NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Safety evaluation of biosimilar trastuzumab in breast cancer: Experience of Colombian institutions
Protocol number	A6181236
Protocol version identifier	1.0
Date	07 October 2022
European Union (EU) Post Authorization Study (PAS) register number	EUPAS49290
Active substance	Trastuzumab
Medicinal product	Biosimilar trastuzumab
Product reference	INVIMA 2019MBT-0019215
Marketing Authorization Holder(s) (MAH)	PFIZER S.A.S. Avenida Suba N° 95-66, Bogota 111211 Colombia
Joint PASS	No
Research question and objectives	**Primary Objective** To describe the frequency of adverse events (AEs) by degree of severity and anatomical group to establish the safety profile of the biosimilar trastuzumab used for breast cancer in Colombian healthcare institutions. **Secondary Objectives** Perform the clinical characterization of patients who were treated with the biosimilar trastuzumab for breast cancer. **Exploratory objectives** ●To calculate the overall survival (OS) and progression-free survival (PFS) in patients treated with the biosimilar trastuzumab for breast cancer. ● To explore the factors associated with effectiveness and safety in patients treated with the biosimilar trastuzumab for breast cancer.
Country(-ies) of study	Colombia

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Anatomical Therapeutic Chemical
AE	Adverse Event
AEM	Adverse event monitoring
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CSA	clinical study agreement
CTCAE	Common Terminology Criteria for Adverse Events
DALYS	Disability-adjusted life years
ECOG	Eastern Cooperative Oncology Group
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agengy
EU	European Union
FDA	Food and Drug Administration
GCP	Guideline for Good Clinical Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good pharmacovigilance practices
HEOR	Health economics and outcomes research
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
INN	International Nonproprietary Names
INVIMA	National Institute for Drug and Food Vigilance (*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*)
IPS	Institutional health service providers (*Instituciones Prestadoras de Servicios de salud*)
IRB	Institutional review board
ISPE	International Society of Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information Technology
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NI	Non-interventional
NIS	Non-interventional study
NNH	Number needed to harm
OS	Overall survival
PAS	Post Authorization Study

PASS	Post-Authorization Safety Study
PFS	Progression-free survival
QALYs	Quality-adjusted life years
RDI	Relative Dose Intensity
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Ricardo Ballesteros Ramírez	Coordinator Investigator, Biol. MSc Econ	Pontificia Universidad Javeriana	Cra. 7 No. 40 – 62, Bogotá
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Juan Manuel Reyes	HEOR (Health economics and outcomes research) Manager, Pharmacist, MSc	Pfizer Colombia	Av. Suba No. 95-66, Bogotá
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Andrea Constanza Rubio	Clinical Epidemiologist, MSc/ HEOR Coordinator	Pfizer Colombia	Av. Suba No. 95-66, Bogotá

3.1. SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

_____	_____	_____
Sponsor Signature	Date of signature (DD Mmm YYYY)	Time (Time zone)

3.2. INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the ICH, GCP, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____	_____	_____
Investigator Signature	Date of signature (DD Mmm YYYY)	Time (Time zone)

4. ABSTRACT

Study title: Safety evaluation of biosimilar trastuzumab in breast cancer: Experience of Colombian institutions					
Protocol number	A6181236	**Phase**	IV	**Type**	Observational
Condition/Disease	Breast cancer				
Number of patients	All patients that meet the inclusion criteria of participating institutions		**Duration of the patients in the study**		2.9 years of retrospective follow-up
Country participants	Colombia		**Duration of the study**		7.5 months

Rationale and background:
The safety and effectiveness of biosimilar biological products has always been a point of discussion for the different actors involved in the use of these drugs in Colombia.(7) Although the decree has been in force since 2014, the search conducted did not find reports of safety for biosimilar in Colombian patients, which is why their behavior in terms of these attributes is unknown in many cases, and decision-makers do not have the technical-scientific information they need.

Thus, using the historical data of patients who received this biosimilar product and establishing the frequency of AEs, together with the clinical outcomes of effectiveness during treatment, we can arrive at a preliminary approximation of the behavior of these products to serve as a basis for their continued use; this would alleviate excess costs associated with these therapies while maintaining safety at the appropriate levels.

Research question and objectives
This descriptive study proposes to profile the safety of the biosimilar trastuzumab with patients using the medication in Colombian institutions.

Primary Objective
To describe the frequency of AEs by degree of severity and anatomical group, to establish the safety profile of the biosimilar trastuzumab used for breast cancer in Colombian healthcare institutions.
Secondary Objectives
Perform the clinical characterization of patients who were treated with the biosimilar trastuzumab for breast cancer.
Exploratory objectives
- To calculate the OS and PFS in patients treated with the biosimilar trastuzumab for breast cancer.
- To explore the factors associated with effectiveness and safety in patients treated with the biosimilar trastuzumab for breast cancer.

Study design:
Descriptive, retrospective study of patients treated with biosimilar trastuzumab according to the approved indications for use in breast cancer at the Colombian institutional health service providers (IPS). The initial follow-up date will be in October 2019, after approval of sanitary registration. The patient's index date will be defined as the date of the first infusion of biosimilar trastuzumab. The

follow-up time will end when the patient discontinues the treatment, dies, is lost to follow-up or until the end of the collection of information in July 2022.
The variables of the study will be collected from patients treated with the biosimilar trastuzumab that are in the database of the IPS participating in the study. Additionally, any clinical information and missing or discrepant treatment in the database will be directly validated in the clinical records of the selected patients by the investigator or their delegate. The database and the clinical records of the patients will be the only secondary sources of information. The clinical and treatment variables collected in the study will be recorded in a Case Report Form (CRF) designed for the study.

Population:
Data for the study will be collected from the database and clinical records available in the IPS participating in the study, which are reference centers for the management of cancer patients in Colombia. The study will only include patients who received treatment from October 2019 to July 2022 and meet the inclusion criteria.

Inclusion criteria:
The selected clinical records must meet all the following inclusion criteria for analysis in the study:

1. Patients who received treatment with the biosimilar trastuzumab according to the approved indications for breast cancer.
2. Patients who received biosimilar trastuzumab from the first cycle and completed a minimum of 2 treatment cycles**.**

Exclusion criteria:
There are no exclusion criteria for this study.

Data Collection:
The information that will be used in the study comes exclusively from a secondary source given by the medical records and datasets available from the participating institutions, for which the researcher will obtain institutional approvals to collect information. The researchers will identify the records of eligible patients according to the inclusion criteria. The data collection will be carried out in a CRF structured for the study.

Variables:

- Safety profile of biosimilar trastuzumab
- OS and PFS
- Tumor response

Data sources:
The information that will be used in the study comes exclusively from a secondary source given by the medical records and datasets available from the participating institutions, for which the researcher will obtain institutional approvals to collect information.

Study size:
There is no a priori hypothesis that indicates that sample size calculations can be applied. For the analysis of the factors associated with effectiveness, the exploratory objective will not be considered for the estimation of the sample size.

Data analysis:
Descriptive statistics will be produced for all variables. These will include estimates of the mean, standard deviation, 95% confidence intervals of the mean, median, interquartile ranges and frequency distributions for continuous scale variables and frequency distributions for categorical scale variables. The normality of the continuous variables will be assessed using the Kolmogorov test or the Shapiro Wilk test according to the number of samples collected.

Time to event data including time to disease progression, death, partial response and complete response will be described using the Kaplan Meier estimator of the Survival Function.

Associated factors of response to treatment will be identified among patient, disease and treatment parameters using Cox Proportional Hazard Models. The main factors that would be assessed in these analyses: Age, Diagnosis date, Stage, Eastern Cooperative Oncology Group (ECOG) Status, Metastasis, Sites of metastasis, treatment received and AE. Log rank test will be used to compare the different curves.

Milestone:

Start of data collection	15 November 2022
End of data collection	15 April 2023
Registration in the EU PAS register	11 October 2022
Final study report	30 June 2023

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Start of data collection	15 November 2022
End of data collection	15 April 2023
Registration in the EU PAS register	11 October 2022
Final study report	30 June 2023

7. RATIONALE AND BACKGROUND

In 2014, Decree 1,782 established regulations for biological drugs in Colombia. This decree considers the pharmacological evaluation, pharmaceutical evaluation and health surveillance of these products that are submitted for registration with the National Institute for Drug and Food Vigilance (INVIMA). Safety monitoring and reporting are established through risk management plans that aim to optimize the effectiveness and safety profile of the treatment in clinical practice.

Additionally, the decree establishes the normative route for biosimilar biologics. According to the Food and Drug Administration (FDA), a biosimilar is a biological product that is very similar and does not have clinically significant differences with respect to an existing product approved by the FDA. Products that have been approved and are being used within hospital institutions are monitored carefully for possible adverse reactions and associated events. Safety reports and follow-up for biosimilar products are necessary, even more so when there may be intrinsic and extrinsic factors in a population that can affect their safety and effectiveness.

Despite the boom of biosimilar products and the approvals that have been granted since 2017, there are still no available reports of safety and effectiveness of these products among Colombian patients. It is necessary to know the safety profile of these products in this population and to evaluate the clinical outcomes along with associated factors that may affect the response to treatments, such as relative dose intensity (RDI).

Considering that each biological drug is different and presents subtle variations, even within batches from the same manufacturer, the safety profile for biosimilar products should be individualized within a logical framework along with that reported for the reference molecule. This project has as its objective a first description of biosimilar trastuzumab and its safety, with data on the Colombian population, which will enrich the knowledge of biological drugs and their effects.

7.1. Overview of biosimilars

Biosimilars are protein products that are sufficiently similar to a biopharmaceutical product already approved by a regulatory agency.(1) These biosimilar products offer an alternative that reduces the cost of biological therapies.(2) However, there are also potential effectiveness and safety implications, and it is important to introduce biosimilars in the oncological environment appropriately. This is where post-marketing pharmacovigilance data is essential to ensure patient safety.(3)

In 2014, Decree 1,782 established the basis for approval of biosimilars through 3 regulatory channels in Colombia: complete file, comparability or abbreviated route, which differ from requirements for sanitary registration and commercialization. The decree establishes regulatory requirements for the pharmacovigilance of these products and the monitoring of AEs and reactions.

7.2. Pharmacovigilance of biosimilars

There are many challenges for the pharmacovigilance of biosimilar products; for example, immunogenicity is 1 of the main concerns since it affects not only patient safety but also effectiveness due to associated immunological phenomena.(4) That is why the collection of post-marketing safety data offers a complement to the data of clinical studies.(5)

Pharmacovigilance for these products in hospital institutions in Colombia has moved from passive to active. In many institutions, the clinical team now follows patients who take these biologics and consider safety as the main axis of clinical decision-making. Returning to the definition of an AE as any unwanted medical situation in a patient or subject who receives a pharmaceutical product, which may not necessarily have a causal relationship, it is of utmost importance to know the safety profiles for these products and their classification according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0).

The pharmacovigilance process for these products does not differ much from the products of chemical synthesis, where there must be a report that meets the technical guidelines of INVIMA and the IPS where the event occurred. On the other hand, in Europe, 13 modules are available that describe good pharmacovigilance practices. In addition, specific guidelines are available for biological products, which also analyze good pharmacovigilance practices. In the United States, there is guidance available for "Good practices in pharmacovigilance and pharmacoepidemiological evaluation" and "Pharmacovigilance planning", and the same orientation is also followed for biological drugs.(6)

7.3. Background on the safety profile of trastuzumab

Among the most serious and/or frequent adverse reactions reported to date with the use of trastuzumab (intravenous and subcutaneous formulations) are cardiac dysfunction, infusion-related reactions, hematotoxicity (particularly neutropenia), infections and pulmonary adverse reactions. Annex 3 shows the frequency of reactions reported for trastuzumab.

7.4. Rationale

The safety and effectiveness of biosimilar biological products has always been a point of discussion for the different actors involved in the use of these drugs in Colombia.(7) Although the decree has been in force since 2014, the search conducted did not find reports of safety for biosimilar in Colombian patients, which is why their behavior in terms of these attributes is unknown in many cases, and decision-makers do not have the technical-scientific information they need.

Thus, using the historical data of patients who received this biosimilar product and establishing the frequency of AEs, together with the clinical outcomes of effectiveness during treatment, we can arrive at a preliminary approximation of the behavior of these products to serve as a basis for their continued use; this would alleviate excess costs associated with these therapies while maintaining safety at the appropriate levels.

This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

This descriptive study proposes to profile the safety of the biosimilar trastuzumab with patients using the medication in Colombian institutions.

8.1. Primary Objective

To describe the frequency of AEs by degree of severity and anatomical group, to establish the safety profile of the biosimilar trastuzumab used for breast cancer in Colombian healthcare institutions.

8.2. Secondary Objectives

Perform the clinical characterization of patients who were treated with the biosimilar trastuzumab for breast cancer.

8.3. Exploratory objectives

- To calculate the OS and PFS in patients treated with the biosimilar trastuzumab for breast cancer.

- To explore the factors associated with effectiveness and safety in patients treated with the biosimilar trastuzumab for breast cancer.

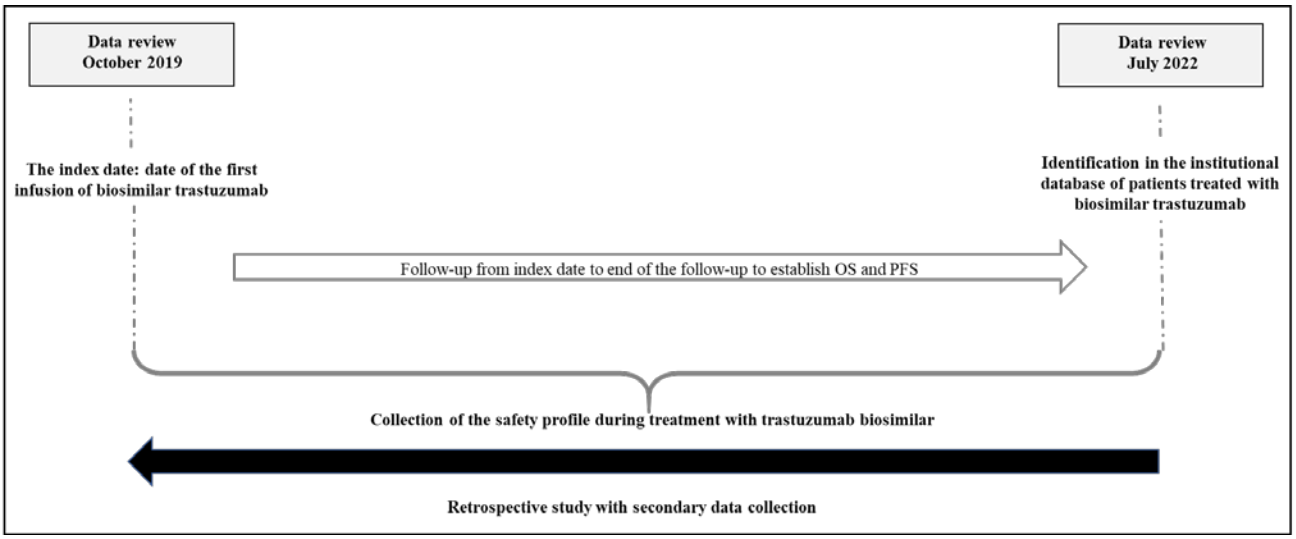
9. RESEARCH METHODS

9.1. Study design

Descriptive, retrospective study of patients treated with biosimilar trastuzumab according to the approved indications for use in breast cancer at the Colombian IPS. The initial follow-up date will be in October 2019, after approval of sanitary registration. The patient's index date will be defined as the date of the first infusion of biosimilar trastuzumab. The follow-up time will end when the patient discontinues the treatment, dies, is lost to follow-up or until the end of the collection of information in July 2022 (See Figure 1).

The variables of the study will be collected from patients treated with the biosimilar trastuzumab that are in the database of the IPS participating in the study. Additionally, any clinical information and missing or discrepant treatment in the database will be directly validated in the clinical records of the selected patients by the investigator or their delegate. The database and the clinical records of the patients will be the only secondary sources of information. The clinical and treatment variables collected in the study will be recorded in a CRF designed for the study.

Figure 1. Study diagram



9.2. Setting

Data for the study will be collected from the database and clinical records available in the IPS participating in the study, which are reference centers for the management of cancer patients in Colombia. The study will only include patients who received treatment from October 2019 to July 2022 and meet the inclusion criteria.

9.2.1 Inclusion criteria

The selected clinical records must meet all the following inclusion criteria for analysis in the study:

1. Patients who received treatment with the biosimilar trastuzumab according to the approved indications for breast cancer.

2. Patients who received biosimilar trastuzumab from the first cycle and completed a minimum of 2 treatment cycles.

9.2.2 Exclusion criteria

There are no exclusion criteria for this study.

9.3. Variables

The variables collected will include but are not limited to:

Table 1. Variable list

Variable	Definition	Role	Type of variable	Data source(s)	Operational definition
Age	age in completed years	Demographic characteristics	Qualitative/ Scalar	IPS dataset/ Medical record	Years
Sex	Female/ Male	Demographic characteristics	Qualitative/ Nominal	IPS dataset/ Medical record	1: Male 2:Female
Weight at the beginning of the first cycle	Kg	Demographic characteristics	Quantitative /Continuous	IPS dataset/ Medical record	kg
Height at the beginning of the first cycle	meter	Demographic characteristics	Quantitative /Continuous	IPS dataset/ Medical record	meters
Body surface area at the beginning of the first cycle	m^2	Demographic characteristics	Quantitative /Continuous	IPS dataset/ Medical record	Body surface area
Disease	Type of neoplasm/Indication for trastuzumab biosimilar	Demographic characteristics	Qualitative/ Nominal	IPS dataset/ Medical record	• Human epidermal growth factor receptor 2 (HER2)-overexpressing metastatic breast cancer • Early-stage HER2-positive breast cancer
Date of diagnosis	Date	Treatment	Quantitative / Scalar	IPS dataset/ Medical record	DD Month YYYY Not available
Stage	Lesion size	Demographic characteristics	Qualitative/ Ordinal	IPS dataset/ Medical record	1: Stage IA 2: Stage IB 3: Stage IIA 4: Stage IIB 5: Stage IIIA 6: Stage IIIB 7: Stage IIIC 8: Stage V 9: Not available

ECOG scale (in the first cycle)	Patient functional status	Demographic characteristics	Qualitative/ Ordinal	IPS dataset/ Medical record	ECOG 0 ECOG 1 ECOG 2 ECOG 3 ECOG 4 ECOG 5 Not available
Metastasis (in the first cycle)	Stage	Demographic characteristics	Qualitative/ Nominal	IPS dataset/ Medical record	1: Yes 2:No
Location of metastases	Site of lesion (multiple choice)	Demographic characteristics	Qualitative/ Nominal	IPS dataset/ Medical record	1: Brain 2: Liver 3: Bone 4: Others 5: None
Date of metastasis	First date metastasis is documented	Demographic characteristics	Qualitative/ Discrete	IPS dataset/ Medical record	DD Month YYYY
Treatment scheme	Received chemotherapy schemes	Treatment	Qualitative/ Nominal	IPS dataset/ Medical record	1: AC x 4 cycles 2: Taxanes x cycles 3: Paclitaxel plus platinum 4: Others 5: None
Treatment scheme according to indication	Received chemotherapy schemes	Treatment	Qualitative/ Nominal	IPS dataset/ Medical record	1. Metastatic breast cancer: a. single agent treatment of HER2-overexpressing breast cancer in patients who have received 1 or more chemotherapy regimens for metastatic disease b. In combination with paclitaxel or docetaxel in those who have not previously received chemotherapy for treatment of metastatic cancer c. In combination with an aromatase inhibitor for the treatment of patients with metastatic cancer with hormone receptors.

					2. Early-stage breast cancer: d. After surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) f. After adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. g. In combination with adjuvant chemotherapy with docetaxel and carboplatin. h. In combination with neoadjuvant chemotherapy followed by adjuvant treatment with trastuzumab, in locally advanced breast cancer, including inflammatory breast cancer, or tumors >2 cm in diameter.
Dose of Treatment	Treatment scheme	Treatment	Qualitative/ Discrete	IPS dataset/ Medical record	Initial dose
Number of cycles	Number of cycles received	Treatment	Qualitative/ Discrete	IPS dataset/ Medical record	Number of cycles received
Start date of treatment/infusion	Date	Treatment	Qualitative/ Scalar	IPS dataset/ Medical record	DD Month YYYY
Date of the last cycle	Date	Treatment	Qualitative/ Scalar	IPS dataset/ Medical record	DD Month YYYY
Reason for treatment discontinuation	vital status	Demographic characteristics	Qualitative/ Nominal	IPS dataset/ Medical record	1. Not registered 2. Adverse event 3. Medical indication 4. Change of treatment 5. Other (describe)

Date of discontinuation	Date	Treatment	Qualitative/ Scalar	IPS dataset/ Medical record	DD Month YYYY
Status at last cycle received	vital status	Outcome	Qualitative/ Nominal	IPS dataset/ Medical record	1. Deceased 2. Live
Date of death	Date	Outcome	Qualitative/ Nominal	IPS dataset/ Medical record	DD Month YYYY
Response categories to the last cycle received	Response treatment	Outcome	Qualitative/ Nominal	IPS dataset/ Medical record	1. Complete response 2. Partial response 3. Progressive disease 4. Stable disease 5. Not available
Progression date	Date	Demographic characteristics	Qualitative/ Scalar	IPS dataset/ Medical record	DD Month YYYY
Adverse event*	Presentation of historical adverse events	Safety profile	Qualitative/ Nominal	IPS dataset/ Medical record	1: Yes 2: No
Anatomical group*	Description of the anatomical group of the adverse event	Safety profile	Qualitative/ Nominal	IPS dataset/ Medical record	Description of the anatomical group
Grade of adverse event*	Classification	Safety profile	Qualitative/ Ordinal	IPS dataset/ Medical record	1: Grade 1 2: Grade 2 3: Grade 3 4: Grade 4 5: Grade 5
Classification*	Description of AE	Safety profile	Qualitative/ Nominal	IPS dataset/ Medical record	1: Diarrhea 2: Rash 3: Fatigue 4: Fever 5: Immune-mediated 6: Neutropenia 7: Anemia 8:Others
Cycle #*	Cycle number	Safety profile	Quantitative / continue	IPS dataset/ Medical record	Patient cycle number in the AE

Dose*	Dose during the event	Safety profile	Quantitative / continue	IPS dataset/ Medical record	Dose
Date of cycle #*	Chemotherapy application date	Safety profile	Qualitative/ Scalar	IPS dataset/ Medical record	DD Month YYYY
* The variables will be collected for each treatment cycle with the biosimilar treatment, in mono or polychemotherapy.					

9.3.1 Definitions

- Real-world tumor responses are assessed based on treating clinician's assessment and will be collected as recorded in the participating institution's medical record or database:
  - Complete response: complete resolution of all visible disease.
  - Partial response: partial reduction in size of visible disease in some or all areas, without any areas of increase in visible disease.
  - Stable disease: no change in overall size of visible disease; also included cases where some lesions increased in size and some lesions decreased in size.
  - Progressive disease: an increase in visible disease and/or presence of any new lesions; included cases where the clinician indicated progressive disease.
- OS is defined as the period of time from the start date of the first infusion that patients diagnosed with the disease are still alive.
- PFS is defined as the time between the date the patient received the first infusion until the date of disease progression or death from any cause.
- The AE is defined as any unwanted medical situation in the patient who received the biological medicine and that has a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintentional sign (including abnormal laboratory findings), symptoms or disease temporarily associated with the biological, established as related to the use of the drug. Any situation found in the clinical record that is susceptible to classification as an AE will be discussed with the medical staff of the study. For example, documented neutropenia after an infusion can be classified under this definition. It is not specified what the term "AE" should mean due to the structure of the medical records.
- The degree of each AE will be categorized according to the NCI-CTCAE version 5.0. For AEs not classified in the common terminology criteria, the following criteria should be used:

- Grade 1: The AE is transitory and easily tolerated by the subject (mild).

- Grade 2: The AE causes discomfort to the subject and interrupts their usual activities (Moderate).

- Grade 3: The AE causes considerable interference with the subject's usual activities and may be disabling; hospitalization or prolongation of hospitalization indicated. (Severe or medically significant, but not immediately life-threatening).

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

9.4. Data sources

The information that will be used in the study comes exclusively from a secondary source given by the medical records and datasets available from the participating institutions, for which the researcher will obtain institutional approvals to collect information. The researchers will identify the records of eligible patients according to the inclusion criteria. The data collection will be carried out in a CRF structured for the study.

9.5. Study size

There is no a priori hypotheses that indicates that sample size calculations can be applied. For the analysis of the factors associated with effectiveness, the exploratory objective will not be considered for the estimation of the sample size.

9.6. Data management

The collection of the information is carried out by the researchers or their delegates following the CRF developed in specialized software, with the relevant validations for the development and management of data in clinical studies. With the objective of unifying criteria and concepts, the template will be parameterized according to the possible answers or options of each of the variables. These will be defined based on medical experience, availability of information and according to what is established in the protocol. The CRF will be validated according to a pilot test of 5 randomly selected medical records to verify the elements selected for each variable and the availability of data from each database.

R v3.6.2 or Stata software will be used for the exploratory analysis of the variables. The data will be stored in a structured database, where the rows will be the cases and the columns will be the selected variables.

Pfizer will supervise the supplier to ensure the protection of the patient's personal data.

9.6.1 Case report forms (CRFs)

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2 Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Descriptive statistics will be produced for all variables. These will include estimates of the mean, standard deviation, 95% confidence intervals of the mean, median, interquartile ranges and frequency distributions for continuous scale variables and frequency distributions for categorical scale variables. The normality of the continuous variables will be assessed using the Kolmogorov test or the Shapiro Wilk test according to the number of samples collected. There will be no imputation or replacement of missing data. All analyses will be performed on observed cases.

Time to event data including time to disease progression, death, partial response and complete response will be described using the Kaplan Meier estimator of the Survival Function.

Associated factors of response to treatment will be identified among patient, disease and treatment parameters using Cox Proportional Hazard Models. The main factors that would be assessed in these analyses: Age, Diagnosis date, Stage, ECOG Status, Metastasis, Sites of metastasis, treatment received and AE. Log rank test will be used to compare the different curves.

9.8. Quality control

The analytic dataset consisting of the collected data will be validated by the investigator or designee who will verify the following:

- Review of illogical data or atypical values
- Verification of conflicted data (i.e.: detecting false answers, such as scale scores out of the limit)
- Review of very high percentages of response as “not known” or “data not available”
- Verification of accuracy of the collected data by comparison with the source documents
- AEs reporting.

9.9. Limitations of the research methods

The study will have the following limitations:

- Taking into account the source of the data and the retrospective nature, it is likely that not all the data of the events or variables of interest that the patient has experienced will be identified in the clinical record. The data related to events and reactions will only be available if the patients were treated within the hospital from which the record was obtained.

- The definitions of the events and some variables may vary according to the treating physician. Therefore, the present protocol tries to guarantee that the events are parameterized by the evaluation of the researchers.

- Considering that all patients will come from participating institutions selected by intention, the demographic and clinical characteristics of the subjects may not represent the entire population that is exposed to the biosimilars under study in Colombia.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society of Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.

The study will be evaluated by the IEC in the category of research without risk. The ethical principles of justice, beneficence, non-maleficence and confidentiality of information established by the Declaration of Helsinki will be followed, in accordance with Resolution No. 8430 of 1993 of the Ministry of Health of Colombia.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This protocol involves the analysis of structured data in addition to human review of unstructured data.

11.1. Structured Data Analysis

This study involves a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing**.** In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool (e.g., chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- For exposure during pregnancy in studies of pregnant women, data on the exposure to drug of interest during pregnancy, are not reportable unless associated with serious or non-serious AEs.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

"All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format."><

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors."*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

At the end of the project, the frequency of AEs in the group of patients who used trastuzumab should be established, enabling construction of a safety profile for these products. We also expect to have an approximation of the OS and event-free survival for this group of patients and a list of factors that may affect clinical outcomes. Finally, the results will be published in an indexed review and presented at an international conference according to the availability of the results.

13. REFERENCES

1. Kay J. Biosimilars: A regulatory perspective from America. Arthritis Research and Therapy [Internet]. 2011 May 12 [cited 2022 May 12];13(3):1–5. Available from: https://arthritis-research.biomedcentral.com/articles/10.1186/ar3310
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7. Gray E, Matejtschuk P, Thorpe R. Quality assessment of biosimilars in Colombia - reducing knowledge gaps. GaBI Journal. 2018;7(2).
8. Cova TFGG, Pereira JLGFSC, Pais AACC. Is standard multivariate analysis sufficient in clinical and epidemiological studies? Journal of Biomedical Informatics. 2013 Feb;46(1):75–86.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	CT24-WI-GL06-RF01	N/A	Study Team Roster_ A6181236

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Safety evaluation of biosimilar trastuzumab in breast cancer: Experience of Colombian institutions

EU PAS Register® number: EUPAS49290
Study reference number (if applicable): A6181236

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 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Progress reports and Interim reports are not a requirement for this study.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
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)	☒	☐	☐	7.4
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
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

There is no a priori hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3

[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
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
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)	☒	☐	☐	9.3-9.4

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.1-9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

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?	☒	☐	☐	9.1-9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.8-9.9

Comments:

Section 8: Effect measure 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)	☒	☐	☐	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)	☒	☐	☐	9.3-9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3-9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3-9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3-9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3-9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
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 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

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
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
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).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.3-10.4
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

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: Ricardo Ballesteros Ramírez

Date: dd/Month/year

Signature: _____

ANNEX 3. ADVERSE REACTIONS FOR TRASTUZUMAB[a]

System organ class	Adverse reaction	Frequency
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Pharyngitis	Common
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common

System organ class	Adverse reaction	Frequency
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1]Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	[+]Cardiac failure (congestive)	Common
	[+1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	[+1] Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	[+]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	[+]Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	[+]Pleural effusion	Common
	[+1]Wheezing	Uncommon
	Pneumonitis	Uncommon
	[+]Pulmonary fibrosis	Not known
	[+]Respiratory distress	Not known
	[+]Respiratory failure	Not known
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known
	[+]Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+]Hypoxia	Not known
	[+]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known

System organ class	Adverse reaction	Frequency
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common

System organ class	Adverse reaction	Frequency
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with administration-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes

[a] Information sourced from the Herceptin technical datasheet, International Nonproprietary Names (INN)-trastuzumab. https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf