Summary Table of Study Protocol

Title	GARDENIA: A Multi-country Observational Serial Chart Review Study of KANJINTI use in Europe
Protocol version identifier	20180020; Version 2.0
Date of last version of the protocol	20 September 2018
EU Post Authorisation Study (PAS) Register No	Not applicable (NA)
Active Substance	KANJINTI (Amgen Trastuzumab biosimilar)
Medicinal Product	KANJINTI
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	Research Question: What are the characteristics of breast cancer patients receiving KANJINTI? Primary objectives: Describe characteristics of breast cancer patients receiving KANJINTI including treatment setting neoadjuvant, adjuvant, or metastatic. Describe if the patient was trastuzumab treatment naïve or if the patient was switched from a different trastuzumab brand. For patients who received Herceptin, which route was used for administration (IV or SC). Gather concurrent chemotherapy, targeted therapies and/or endocrine therapy which are given with KANJINTI Describe reasons for KANJINTI discontinuation and subsequent treatment plan
Country(-ies) of Study	Approximately 8 European countries
Author	PPD [redacted]

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Ltd
MAH Contact	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda The Netherlands

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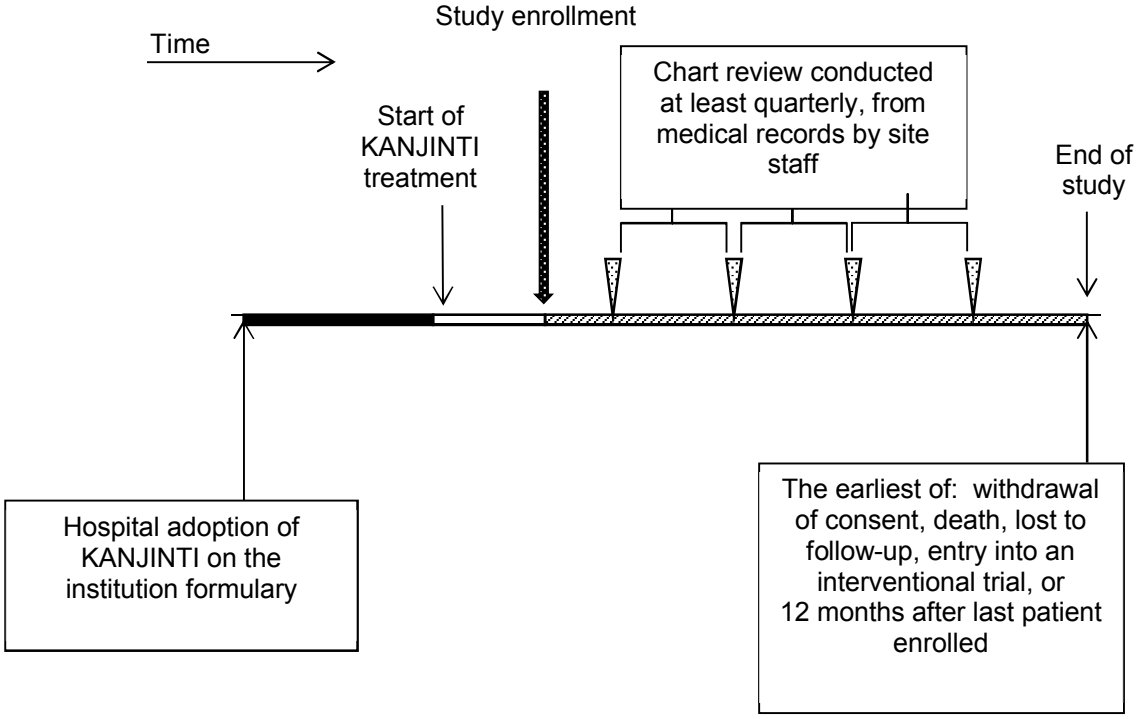
Investigator's Agreement

I have read the attached protocol entitled GARDENIA: A Multi-country Observational Serial Chart Review Study of KANJINTI Use in Europe dated 16 April 2019, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator <<*Coordinating Investigator*>>	Date (DD Month YYYY)

Study Design Schema



= Data collection of treatment history, demographics, and disease history up to 4 months prior to KANJINTI initiation (retrospective)

= Patient data after KANJINTI initiation (retrospective)

= Prospective data collection after study enrollment

1. Table of Contents

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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
CHMP	Committee for Medicinal Products for Human Use
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	estrogen receptor
EU	European Union
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated acquisition
NA	not applicable
ORR	overall response rate
pCR	pathologic complete response
PAS	Post Authorisation Study
PASS	Post Authorization Safety Study
PFS	progression-free survival
PR	progesterone receptor
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOP	standard operating procedure

3. Responsible Parties

Sponsor	Amgen Limited 1 Uxbridge Business Park Sanderson Rd Uxbridge UB8 1DH, United Kingdom

Amgen Ltd is responsible for all aspects of study execution, conduct, and reporting.

4. Abstract

- Study Title

GARDENIA: A Multi-country Observational Serial Chart Review Study of KANJINTI Use in Europe

- Study Background and Rationale

KANJINTI was approved in the European Union (EU) in May 2018 as a biosimilar of Herceptin for treatment of human epidermal growth factor receptor 2 positive (HER2+) early and metastatic breast cancer as well as metastatic gastric cancer. The biosimilar regulatory approval pathway allows for approval across all indications after the conduct of one phase 3 trial conducted in a sensitive population with sensitive endpoints, with extrapolation of other indications based upon knowledge of the reference product, the totality of evidence (functional, analytic, preclinical, and clinical) data package, and scientific justification. The phase 3 trial for KANJINTI was conducted in the neoadjuvant and adjuvant early HER2+ breast cancer setting. KANJINTI received approval for all Herceptin approved indications by justified extrapolation. Information on how the product is being used in clinical practice, and in which patients and chemotherapy combinations will provide real-world evidence. This study is therefore being conducted in an effort to understand patterns of KANJINTI use, whether in patients switched from Herceptin intravenous (IV) or subcutaneous (SC) therapy or switched from another trastuzumab biosimilar (eg, Herzuma, Ontruzant) or in those patients who are trastuzumab treatment naïve. Information on association of biosimilar use with stage of disease, treatment phase (neoadjuvant, adjuvant, metastatic, and line of metastatic treatment), and medical history will be gathered. Data will also be collected on treatment history, demographics, and disease history up to 4 months prior to KANJINTI initiation, as well as during follow-up from KANJINTI initiation to withdrawal of consent, death, lost to follow-up, entry into interventional trial, or end of study (12 months after last patient enrolled), whichever occurs earliest. From enrollment onwards, data will be abstracted (at least) quarterly from the medical records until the follow-up period ends.

- Research Question and Objective(s)
  - Primary Objective(s)
    - Describe characteristics of breast cancer patients receiving KANJINTI including treatment setting neoadjuvant, adjuvant, or metastatic.
    - Describe if the patient was trastuzumab treatment naïve or if the patient was switched from a different trastuzumab brand. For patients who received Herceptin, which route was used for administration (IV or SC).

    - Gather concurrent chemotherapy, targeted therapies and/or endocrine therapy which are given with KANJINTI
    - Describe reasons for KANJINTI discontinuation and subsequent treatment plan
  - Secondary Objective(s)
    - Not Applicable
  - Estimation
    - The study will be descriptive in nature and as such, no formal hypothesis will be tested. Instead, characteristics of patients treated with KANJINTI and KANJINTI usage will be described.
- Study Design/Type

This is a single arm, observational, serial chart review of adult HER2+ breast cancer patients receiving or having received KANJINTI.

- Study Population or Data Resource

Human epidermal growth factor receptor 2 positive overexpressing breast cancer patients who are receiving or have received KANJINTI either in the neo/adjuvant or metastatic settings, including maintenance treatment. Chart data extractions are anticipated at least every quarter over the course of the study.

- Summary of Patient Eligibility Criteria
  - Key Inclusion Criteria
  - Patients are eligible to take part in the study if they meet the following criteria:
    - Patients who have HER2+ breast cancer in any stage of disease whether metastatic or early
    - Patients receiving or having received KANJINTI treatment according to the judgment of the physician, after adoption of KANJINTI on the institution formulary, in routine clinical practice
    - Patients are aged ≥ 18 years at KANJINTI initiation
  - Key Exclusion Criteria
  - Patients are excluded from the study if they meet any of the following criteria:
    - Currently participating or planning to participate in a concurrent interventional clinical trial involving therapeutic agent(s)
    - Have other cancer type(s), concurrent to breast cancer
    - Patients that have not provided an informed consent where required per country-specific regulations
    - Patients whose medical chart is not available for data extraction

- Follow-up

The follow-up period for a patient is defined as the period from KANJINTI initiation to withdrawal of consent, death, lost to follow-up, entry into interventional trial, or end of study (12months after last patient enrolled), whichever occurs earliest. Follow-up data will be collected through serial review of patients' medical charts.

- Variables
  - Outcome Variable(s):

    Baseline Demographics

    - Age, sex, weight, height

    Disease History Characteristics

    - Date of initial breast cancer diagnosis
    - HER2+ assessment: method
    - Breast cancer stage at baseline
    - Breast cancer stage at diagnosis
    - Prior surgery for breast cancer
    - Lymph node involvement
    - Tumor classification
    - Nodes classification
    - Histological grading
    - Estrogen receptor (ER)/progesterone receptor (PR) status
    - Metastatic disease (yes, no), if yes, site of metastases: liver, lung, bones, brain, other
    - Other relevant medical history and/or relevant comorbidities
    - Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline

    Treatment History

    - All anti-breast cancer regimens 4 months prior to KANJINTI initiation (including starting date, end date, route and other trastuzumab brand)
    - Presence of an IV infusion port / catheter port (eg, Port-A-Cath) / pic line

    KANJINTI Regimen

    - Treatment setting (neoadjuvant, adjuvant, metastatic)
    - Line of therapy: 1, 2, 3 or maintenance (metastatic setting)

- Concomitant cancer therapy, chemotherapy, hormonal therapy, targeted therapy
- KANJINTI dose and schedule
- Reason for ending KANJINTI and subsequent treatment plan

– Exposure Variable:
- All patients enrolled in the study will be exposed to KANJINTI.

– Other Covariates:
- Apart from country, there are no other specific subgroups of interest.

- Study Sample Size

The study is planned to enroll approximately 500 patients across approximately 8 countries in Europe with a maximum of 150 patients in any one country. Data summaries are intended to be descriptive in nature and are required at a country and sub-population level (eg, metastatic patients).

- Data Analysis

The approach to the statistical analysis will be generally descriptive; no formal hypotheses will be tested. Categorical data will be summarized by the number and percentage of patients in each category. Two-sided 95% CIs calculated using Wilson's method where appropriate will be presented. Continuous data will be summarized by mean (and 95% CI where appropriate), SD, median, lower and upper quartiles, and minimum and maximum values. Time-to-event endpoints (time from KANJINTI initiation to the specific events) will be summarized using Kaplan-Meier methodology.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
Superseding amendment 1	16 April 2019	Amendments are being made to study duration and timelines due to 6 month operational delay of study and safety form updates provided		

Milestones

Milestone	Planned date
Start of data collection	Q3 2019*
End of enrollment	Q3 2020*
End of data collection	Q3 2021*
Interim analysis	Q1 2020

Final report of study results	Within 12 months of end of data collection

Q = quarter
*Dependent on country approvals

6. Rationale and Background

This study is designed to document the use of KANJINTI in routine clinical practice. KANJINTI was approved in the EU in May 2018 as a biosimilar of Herceptin for treatment of human epidermal growth factor receptor 2 positive (HER2+) early and metastatic breast cancer as well as metastatic gastric cancer (European Medicines Agency, 2018). The biosimilar regulatory approval pathway allows for approval across all indications after the conduct of one phase 3 trial conducted in a sensitive population with sensitive endpoints, with extrapolation of other indications based upon knowledge of the reference product, the totality of evidence (functional, analytic, preclinical, and clinical) data package, and scientific justification. The phase 3 trial for KANJINTI was conducted in the neoadjuvant and adjuvant early HER2+ breast cancer setting. KANJINTI received approval for all Herceptin approved indications by justified extrapolation (European Medicines Agency, 2018; KANJINTI SmPC, 2018). This serial chart review will provide information on how KANJINTI is adopted for use in routine, daily clinical practice. Follow-up will provide additional information on its safety, efficacy, and combination use in routine clinical practice in all indications approved for the reference drug, Herceptin. Additionally, it is anticipated that some Health Technology Agencies would require local real-world evidence on how the product is being used in routine clinical practice, during access and price re-negotiation.

6.1 Diseases and Therapeutic Area

Breast cancer is the most common malignancy in women, and is the leading cause of cancer-related death in women (Jemal et al, 2011). The number of women diagnosed as having breast cancer has increased by 1.5% annually since 1990, mostly due to mammographic screening and an ageing population. Mortality rates, however, have been decreasing steadily in most western countries since the early 1990s, as a result of advances in early detection and treatment (Cardoso et al, 2010).

Approximately 20% to 30% of women with breast cancer overexpress the human epidermal growth factor receptor 2 (HER2) protein, which is correlated with a worsened prognosis when compared to patients without HER2 amplification.

Trastuzumab has revolutionized the treatment of HER2-overexpressing breast cancer patients and is approved in all stages of disease including adjuvant, metastatic, and most recently as neoadjuvant treatment of early breast cancer (Aebi et al, 2010; Cardoso et al, 2010; National Comprehensive Cancer Network, 2010; EMA, 2015).

Trastuzumab is marketed globally under the registered trade name Herceptin® (Hoffmann-La Roche) and lost patent exclusivity in the EU in 2014. As a result of patent exclusivity expiration, biosimilars to trastuzumab have been developed and now approved in the EU. Biosimilar therapies can help in providing alternative, effective medicines at reduced costs, thereby enabling access to therapy for more patients, who are suitable candidates for the therapy.

KANJINTI has been developed as a biosimilar to Herceptin® (trastuzumab). Similarity of KANJINTI to trastuzumab has been shown using bioanalytical methods, pre-clinical studies, and clinical studies including a phase 1 study, where the pharmacokinetic profile of KANJINTI demonstrated bioequivalence to trastuzumab (Hanes et al, 2017). More recently, the phase 3 LILAC trial demonstrated no clinically meaningful differences between KANJINTI and trastuzumab in HER2+ early breast cancer (von Mickwitz et al, 2018). Consequently, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 22 March 2018, recommending the granting of a marketing authorization for KANJINTI in the treatment of HER2+ breast cancer (both early and metastatic) and metastatic HER2+ gastric cancer (EMA CHMP, 2018); KANJINTI was then approved in the EU in May 2018 (EMA, 2018).

Refer to the Summary of Product Characteristics (SmPC) for KANJINTI and the European Public Assessment Report (EPAR) to obtain additional information.

6.2 Rationale

The biosimilar regulatory approval pathway allows for approval across all indications after the conduct of one phase 3 trial conducted in a sensitive population with sensitive endpoints, with extrapolation of other indications based upon knowledge of the reference product, the totality of evidence (functional, analytic, preclinical, and clinical) data package, and scientific justification. The phase 3 trial for KANJINTI was conducted in the neoadjuvant and adjuvant early HER2+ breast cancer setting. KANJINTI received approval for all Herceptin approved indications by justified extrapolation. Information on how the product is being used in clinical practice, and in which patients and chemotherapy combinations will provide real-world evidence.

6.3 Statistical Inference (Estimation or Hypothesis)

This study will describe patient characteristics and the utilization of KANJINTI in routine clinical practice. Descriptive statistics such as number and percentage of patients, mean, SD, median, upper and lower quartiles, minimum and maximum values will be

provided. Precision will be given in terms of 95% CIs or SD where appropriate. Formal hypotheses will not be tested.

7. Research Question and Objectives

Research Question: What are the characteristics of breast cancer patients receiving KANJINTI?

7.1 Primary

- Describe characteristics of breast cancer patients receiving KANJINTI including treatment setting neoadjuvant, adjuvant, or metastatic.
- Describe if the patient was trastuzumab treatment naïve or if the patient was switched from a different trastuzumab brand. For patients who received Herceptin, which route was used for administration (IV or SC).
- Gather concurrent chemotherapy, targeted therapies, and/or endocrine therapy which are given with KANJINTI
- Describe reasons for KANJINTI discontinuation and subsequent treatment plan

7.2 Exploratory

- Evidence of communication and/or patient consent with respect to being informed that they are being prescribed a biosimilar
- Safety in patients administered KANJINTI in an observational setting will be monitored, including adverse event categories of interest: cardiac dysfunction, administration/infusion-related reactions, neutropenia, pulmonary disorders, and infections
- Efficacy of treatment including pathologic complete response rate (pCR; neoadjuvant), time to disease progression (adjuvant and metastatic setting), progression-free survival (PFS; adjuvant and metastatic setting), and overall response rate (ORR; complete response rate plus partial response rate [metastatic])

8. Research Methods

8.1 Study Design

This is a single-arm, observational, serial chart review of adult HER2+ breast cancer patients receiving KANJINTI, in an effort to understand patterns of KANJINTI use. Data from each patient will include firstly, baseline demographics, disease history and breast cancer treatment history, gathered retrospectively from patients medical charts prior to KANJINTI initiation and; secondly follow-up data, from KANJINTI initiation date up to withdrawal of consent, death, lost to follow-up, entry into interventional trial, or end of study (12months after last patient enrolled), whichever occurs earliest. It is important to note that part of the follow-up data (follow-up following KANJINTI initiation), will be collected retrospectively from the enrollment date.

For each site, all consecutive eligible patients will be enrolled until the targeted number of patients for the site is met. Patient's informed consent (where required per country regulation) to be part of the study will be requested only after the patient has initiated KANJINTI.

8.2 Setting and Study Population

8.2.1 Study Period

The total enrollment period for the study is planned for a period of approximately 12 months, anticipating an observational period of maximum 24months per patient. The overall study duration will be approximately 24months. An interim analysis is planned for Quarter 1 in 2020. A final report is due 12 months after the end of data collection.

8.2.2 Selection and Number of Sites

Country level enrollment will allow sufficient numbers to facilitate the representativeness of each country and to ensure appropriate level of data collection to support planned analysis. A country-specific cap will be applied to limit the maximum enrollment in any one country. However, this cap may be lifted in cases of serious enrollment challenges in certain countries. Site selection will be carried out according to normal site evaluation processes. Selection will be based on, desire to have a representative sample, interest in study participation, and willingness and capacity to comply with protocol and data entry conventions. Sites will be considered active after fulfilling all legal, regulatory and ethical requirements. To avoid the possibility of site study participation influencing prescribing practices, sites will not be approached about potential study participation for at least 2 months following site-specific KANJINTI access (ie, ≥ 2 months after known date of first drug order or date of first drug administration). Additionally, patient informed consent (where required per country regulations) to be part of the study will be requested only after the patient has initiated KANJINTI.

In total, approximately 500 patients will be included across approximately 8 European countries with a maximum of 150 patients in any one country.

8.2.3 Patient Eligibility

8.2.3.1 Inclusion Criteria

Patients are eligible to take part in the study if they meet the following criteria:

- Patients who have HER2+ breast cancer in any stage of disease whether metastatic or early
- Patients receiving or having received KANJINTI treatment according to the judgment of the physician, after adoption of KANJINTI on the institution formulary, in routine clinical practice
- Patients are aged ≥ 18 years at KANJINTI initiation

8.2.3.2 Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria:

- Currently participation or planning to participate in a concurrent interventional clinical trial involving therapeutic agent(s)
- Have other cancer type(s), concurrent to breast cancer
- Patients that have not provided an informed consent, where required per country-specific regulations
- Patients whose medical chart is not available for data extraction

8.2.4 Baseline Period

The baseline period is defined as, for each patient, the period up to 4 months prior to KANJINTI initiation. Entries recorded during this baseline period in a patient's medical chart will be reviewed to obtain information on demographic factors, disease and treatment history (including the most recent anticancer therapies prior to KANJINTI initiation), and medical history. Summaries of baseline characteristics will reflect patient status on the date of the first dose of KANJINTI (eg, age, stage of disease, concomitant anticancer therapies).

8.2.5 Study Follow-up

The follow-up period for a patient is defined as the period from KANJINTI initiation to withdrawal of consent, death, lost to follow-up, entry into interventional trial, or end of study (12months after last patient enrolled), whichever occurs earliest. Follow-up data will be collected through serial review of patients' medical charts.

8.3 Variables

8.3.1 Exposure Assessment

All patients enrolled in the study will be exposed to KANJINTI. The treatment setting (neo-adjuvant, adjuvant, metastatic) will be collected. Subjects who have ever been

administered trastuzumab prior to KANJINTI will be categorized as switchers, otherwise they will be categorized as trastuzumab treatment naïve.

8.3.2 Outcome Assessment

8.3.2.1 Primary Outcome Measures:

Baseline Demographics:

- Age, sex, weight, height

Disease History Characteristics:

- Date of initial breast cancer diagnosis
- HER2+ assessment: method
- Breast cancer stage at baseline
- Breast cancer stage at diagnosis
- Prior surgery for breast cancer
- Lymph node involvement
- Tumor classification
- Nodes classification
- Histological grading
- ER/PR status
- Metastatic disease (yes, no), if yes, site of metastases: liver, lung, bones, brain, other
- Other relevant medical history and/or relevant comorbidities
- Eastern Cooperative Oncology Group Performance Status at baseline

Treatment History

- All anti-breast cancer regimens 4 months prior to KANJINTI initiation (including starting date, end date, route and other trastuzumab brand)
- Presence of an IV infusion port / catheter port (eg, Port-A-Cath) / pic line

KANJINTI Regimen

- Treatment setting (neoadjuvant, adjuvant, metastatic)
- Line of therapy: 1, 2, 3 or maintenance (metastatic setting)
- Concomitant cancer chemotherapy, chemotherapy, hormonal therapy, targeted therapy, select all that apply:
  - as monotherapy
  - in combination with paclitaxel, if yes, every 3 weeks or weekly
  - in combination with docetaxel
  - in combination with an aromatase inhibitor

  - in combination with pertuzumab
  - in combination with lapatinib
  - Other
- KANJINTI dose and schedule
- Reason for ending KANJINTI and subsequent treatment plan

8.3.2.2 Exploratory Outcome Measures:

- Evidence of documentation in patients chart of patient education or information on biosimilar (yes, no). If yes:
  - Patient consent
  - Hospital policy on biosimilar use documented
  - Was the brand name KANJINTI specified?
  - Who provided the information?
  - Was a patient package leaflet for KANJINTI provided?
- Safety
  - Overall safety of KANJINTI in patients administered KANJINTI in an observational setting will be monitored (specified adverse events will be exempt from collection – Section 10.2)
  - Adverse events of interest will be collected: cardiac dysfunction, administration/Infusion-related reactions, neutropenia, pulmonary disorders, and infections. Time from KANJINTI initiation to their occurrence date will also be derived.
- Cardiac assessments at baseline and follow-up (ejection fraction %, method of assessment – echocardiogram [ECHO] or multigated acquisition [MUGA] scan)
- Breast cancer stage at follow-up
- Disease response assessments, together with time from KANJINTI initiation to these disease responses
- Eastern Cooperative Oncology Group Performance Status during follow-up

8.3.3 Validity and Reliability

The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making for a patient's care. The data will be abstracted from the medical records and entered into the electronic case report form (eCRF). Site staff will be trained on the electronic abstraction form (use of the eCRF) to ensure that data entered are accurate.

8.4 Data Sources

Data will be obtained from routine clinical records at least quarterly and transcribed by site staff onto an eCRF. At evaluation stage, consideration will be made to ensure all

types of settings caring for HER2+ patients with KANJINTI, in the country, are represented in the sample.

The data from these chart reviews will be merged to form a longitudinal cohort for analysis. Since the data collected are per routine practice for patient care, information on KANJINTI administration and adverse events of interest are expected to be reasonably complete, although some missing data can be expected.

Collection of follow-up data will be carried out retrospectively (ie, data prior to patient enrollment) and prospectively (ie, data after patient enrollment, collected through serial review of patients' medical charts).

8.5 Study Size

The primary objective of this study is to describe the characteristics of patients treated with KANJINTI for HER2+ breast cancer (eg, demographics, disease characteristics, treatment history, prior trastuzumab therapy). The study is planned to enroll approximately 500 patients across approximately 8 countries in Europe with a maximum of 150 patients in any one country. Data summaries are intended to be descriptive in nature and may be required at a country or sub-population level (eg, metastatic patients). Table 1 shows the precision that may be obtained, in terms of 95% CI half-widths, for estimates of proportions for various sub-population sample sizes and the overall total sample size of 500.

Table 1. Expected Precision for Estimating Proportions

Sample Size	95% CI Half-width (%) for Proportion					
	5%	10%	20%	30%	40%	50%
25	10.0	12.2	15.1	16.9	17.9	18.2
50	6.5	8.5	10.9	12.3	13.1	13.4
100	4.5	6.0	7.8	8.8	9.4	9.6
200	3.1	4.2	5.5	6.3	6.7	6.9
500	1.9	2.6	3.5	4.0	4.3	4.4

For example, a sample size of 500 patients would ensure that the half width of the 95% CI for the proportion of patients on KANJINTI that switched from trastuzumab or another biosimilar, calculated using the Wilson Score method, is within 2.6 percentage points if the point estimate is 10% and within 4.4 percentage points if the point estimate is 50%.

8.6 Data Management

Data are abstracted by site staff from patient notes into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all staff delegated to abstract patient data. An eCRF Completion Guideline is provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, case report forms [CRFs] and other pertinent data) provided that patient confidentiality is respected.

The clinical monitor or designee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of research. The Clinical Monitor or designee is to have access to patient medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all patients and sites, a clinical data management review is performed on patient data received at Amgen. During this review, patient data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the electronic data capture (EDC) system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and site notifications, and agrees with the content.

8.6.1 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Interim Analysis/Analyses

A limited number of interim analyses may be performed to meet requirements from local reimbursement agencies of the countries participating in the study and/or for publication purposes. These analyses will be described in the statistical analysis plan and are anticipated to include an analysis approximately 6months after the first patient enrolled. All patients enrolled by the data cutoff date will be included. The results of interim analyses are not anticipated to alter the conduct of the study. Additional interim analyses may be performed if necessary according to country-specific and/or reimbursement agency requests

8.7.1.2 Primary Analysis

The primary analysis will be conducted after the last patient has ended study follow-up, as described in Section 8.2.5.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

The approach to the statistical analysis will be generally descriptive. No formal hypotheses will be tested.

Categorical data will be summarized by the number and percentage of patients in each category. Two-sided 95% CIs calculated using Wilson's method where appropriate will be presented. Continuous data will be summarized by mean (and 95% CI where appropriate), SD, median, lower and upper quartiles, and minimum and maximum values. Time-to-event endpoints (time from KANJINTI initiation to the specific events) will be summarized using Kaplan-Meier methodology.

Analyses will be presented by treatment setting (neo-adjuvant, adjuvant, and metastatic) and trastuzumab initiation status (naïve new starter, switcher).

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The eCRFs will be designed to minimize missing data and to optimize the integrity of collected data. Patients' records will not be excluded because of missing data and missing data will not be imputed. For categorical variables, missing responses will be shown as a category in the analysis. For numeric variables, the number of non-missing observations will be presented and analyzed.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

The number of patients enrolled and the number in each analysis set will be summarized. Patients who were not enrolled but who met the eligibility criteria will be listed in a non-participant log, along with reason for nonenrollment, by country. Patient enrollment by country, indication for KANJINTI use, stage of disease, and investigator will be summarized.

8.7.2.3.2 Description of Patient Characteristics

Baseline demographic and disease characteristics will be summarized descriptively as outlined in Section 8.7.2.1.

8.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

All analyses are descriptive and will be analyzed as outlined in Section 8.7.2.1. Patients' demographic characteristics, disease history, and breast cancer treatment history at KANJINTI initiation date will be summarized. We will be distinguishing switcher (patients with a history of trastuzumab treatment) from naïve patients (patients with no history of trastuzumab treatment). Patients will also be presented by setting (neoadjuvant, adjuvant and metastatic). Medications taken concomitantly to KANJINTI will also be described.

Disease response will be analyzed by treatment setting and will include the following: for adjuvant and metastatic patients the disease progression rate will be calculated, and time to disease progression and progression-free survival (PFS) will be analyzed using Kaplan-Meier. For neo-adjuvant patients the pCR rate will be calculated. For metastatic patients the ORR will also be calculated, defined as best overall response of partial response or better.

Also, for some of the adverse events of interest, where sample size allows, time to their occurrence will be analyzed using Kaplan-Meier.

8.7.2.4.1 Subgroup Analysis

Apart from country, there are no other specific subgroups of interest.

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

The patient incidence of all treatment-emergent adverse events of interest will be summarized by system organ class, by preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later. This summary for these treatment-emergent adverse events will include the following categories:

- All adverse events
- All serious adverse events
- Fatal adverse events
- Serious treatment-emergent adverse events
- Treatment-related adverse events
- Treatment-emergent adverse events of interest from the following categories: cardiac dysfunction, administration/infusion-related reactions, neutropenia, pulmonary disorders, and infections. Medical Dictionary for Regulatory Activities search strategies for the adverse events of interest categories will be specified in the study statistical analysis plan.
- Adverse events leading to investigational product discontinuation

8.7.3.1 Additional Analyses of Adverse Events of Interest

If sample size allows, time from KANJINTI initiation to occurrence of specified adverse events/ adverse event categories will also be explored (see statistical analysis plan).

8.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen standard operating procedures (SOPs).

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Documents to be maintained for the study are as follows:

- patient files containing the completed eCRF, informed consent forms, as applicable, and patient identification list
- study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs, and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

As with most of the chart reviews, there is considerable risk of misclassifying some of the exposed patients with respect to a particular condition as nonexposed. Indeed, absence of information, in a patient chart, on a particular event and/or condition may not necessarily be an absence of the occurrence of that event to the particular patient. However, because of the seriousness of the condition under investigation here, it is expected that patients are closely monitored and as such events occurring and/or any interventions are fully documented into the patient medical records, limiting the risk of misclassifications.

8.9.1.2 Information Bias

The study is a chart review and as such, it is possible that we do not find all the relevant information in the patients' medical chart. Absence of information on a particular event and/or condition may not necessarily be an absence of the occurrence of that event to the particular patient, particularly for sicker and frailer patients. This could exacerbate misclassification and thus contribute to bias analyses.

8.9.1.3 Selection Bias

In countries where patient informed consent is required to access medical records, selection/volunteer bias could be an issue if, for example, sicker patients are less likely to consent.

To minimize bias, eligibility criteria have been kept broad. Also, each site will document any eligible patients that are not subsequently enrolled to the study. This could help assess, posthoc, the potential impact of consenting on sample selection.

The study population could be skewed toward healthier patients because they are perceived by investigators to be easier to manage with the required data input needed. However, hopefully, by trying to enroll successive eligible patients, this will minimize this potential selection bias.

8.9.1.4 Confounding

No formal comparisons of outcomes between subgroups are planned for this study, thereby eliminating the risk of confounding bias.

8.9.2 External Validity of Study Design

Healthcare systems and reimbursement decisions may vary between the countries anticipated to take part in the study. Therefore, some of the outcomes may not be informative to summarize across the entire study due to inherent biases (eg, if a country imposes a cap on the maximum number of reimbursed cycles of treatment). However we do expect the study carry some external validity within specific countries, given all the effort taken to have a representative sample within the country. At evaluation stage, consideration will be made to ensure all types of settings caring for HER2+ patients with KANJINTI, in the country, are represented in the sample.

8.9.3 Analysis Limitations

The precision of estimates will depend on the number of patients enrolled in each country or subgroup. The precision of time-to-event analyses will depend on the number of events observed during the study follow-up.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

An important limitation will relate to missing information since the data for this study will be abstracted from medical charts. The eCRF will prompt recording of any information that is available, but the data being abstracted were recorded for patient care and not research purposes. Therefore, information that is not deemed relevant to the care of that patient might not be captured in the chart, resulting in missing or incomplete data.

For categorical data, missing responses will impact the resulting proportions of patients with nonmissing values. Another potential limitation of the study could be the inclusion of a skewed population of healthier patients into the chart review because they are perceived to be easier to manage with the required data input needed. However, hopefully, by trying to enroll successive eligible patients, this will minimize this potential selection bias.

9. Protection of Human Patients

This study will comply with all relevant ethical and regulatory requirements in each country, and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen adverse event reporting SOPs. This study and data collection will be conducted in accordance with the relevant local laws.

The responsible physician is also responsible for following documents to Amgen or its representative for review before study initiation occurs:

- Signed and dated protocol signature page (Responsible Physician's Agreement)
- Copy of the Central Ethics Board approval of the protocol, waiver for requirement of informed consent where applicable
- Patient or patient's legally acceptable representative has provided informed consent (for countries where required per local regulations)
- Up-to-date curriculum vitae of responsible physician and all co/sub-physicians
- Signed confidentiality agreement
- Signed study contract

The responsible physician will be charged with maintaining correct and comprehensive documentation, while the Amgen monitor/designee is tasked to ensure that the responsible physician is following the correct study protocol.

9.1 Informed Consent

For countries where written informed consent is required, an initial sample informed consent form will be provided by Amgen for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Regional Clinical Trial Manager to the investigator. The written informed consent document is to be prepared in the language of the potential patient population. Where required by participating clinical sites for the collection of anonymized medical chart data, and before a patient's participation in the study, the investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the patient or legally acceptable representative.

The acquisition of informed consent is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient or legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative. If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

9.2 Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, where applicable, other written patient information, and any proposed advertising material must be submitted to the IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent form, where applicable, must be received by Amgen before study can be executed.

The investigator must submit and, where necessary, obtain approval from the IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The investigator is to notify the IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

9.3 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

9.4 Patients Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

10. Collection, Recording and Reporting of Safety Information and Product Complaints

10.1 Definition of Safety Events

10.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

10.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- Is fatal
- Is life threatening (places the patient at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization, but may

jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product
- Pregnancy and lactation exposure
- Transmission of infectious agents
- Reports of uses outside the terms for authorized use of the product including off-label use
- Occupational exposure
- Any lack or loss of intended effect of the product(s)

10.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s), or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

Retrospective Chart Review (from KANJINTI initiation to study enrollment):

This study is analyzing secondary data from medical charts. The safety outcomes that are listed in Section 8.3.2.2 (from KANJINTI initiation to subject enrollment) will be documented in the medical charts and analyzed as described in Section 8.7.3 and Section 8.7.3.1. During this period, the retrospective part of the study, safety events (all observed adverse events, serious adverse events, product complaints, and other safety findings) excluding those exempted (see below and Appendix F) will be collected from KANJINTI initiation to study enrollment. These will be reported in aggregate in the final study report as described in Section 8.7.3 (the patient incidence of treatment emergent adverse events will be summarized by system organ class, by preferred term according

to the MedDRA version 21.0 or later). Submission of safety outcomes as individual safety reports to Amgen for retrospective chart review data is not required. As per routine clinical practice, safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

Prospective Observation Period (time period from study enrollment to final study contact/end of study):

This study is also collecting information prospectively from study enrollment date until withdrawal of consent, death, lost to follow-up, entry into interventional trial, or end of study (12months after last patient enrolled), whichever occurs earliest, from breast cancer patients receiving KANJINTI. Data will be routinely recorded on patient's charts, as per clinical practice, and data for the study will be recorded through at least quarterly serial chart reviews of patient's charts. All safety events (adverse events, product complaints and other safety findings) considered to have occurred following patient exposure to KANJINTI will be collected from study enrollment until withdrawal of consent, death, lost to follow-up, entry into interventional trial, or end of study (12months after last patient enrolled), whichever occurs earliest, with the exception of the protocol-exempted events listed below. The investigator is responsible for recording safety events that they become aware of during study period in the patient's appropriate study documentation. Also, collected safety events which are considered serious must be submitted as individual safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of investigator awareness. Nonserious adverse events must be reported in an expeditious manner, not to exceed 15 calendar days of investigator awareness.

Protocol-exempted Events

The safety profile of the innovator product for KANJINTI is well characterized, leading to a detailed safety profile being included in the SmPC for the biosimilar product KANJINTI.

Together with other safety findings and product complaints, the adverse events to be collected in this study should include all adverse events, serious adverse events, and adverse events of interest (excluding the list of adverse events in Appendix F, where there is a table that has been modified from the table in Section 4.8 of the EU SmPC for KANJINTI).

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of investigator awareness.

All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.

As per routine clinical practice, protocol-exempted events and safety events that are suspected to be related to any medicinal product other than KANJINTI should be reported to the local authority in line with the local country requirements.

If the EDC system is unavailable to the site staff, the adverse event, which is considered serious must still be reported to Amgen within 1 business day of the investigator's awareness, using the paper Adverse Event Contingency Report Form. Nonserious adverse events must be reported in an expeditious manner, not to exceed 15 calendar days of investigator awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix B for a Sample Safety Report Form, Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy and Lactation Notification Worksheets. The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

10.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, investigators/institutions, IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The investigator is to notify the appropriate IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the investigator must be obtained where applicable per local governing

law and/or regulations. The IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual agreement. The investigator is to notify the IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

Final results of the study will be disseminated in the form of a manuscript in the peer-reviewed literature. In addition, where relevant, data from potential interim analyses will be presented at (a) relevant congress(es).

12.1 Publication Policy

The results of the study will be submitted for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. References

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14. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. Sample Safety Reporting Form

AMGEN Study # 20180020 KANJINTI (ABP 980) *(trastuzumab biosimilar)*	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg, Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day____ Month_____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of drug under study	Is event serious?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by Amgen drug under study (Kanjinti /ABP 980) or an Amgen device used to administer the Amgen drug under study? Kanjinti No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20180020 KANJINTI (ABP 980) *(trastuzumab biosimilar)*	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
KANJINTI (ABP 980)	☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20180020 KANJINTI (ABP 980) *(trastuzumab biosimilar)*	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the Common Terminology Criteria for Adverse Events (CTCAE) version 4 is to be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix D. Pregnancy and Lactation Notification Worksheets

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180020

Study Design: ☐ Interventional ☒ Observational (If Observational: ☒ Prospective ☒ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180020

Study Design: ☐ Interventional ☒ Observational (If Observational: ☒ Prospective ☒ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix E. Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken M et al, 1982

Appendix F. List of Protocol-exempted Events

Appendix F should be read in conjunction with Section 10.2.

The following table, which is modified from Section 4.8 of the European Union (EU) Summary of Product Characteristics (SmPC) for KANJINTI, lists the adverse event terms that are not required to be collected in this study.

System Organ Class	Adverse Reaction	Frequency
Blood and lymphatic system disorders	Anaemia	Very common
	White blood cell count decreased/leukopenia	Very common
	Thrombocytopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
	Thinking abnormal	Common
	Dizziness	Very common
	Paraesthesia	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known

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Footnotes are defined on last page of the table

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
Vascular disorders	Hot flush	Very common
	Vasodilatation	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Pancreatitis	Common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
	Hepatic failure	Not known
Skin and subcutaneous tissue disorders	Erythema	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

Footnotes are defined on last page of the table

System Organ Class	Adverse Reaction	Frequency
Skin and subcutaneous tissue disorders	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	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
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Fatigue	Very common
	Pain	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
General disorders and administration site conditions	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

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Note: If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day of investigator awareness. As per routine clinical practice, protocol-exempted events and safety events that are suspected to be related to any medicinal product other than KANJINTI should be reported to the local authority in line with the local country requirements.