in the EU for the treatment of advanced HER2+ breast cancer: trastuzumab (a humanized monoclonal antibody that targets subdomain IV of HER2), lapatinib (a HER1/HER2 dual tyrosine kinase inhibitor) and, more recently, pertuzumab (a humanized monoclonal antibody that targets domain II of HER2) and trastuzumab emtansine (an antibody-drug conjugate). Three of these

agents have been approved in combination with chemotherapy: trastuzumab, lapatinib (also authorized in combination with trastuzumab), and pertuzumab. Trastuzumab emtansine (T-DM1) is the only targeted agent currently approved as monotherapy. The addition of pertuzumab (Perjeta®) to trastuzumab plus chemotherapy (docetaxel) in first line treatment of HER2-positive metastatic breast cancer obtains a significant and clinically relevant increase in median PFS of 6.1 months. Both Kadcyla® and Perjeta® were available under those special access systems. In order to be eligible for CU of Trastuzumab emtansine (T-DM1) or Pertuzumab, patients had to meet the some prespecified criteria. After the EU approval, oncologists could prescribe the product to specific patients through the Early Access Program, provided that the local or regional responsible people accept payment.

In order to evaluate the effectiveness and safety of Trastuzumab emtansine (T-DM1) and Pertuzumab in HER2-positive metastatic breast cancer under real-world disease conditions, is proposed a retrospective observational cohort non-comparative study / registry in Spain.

The analysis of the efficacy and safety results obtained in patients receiving pertuzumab or TDM1 in those early access systems is of utmost importance. These real-world patients with advanced breast cancer may have different characteristics than those enrolled in clinical trials and clinicians must often extrapolate into therapeutic decisions not fully supported by a robust evidence. Furthermore, as therapy evolves and new treatments are available, it becomes difficult to conduct randomized controlled trials of all potential sequences and combinations. In this context, the analysis of data from our early access cohort is an opportunity for obtaining additional information in specific conditions different to those included in clinical trials and similar to those found in many real-world patients

Research question and objectives: The overall study objective is to evaluate the effectiveness and safety of Trastuzumab emtansine (T-DM1) and Pertuzumab under real-world disease conditions in the Spain, and specifically in patients treated under compassionate use or early access program

- **Primary objective:**

To evaluate the effectiveness of Trastuzumab emtansine (T-DM1) and Pertuzumab in patients with HER2-positive MBC treated under compassionate use or early access program.

- **Secondary objectives:**

- To evaluate the safety of T-DM1 and Pertuzumab in patients with HER2-positive MBC under compassionate use or early access program in terms of severe or life-threatening/ disabling adverse reactions (grade 3/4/5) , adverse events of special interest and other AEs of scientific interest. The incidence of pertuzumab/T-DM1 induced cardiac dysfunction will be estimated in our population.
- To describe anti-HER2 outcome in later lines
- To describe the rate of re-biopsies and the changes of HER 2 status.
- To describe the efficacy of pertuzumab and T-DM1 in rebiopsed/retested HER2-positive breast cancer patients.
- To evaluate the delay in the early access procedure in real world, as measured by time elapsed since physician's first request to time of medicine administration to the

patient.
- To describe the use of different treatment regimens and the sequences of treatment regimens across the advanced disease.
- To describe characteristics of patients with HER2-positive MBC treated with Trastuzumab Emtansine (T-DM1) or Pertuzumab in the context of the early access systems, and to compare the characteristics of this cohort with the population included in clinical trials.
- To examine utilization or adherence to pre-defined clinical guidelines and Summary of product characteristics (SPC).

Study design: This is a retrospective, non-interventional, non-comparative, observational cohort study / registry in the Spain. The study design will reflect real-life clinical management of patients with HER2-positive MBC. Type and frequency of actual patient visits and all evaluations will be done as for routine clinical practice.

Population: This study will include a cohort of approximately 600 adult patients with HER2-positive MBC and who are treated with Trastuzumab emtansine (T-DM1) and Pertuzumab under under compassionate use or early access program.

Variables / Outcomes:

- ***Study treatment exposure:*** Trastuzumab emtansine (T-DM1) and Pertuzumab
- ***Patient, disease, and clinical characteristics***
- ***Safety:*** Adverse events will be registered, coded, and categorized using the Medical Dictionary for Regulatory Activities (MedDRA).
- ***Effectiveness:*** The measures include overall survival (OS) and progression-free survival (PFS), Best overall response rate, duration of response (DOR), time to treatment failure, time to Objective Response and time to change treatment.

Data sources: Compassionate and early access existing registries for Trastuzumab emtansine and Pertuzumab and individual Patient medical records. Data will be transferred to the specific electronic case report forms (eCRFs).

Study size: It is a descriptive study, in which we intend to include the majority of the patients who were treated in the context of Early Access. A number of 709 patients have been included in the CU and early access program and all of them are potential study cases. It is expected that more than 500 patients will be included into the anonymized study database. This amount is approximately 70% of the total population of potential patients, so it can be considered representative of the population; also all patients included in the final database will be evaluated without any restrictions or additional conditions.

Data analysis: A descriptive analysis will be conducted to evaluate the safety of Trastuzumab emtansine (T-DM1) and Pertuzumab. Categorical measures will be summarised as counts and percentages, while continuous measures will be summarised using mean, median, standard deviation, and range.For effectiveness outcomes, OS and PFS, Kaplan-Meier estimates (including curves) will be generated. The median and survival rates at given time points (for example, 3 months, 6 months, 9 months, 12 months) will be computed together with their

95% CIs using the Kaplan-Meier method. Best tumour response, treatment patterns and drug accessibility will be summarised descriptively.

5 Amendments and updates

6 Milestones

Milestone	Planned Date
Final design and AEMPS classification	November 2015
Regulatory procedures for PAS studies	December 2016
Start of data collection	January 2017
End of data collection	April 2017
Final report of study results	June 2017

7 Rationale and background

Breast cancer is the most commonly diagnosed cancer in women. In Spain, 25.215 new cases of breast cancer were diagnosed in 2012 (1). Most cases of breast cancer are diagnosed at localized stages but approximately 5% of patients have metastases at diagnosis, and around 20% of patients with localized disease will eventually relapse. In Spain, the 5-year survival rate for patients with disseminated disease is 20-30% (2, 3).

Between 15-20% of invasive breast cancers are HER2+ (4) whose prognosis has improved significantly with the availability of targeted anti-HER2 therapies. Currently, four targeted anti-HER2 agents are available in the EU for the treatment of advanced HER2+ breast cancer: trastuzumab (a humanized monoclonal antibody that targets subdomain IV of HER2), lapatinib (a HER1/HER2 dual tyrosine kinase inhibitor) and, more recently, pertuzumab (a humanized monoclonal antibody that targets domain II of HER2) and trastuzumab emtansine (an antibody-drug conjugate). Three of these agents have been approved in combination with chemotherapy: trastuzumab, lapatinib (also authorized in combination with trastuzumab), and pertuzumab. Trastuzumab emtansine (T-DM1) is the only targeted agent currently approved as monotherapy.

Pertuzumab (Perjeta®) is a humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. The addition of pertuzumab (Perjeta®) to trastuzumab plus chemotherapy (docetaxel) in first line treatment of HER2-

positive metastatic breast cancer obtains a significant and clinically relevant increase in median PFS of 6.1 months (from 12.4 months to 18.5 months, hazard ratio [HR] = 0.62; 95 %: 0.51 to 0.75; P <0.001) and in median of OS of 15.7 months (from 40.8 months to 56. 5 months, hazard ratio [HR] = 0.68; 95 %: 0.56 to 0.84; P <0.001) , according to results of the phase III CLEOPATRA clinical trial (5,6).

Perjeta® obtained in March 2013 a marketing authorization valid in all the European Union for its use, in combination with trastuzumab, in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Perjeta® was included in the Spanish National Health System in July 2014, 16 months after the approval and 30 months after the scientific first publication of the CLEOPATRA clinical trial results (5).

Trastuzumab etamsine, (T-DM1, Kadcyla®), is a HER2-targeted antibody-drug conjugate which contains trastuzumab, covalently linked to the microtubule inhibitor DM1. Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1 and conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells. In Phase III clinical trial EMILIA (13), Kadcyla® was related to a significant and clinically relevant increase of PFS, increasing median from 6.4 months to 9.6 months (HR = 0.65; 95% CI: 0.55 to 0.77; p <0.001) as compared with the combination of Lapatinib plus capecitabine in patients with advanced breast cancer HER2 positive and that had progressed after previous treatment with Herceptin plus a taxane (7). It also produced a significant increase of OS from 25.1 months to 30.9 months (HR = 0.68, 95% CI: 0.55 to 0.85; P < 0.001) (8).

Kadcyla® was approved in the European Union in November 2013 for its use, as a single agent, as treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. In July of 2015, it was included in the National Health System, 20 months after the approval and 33 months after the scientific publication of the main clinical trial results (7).

In Spain, a new medicine cannot be launched until the decision of price and reimbursement within the National Health System is taken. This implies a variable delay from first publication of efficacy results or regulatory approval until full commercial availability. A substantial number of patients could receive a new medicinal product in Spain, before the start of regular commercial use, under the so called “access in special conditions”. This special access includes

compassionate use (CU) and early access programs (EAP). CU refers to access before the EU approval and EAP refers to access during the period elapsed between the EU approval and the commercialization in Spain.

Both Kadcyla® and Perjeta® were available under those special access systems. In order to be eligible for CU of Trastuzumab emtansine (T-DM1) or Pertuzumab, patients had to meet the some prespecified criteria. After the EU approval, oncologists could prescribe the product to specific patients through the Early Access Program, provided that the local or regional responsible people accept payment.

Under CU, 51 patients received pertuzumab and 68 received TDM 1 as compassionate use. Within the EAP, 166 patients received pertuzumab and 424 received TDM1. Patients were included in 166 different hospitals in Spain. All patients had been followed according to clinical practice standards and also complying with the requirements of the compassionate or early access program, including local or regional requirements for register and follow-up.

The analysis of the efficacy and safety results obtained in patients receiving pertuzumab or TDM1 in those early access systems is of utmost importance. These real-world patients with advanced breast cancer may have different characteristics than those enrolled in clinical trials and clinicians must often extrapolate into therapeutic decisions not fully supported by a robust evidence. Furthermore, as therapy evolves and new treatments are available, it becomes difficult to conduct randomized controlled trials of all potential sequences and combinations. In this context, the analysis of data from our early access cohort is an opportunity for obtaining additional information in specific conditions different to those included in clinical trials and similar to those found in many real-world patients.

8 Research question and objectives

Primary Objective

To evaluate the effectiveness of Trastuzumab emtansine (T-DM1) and Pertuzumab in patients with HER2-positive MBC treated under compassionate use or early access program.

Secondary Objectives

The secondary objectives for this study are as follows:

- To evaluate the safety of T-DM1 and Pertuzumab in patients with HER2-positive MBC

under compassionate use or early access program in terms of severe or life-threatening/ disabling adverse reactions (grade 3/4/5) , adverse events of special interest and other AEs of scientific interest. The incidence of pertuzumab/T-DM1 induced cardiac dysfunction will be estimated in our population.

- To describe anti-HER2 outcome in later lines
- To describe the rate of re-biopsies and the changes of HER 2 status.
- To describe the efficacy of pertuzumab and T-DM1 in rebiopsed/retested HER2-positive breast cancer patients.
- To evaluate the delay in the early access procedure in real world, as measured by time elapsed since physician's first request to time of medicine administration to the patient.
- To describe the use of different treatment regimens and the sequences of treatment regimens across the advanced disease.
- To describe characteristics of patients with HER2-positive MBC treated with Trastuzumab Emtansine (T-DM1) or Pertuzumab in the context of the early access systems, and to compare the characteristics of this cohort with the population included in clinical trials.
- To examine utilization or adherence to pre-defined clinical guidelines and Summary of product characteristics (SPC).

9 Research methods

9.1 Study design

This is a multicenter, retrospective study to describe the results obtained in patients treated with pertuzumab or T-DM1 under early access programs for their HER2-positive metastatic or locally recurrent unresectable breast cancer in Spain.

Patients to be analyzed are those that have received T-DM1 or Pertuzumab (together with Trastuzumab) in Spain before commercial accessibility (30th June 2014 for pertuzumab and 17th June 2015 for TDM-1). All cases have been approved through the special access medicines system of the Spanish Medicines Agency (AEMPS), after submission of the clinical report by the

responsible physician with the agreement of the hospital. Patients had given their informed consent for the treatment and had been treated and followed in accordance with their treating physician's standard practice and the local or regional requirements.

The proposed study is a collection of data from the medical records or from local or regional existing registers. The registered cohort includes 709 patients distributed in 166 centers nationwide. All Medical Oncology departments of all hospitals with at least one patient will be invited to participate. Clinical data will be collected by the clinical site personnel and entered into a specific electronic case report forms via a Web-based password-protected/HIPAA compliant system.

A specifically trained health care professional will visit the clinical centers in the period between mid-February 2016 and 30st of April 2017 (approximate period) in order to monitor the quality and accuracy of collected data. Only one visit per centre is planned.

9.2 Setting

The study population will be all HER2-positive BC patients who were entered into the Spanish compassionate use or Early Access Program of T-DM1 or Pertuzumab and their responsible physician has introduced their data into the study database. Type and frequency of actual patient visits and all evaluations have been cdone as for routine clinical practice.

9.2.1 Definition of the Disease

HER2-positive metastatic or locally recurrent unresectable breast cancer

9.2.2 Study Population

This study will include a cohort of approximately 700 adult patients from the Spain with HER2-positive metastatic or locally recurrent unresectable breast cancer and who are treated with Trastuzumab emtansine (T-DM1) and Pertuzumab under compassionate use or early access program. The decision to initiate use of Trastuzumab emtansine (T-DM1) and Pertuzumab is made independently by the participant and their health care provider and is not mandated by the study design or protocol.

9.2.2.1 Inclusion Criteria

[1] Adult patients (age $\geq$ 18 years at enrolment) with HER2-positive metastatic or locally recurrent unresectable breast cancer and who are treated with

[2] Patients who initiate Trastuzumab emtansine (T-DM1) and Pertuzumab under Spanish compassionate use or early access program.

9.2.2.2 *Exclusion Criteria*

Given the characteristics of the study there are no exclusion criteria.

9.2.3 Duration of the Study

The collection of data from patient's hospital medical records will be performed in a 3 months period .

9.2.4 Site Recruitment and Physician Selection

The study will be implemented in a total of 166 sites in Spain; these hospitals were those that requested the compassionate use for at least one patient. All patients had been followed according to clinical practice standards and also complying with the requirements of the compassionate or early access program, including local or regional requirements for register and follow-up.

9.3 Variables

9.3.1 Patients and disease characteristics

The following information will be collected if available:

- Patients: age, BSA, race and ethnicity, menopausal status, ECOG PS, concomitant disease
- "de novo" metastatic disease/ recurrent breast cancer
- Tumour: TNM, ER, PgR and HER2 status, histological type, histological grade, Ki67 and any other biomarker or genetic platform performed (at diagnosis and at recurrence if available), type of metastasis sites, visceral disease/ no visceral disease, diagnosis date.

9.3.2 Anti-cancer Treatment

The following information regarding study treatment administration will be collected, if available:

- (Neo) Adjuvant treatment: dates, names(by Anatomical Therapeutic Chemical (ATC)Classification System)

- Treatment for advanced cancer
    - Surgery: date, type of surgery
    - Radiation therapy: dates of initiation and finalisation
    - Chemotherapy: dates, names (by Anatomical Therapeutic Chemical (ATC)Classification System)
    - Endocrine therapy: dates, names (by Anatomical Therapeutic Chemical (ATC)Classification System)
    - Targeted therapy: dates, names, administration route, doses and number of cycles per regimen (by Anatomical Therapeutic Chemical (ATC)Classification System)

9.3.3 Effectiveness Outcome Measures

- Overall survival. Defined as the time between the date of start of treatment and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.
- Progression free survival. Defined as the time from start of treatment to the date of the first documented tumour progression as determined by the clinician (may be based on clinical examination or radiographic or laboratory features).
- Best overall response rate. Response rate is defined as the proportion of patients with complete response (CR) or partial response (PR) based on their best overall response as written in the medical record.
- Duration of response (DOR). Defined as the time between the date of first confirmed response to the date of the first documented tumour progression, or death due to any cause, whichever occurs first. At the time of the analysis, several limitations should be taken into consideration for this restrospective study: DOR is only appraisable if measurable disease and DOR data availability in the medical records (ideally assessed with the RECIST criteria) could be incomplete.
- Time to treatment failure (ie, time from start of treatment to date of investigator-assessed disease progression, treatment discontinuation due to toxicity or death from any cause).

- Time to Objective Response, defined as the time from start of treatment to the date of the first confirmed response (evaluated for responders only).
- Time to change treatment, time from start of treatment to date of end/discontinuation treatment.
- Time to next treatment (TTNT), time from end of primary treatment to institution of next therapy.

9.3.4 Safety Outcome Measures

In this study retrospective data will be collected from medical records or from local or regional existing registers. Data come from usual clinical practice and no mandatory schedule of assessment was in place. Due to this fact, only the following adverse events (AE) occurred since the start of treatment until 30 days after the end of treatment will be extracted from medical records:

- All suspected Grade 3/4/5 adverse reactions
- Adverse events of special interest to anti HER2 Mab (AESI), as reported by the oncologist in the medical record:
    - AESIs regarding treatment with T-DM1: Hepatic disorder (specific analytical alteration)
    - AESIs regarding treatment with Pertuzumab: Interstitial Lung Disease
- Other AEs of scientific interest (selected by the scientific committee)
    - An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment (regarding treatment with T-DM1 and Pertuzumab)
    - Other AEs leading to treatment discontinuation

For all extracted AE related to pertuzumab, the occurrence during chemotherapy or after chemotherapy discontinuation will be recorded.

Adverse events will be registered, coded, and categorized using the Medical Dictionary for Regulatory Activities (MedDRA).

9.3.5 Drug accessibility

- Date of first documented medical decision to treat or date of first documented action intended to obtain access to medicine
- Date of reception of the application by the Spanish Regulatory Agency
- Date of obtention of the administrative authorisation by the Spanish Regulatory Agency
- Date of receipt of the application by the marketing authorisation holder
- Date of delivery of medicine to the hospital pharmacy.
- Date of drug administration

9.4 Data sources

Information recorded per routine clinical practice in medical records (as described in Section 9.3) and in early access/compassionate use registries will be transcript to an electronic data capture (EDC) system. To ensure accurate, complete, and reliable data, the study physician will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the data entered by the site into the provided EDC system for this study. All data reported on the electronic case report form (eCRF) must be derived from and be consistent with the source documents, or the discrepancies must be explained.

9.5 Study size

It is a descriptive study, in which we intend to include the majority of the patients who were treated in the context of Early Access. A number of 709 patients have been included in the CU and early access program and all of them are potential study cases. It is expected that more than 500 patients will be included into the anonymized study database. This amount is approximately 70% of the total population of potential patients, so it can be considered representative of the population; also all patients included in the final database will be evaluated without any restrictions or additional conditions.

9.6 Data management.

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. Data quality standards will be maintained and processes and procedures will be utilised to ensure

that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

Datasets and analytic programs will be kept on a secure server and archived These datasets and analysis programs will be transferred to a data repository via a secure transfer system

9.6.1 Data Collection Schedule

This is an observational restrospective study, and the type and frequency of actual patient visits and evaluations have been done as for routine clinical practice. The physician will review the eligibility criteria (that is, patients with with HER2-positive MBC advanced whom a treated with Trastuzumab emtansine (T-DM1) or Pertuzumab under compassionate use or early access program) prior to data recollection.

9.6.2 Data to Be Collected

9.6.2.1 Patient Data

Information collected (as described in Section 9.3) as part of routine clinical practice will be transcribed to an eCRF. All data will be collected and entered directly into the EDC system. All participating sites will have access to the data entered regarding the individual sites own enrolled patients. Sites will be responsible for entering extracted patient data into a secure internet-based EDC database via the eCRF. Study physicians and site personnel will be able to access their account with a username and password.

The eCRF should be reviewed, electronically signed, and dated by the study physician. All changes or corrections to eCRFs should be documented in an audit trail and an adequate explanation is required. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

9.6.2.2 Missing Data

The eCRF will be designed to require certain items to be completed prior to advancing to the next item, thereby minimising missing data for required items. Select items may not be applicable to all patients and will be recorded appropriately in the eCRF.

9.6.2.3 Patient Withdrawal

Given the observational and retrospective nature of the study this section is not applicable.

9.6.3 File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the study sponsor, the physician agrees to keep records, including the identity of all participating patients, source documents, and adequate documentation of relevant correspondence. The records should be retained by the physician according to local regulations.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 12 years after completing participation in the study. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the study sponsor.

9.7 Data analysis

The study will be analyzed according to the Statistical Analysis Plan (SAP). All data will be analyzed. All included patients (Full Analysis Set) will be the primary analysis population for safety and efficacy parameters. Other analysis populations may be defined based on more restrictive criteria, such as patient receiving at least one anti-cancer treatment.

The analysis of the present study will primarily make use of descriptive statistical methods (i.e. number, mean, median, standard deviation, rate, range, and IC95% for the estimated parameters).

Where possible, and if allowed by the number of enrolled patients receiving different treatment regimens, a comparative analysis of the outcomes across various groups will also be performed.

If applicable, it will be calculated IC 95% for the estimated parameters in relevant subgroups, analysis of variance (t test or F test) or non-parametric testing, such as Wilcoxon's rank-sum test or Kruskal–Wallis test, will be used to test group differences on the continuous variables. All test performed will be two-sided and carried out with a 5% α-error rate without correction for multiplicity.

Categorical variables will be summarized by numbers and proportions, and, where applicable, chi-squared testing will be used to test group differences. The distribution of patients, as well

as the duration of receiving unique treatment regimens or sequences of treatment regimens for HER2-positive MBC, will be summarized by each line of treatment.

Time-to-event end points will be summarized by the Kaplan-Meier method, and multivariate Cox regression analysis will be performed to identify factors associated with these end points. .

9.8 Quality control

9.8.1 Data management.

The investigator will comply with the protocol (which has been given favorable opinion by the competent health authority), ICH GCP and applicable regulatory requirements as described in the Non-interventional Trial Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the responsible party.

9.8.2 Data Collection, Validation, and Quality Control

Information recorded as part of routine clinical practice will be transcribed to an eCRF.

Computerized handling of the data by the coordinator group may generate data queries to which the participating physician will be requested to respond by confirming or modifying the data questioned. In addition, data collection and validation procedures will be detailed in appropriate operational document.

9.8.3 Data Quality Control at Site Level

Data quality control will be performed on active sites (which have enrolled at least 1 patient).

Quality control will be performed by qualified designated personnel.

9.9 Limitations of the research methods

This retrospective, uncontrolled, observational, open-label, non-interventional multicenter cohort study will provide a real-life insight on the use of Trastuzumab emtansine (T-DM1) and Pertuzumab in patients with HER2-positive MBC treated under compassionate use or early access program. Given the observational and retrospective nature of the study, data collection will be limited to the extent of data available in the medical records.

Robust quality of clinical variables is expected, as the information is directly collected by the physicians.

Further, this study should provide a good overview of the target population treated in real world conditions, and the patients enrolled in this study should be comparable to ongoing trial populations

9.10 Other aspects.

9.10.1 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (that is substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant independent ethics committee (IEC) for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favourable opinion has been obtained.

9.10.2 Financing

The study will receive the support from the IIS Puerta de Hierro plus a grant from Roche intended to support the monitoring of the quality of the study data.

10 Protection of human subjects.

The study will be submitted to the Research Ethics Committee (REC) of the IIS Puerta de Hierro for revision and approval before start. A waiver for specific informed consent for this study will be sought, based on the study design and the adopted confidentiality measures. All patients have given their informed consent to be treated under early access conditions and to be included into the special register of early access

From a regulatory point of view, the study is planned as a retrospective observational study of an already existing cohort of patients. The cohort is composed by the patients treated before the approval of the medicinal product according to the data contained in the specific early access registers and the medical records. The study was sent to the Spanish Regulatory Agency (AEMPS) and was classified as a Post-authorisation study (PAS) with medicinal products with no prospective follow up. According to PAS regulation in Spain, the study will be notified to the AEMPS before starting data collection. Applicable regional procedures for non-prospective PAS will be followed in all involved regions.

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology

Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008) and the ethical principles laid down in the Declaration of Helsinki and its amendments.

11 Management and reporting of adverse events/adverse reactions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

For this study, all adverse events extracted as per protocol will be summarized in the CSR. This information will be summarised in separate tables with the information listed in section 9.3.4.

The study physician will record via eCRF all AEs ocurred in temporal association with drug under evaluation (Trastuzumab emtansine (T-DM1) and Pertuzumab) as defined in this protocol; as well as the following information for Trastuzumab emtansine (T-DM1) and Pertuzumab (regardless of whether there is an associated serious or non-serious AE);

- pregnancy exposures
- breast-feeding exposures
- overdoses
- misuse
- abuse
- off-label use
- medication error
- lack of drug effect
- suspected transmission of infectious agent

11.1 Serious Adverse Events

Study site personnel will extract from medical reports any SAEs occurring in temporal association with Trastuzumab emtansine (T-DM1) and Pertuzumab. A SAE is any AE from this study that results in 1 of the following criteria:

- death or death due to disease progression should not be reported as an SAE unless the physician deems it to be possibly related to the study drug
- initial or prolonged inpatient hospitalisation
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- or is considered significant by the physician for any other reason.

11.2 Adverse Event of Special Interest (AESIs)

Key selected adverse events (AESI) for this study have been defined in section 9.3.4. All the AESI identified in the medical records will be recorded in the eCRF.

12 Plans for disseminating and communicating study results

The investigator will comply with the publication policy as described in the Noninterventional Trial Agreement.

The study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Additionally, the study findings may be presented at a scientific congress and submitted to a peer-reviewed journal.

13 References

1. Sociedad Española de Oncología Médica (SEOM) 2014. Las Cifras del Cáncer en España 2014. Disponible en : http://www.seom.org/seomcms/images/stories/recursos/Las_cifras_del_cancer_2014.pdf (acceso abril 2015)
2. Martin M, Mahillo E, Llombart-Cussac A, et al. The “El Álamo” project (1990-1997): two consecutive hospital-based studies of breast cancer outcomes in Spain. Clin Transl Oncol 2006; 8(7):508-18.
3. Sant M, Allemani C, Berrino F, Coleman MP, Aareleid T, Chaplain G, et al. Breast carcinoma survival in Europe and the United States. Cancer. 2004 Feb 15;100(4):715-22.

4. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013 Nov 1;31(31):3997-4013

5. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366:109-19.

6. Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013; 14:461-71.

7. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367:1783-91.

8. Krop IE et al. Lancet Oncol.2014 Jun;15(7):689-99

Annex 1. List of stand-alone documents

Annex 2. ENCePP checklist for study protocols

Study title:
OUTCOMES OF THE SPANISH COHORT OF EARLY ACCESS TO PERTUZUMAB AND TRASTUZUMAB EMTANSINE

Study reference number:
ML29844

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-	☒	☐	☐	9.1

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
control, cross-sectional, new or alternative design)				
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☒	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.5
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9.2.2
4.2.1 Study time period?	☒	☐	☐	9.2.2
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☒	☐	☐	9.2.2
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3.5

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.1
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.3.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	11; 9.3.4
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6; 2.2
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.3
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6.3

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	10,1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5; 9.10.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: __Dra Ruiz Antorán_____

Date: 11/10/2016

Signature: _____

Annex 3. Additional information