EUROPEAN UNION RISK MANAGEMENT PLAN

KANJINTI® (trastuzumab)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	2.0
Date:	15 June 2026
Supersedes:	Version 1.0, dated 13 October 2021

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	2.0
Data lock point of this RMP:	14 April 2026
Date of final sign-off:	15 June 2026
Rationale for submitting an updated RMP	To update the safety concerns in alignment with the reference medicinal product, Herceptin® RMP.

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SV: Postauthorization Experience	Updated postmarketing exposure to a data cut-off date of 14 April 2026 Updated Japan licensing information	Version 2.0, 15 June 2026
SVII: Identified and Potential Risks	Removed missing information 'Safety of 75 mg/m^2 versus 100 mg/m^2 Docetaxel dose' from the list of safety concerns to align with the reference medicinal product, Herceptin®	Version 2.0; 15 June 2026
SVIII: Summary of the Safety Concerns	Updated to reflect the changes made in section SVII	Version 2.0, 15 June 2026
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Removed specific adverse reaction follow-up questionnaires to align with reference medicinal product, Herceptin® ○ Report of suspected ABP 980 associated cardiac adverse event ○ Report of suspected ABP 980 associated adverse event administration-related reactions	Version 2.0, 15 June 2026

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)	Updated to reflect the changes in section SVII	Version 2.0, 15 June 2026
Part VI: Summary of the Risk Management Plan	Updated as per changes in Module SVII and SVIII of Part II, Part III, and Part V of this RMP	Version 2.0, 15 June 2026
Part VII: Annexes		
Annex 4: Specific Adverse Drug Reaction Follow-up Forms	Removed specific adverse drug reaction follow-up forms ○ Report of suspected ABP 980 associated cardiac adverse event. ○ Report of suspected ABP 980 associated adverse event administration-related reactions.	Version 2.0, 15 June 2026

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
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Details of the currently approved RMP:	
Version number:	1.0
Approved with procedure:	EMEA/H/C/004361/IB/0020/G
Date of approval (opinion date):	18 November 2021
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ADCC	antibody-dependent cell-mediated cytotoxicity
ARR	administration-related reaction
ATC	Anatomical Therapeutic Chemical
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
EBC	early breast cancer
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ErbB2	receptor tyrosine-protein kinase ErbB2 other abbreviations are HER2 and HER2/neu
EU	European Union
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2; other abbreviations are ErbB2 and HER2/neu
HER2/neu	receptor tyrosine-protein kinase ErbB2; also known as human epidermal growth factor receptor 2 (HER2)
IgG1	immunoglobulin G1
ILD	interstitial lung disease
INN	International Nonproprietary Name
IV	intravenous
LVEF	left ventricular ejection fraction
MAH	marketing authorization holder
MBC	metastatic breast cancer
MGC	metastatic gastric cancer
NYHA	New York Heart Association
PI	Product Information
PL	Package Leaflet
QPPV	Qualified Person for Pharmacovigilance
RCT	randomized controlled trial

Term/Abbreviation	Explanation
RMP	Risk Management Plan
RR	relative risk
SC	subcutaneous
SmPC	Summary of Product Characteristics
US	United States

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Note to Reviewers: ABP 980 was developed as a biosimilar candidate to Herceptin® (trastuzumab). Herceptin (trastuzumab) that is approved in, and sourced from, the United States (US) is referred to as "trastuzumab (US)." Herceptin (trastuzumab) that is approved in, and sourced from, the European Union (EU) is referred to as "trastuzumab (EU)." When reference is made to the generalized term "trastuzumab," the information provided is referring to aspects of the reference product that are not region-specific. Such aspects may include but are not limited to Roche's multiregional development program, scientific information, and publicly available literature for trastuzumab. The comparator reference medicinal product, Herceptin, is referred to as trastuzumab in ABP 980 studies to be consistent with marketing application. In all other contexts in this document it is referred to as Herceptin. The biosimilar candidate to Herceptin is referred to as ABP 980 in the Amgen-sponsored studies to be consistent with the marketing application. In all other contexts in this document it is referred to as KANJINTI.

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Trastuzumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Antineoplastic and immunomodulating, antineoplastic agents, monoclonal antibodies, and antibody drug conjugates (L01FD01)
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	KANJINTI
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Antineoplastic agents, monoclonal antibodies
Summary of mode of action	Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of human epidermal growth factor receptor 2 (HER2)'s extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signaling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.
Important information about its composition	KANJINTI was developed as a biosimilar to Herceptin (trastuzumab). Trastuzumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody against HER2.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.

Table 1. Product(s) Overview

Indication(s) in the EEA Current	<u>Metastatic breast cancer</u> KANJINTI is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC). • as monotherapy for the treatment of those patients who have received at least 2 chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor-positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. • in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable. • in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. • in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. <u>Early breast cancer</u> KANJINTI is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC): • following surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable). • following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. • in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. • in combination with neoadjuvant chemotherapy followed by adjuvant KANJINTI therapy, for locally advanced (including inflammatory) disease or tumors > 2 cm in diameter. KANJINTI should only be used in patients with metastatic or early breast cancer whose tumors have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Table 1. Product(s) Overview

Indication(s) in the EEA	
Current (continued)	Metastatic gastric cancer KANJINTI in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. KANJINTI should only be used in patients with metastatic gastric cancer (MGC) whose tumors have HER2 overexpression as defined by IHC 2+ and a confirmatory silver in situ hybridization or fluorescent in situ hybridization result, or by an IHC 3+ result. Accurate and validated assay methods should be used.
Proposed (if applicable)	Not applicable
Dosage in the EEA	
Current	Metastatic breast cancer • Three-weekly schedule: The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at 3 weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the loading dose. • Weekly schedule: The recommended initial loading dose of KANJINTI is 4 mg/kg body weight. The recommended weekly maintenance dose of trastuzumab is 2 mg/kg body weight, beginning 1 week after the loading dose. • Administration in combination with paclitaxel or docetaxel: In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab (for dose, see the Summary of Product Characteristics [SmPC] for paclitaxel or docetaxel) and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated. • Administration in combination with an aromatase inhibitor: In a pivotal trial (BO16216), trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors).

Table 1. Product(s) Overview

Dosage in the EEA Current (continued)	<u>Early breast cancer</u> • Three-weekly and weekly schedule: As a 3-weekly regimen the recommended initial loading dose of KANJINTI is 8 mg/kg body weight. The recommended maintenance dose of KANJINTI at 3-weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the loading dose. As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. <u>Metastatic gastric cancer</u> • Three-weekly schedule: The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at 3-weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the loading dose. <u>Breast cancer and gastric cancer</u> • Duration of treatment: Patients with MBC or MGC should be treated with KANJINTI until progression of disease. Patients with EBC should be treated with KANJINTI for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond 1 year is not recommended. • Dose reduction: No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel, or aromatase inhibitor for information on dose reduction or delays. If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of KANJINTI should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Table 1. Product(s) Overview

Dosage in the EEA	
Current (continued)	• Missed doses: If the patient has missed a dose of KANJINTI by 1 week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; 3-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or 3-weekly schedules, respectively. If the patient has missed a dose of KANJINTI by more than 1 week, a re-loading dose of KANJINTI should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; 3-weekly regimen: 8 mg/kg) as soon as possible. Subsequent KANJINTI maintenance doses (weekly regimen: 2 mg/kg; 3-weekly regimen 6 mg/kg, respectively) should be administered 7 days or 21 days later according to the weekly or 3-weekly schedules, respectively. • Special populations: Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition. • Paediatric population: There is no relevant use of trastuzumab in the paediatric population.
Proposed (if applicable):	Not applicable
Pharmaceutical form(s) and strength(s)	
Current (if applicable):	KANJINTI is supplied as a white to pale yellow lyophilized powder for concentrate for solution for infusion. It is supplied either in 20 mL or 50 mL type 1 glass vials. Each single-use vial contains either 150 mg or 420 mg KANJINTI. The reconstituted solution contains 21 mg/mL of trastuzumab.
Proposed (if applicable):	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

As per the Guideline on Good Pharmacovigilance Practices Module V - Risk management systems (EMA/838713/2011 Rev 2) Part II Module SI may be omitted from the EU RMP for applications for similar biological products.

Part II: Module SII - Nonclinical Part of the Safety Specification

ABP 980 is a biosimilar to Herceptin (trastuzumab), the reference medicinal product, under the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I. The active ingredient of ABP 980 is a recombinant humanized IgG1 monoclonal antibody directed against HER2 with an amino acid sequence identical to trastuzumab (with the exception that the coding sequence for the C-terminal lysine was removed from the DNA vectors for expression of ABP 980). Guidelines outlining required biosimilar antibody therapeutic studies indicate that developmental and reproductive toxicity, genotoxicity, carcinogenicity, and drug interaction studies are not warranted when the proposed product has been demonstrated to be highly similar to the reference medicinal product, Herceptin, through extensive structural and functional characterization and animal toxicity studies (Committee for Medicinal Products for Human Use [CHMP] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev 1], [European Medicines Agency, 2015]). There is extensive clinical and postmarketing experience and use with the reference medicinal product, Herceptin, and since this is a biosimilar, the information being referred from the Herceptin package is thus relevant in this section.

Comparative toxicology studies were performed for detection of any meaningful toxicological differences between ABP 980 and trastuzumab in terms of nonclinical safety and toxicokinetics. The toxicology program with ABP 980 and trastuzumab included a comparative 1-month repeat-dose monkey toxicology study (Study 37630 TSP), a 14-day repeat-dose rat toxicology study (Study 118501), and a tissue cross-reactivity study with frozen human tissues (Study 37629 CRE). The dose, regimen, duration, and test species for the comparative monkey toxicology study were selected to allow detection of any meaningful toxicological differences between ABP 980 and trastuzumab.

A 1-month Good Laboratory Practice-compliant ABP 980 comparative toxicology study was performed in female cynomolgus monkeys (Study 37630 TSP). Six female monkeys/group were administered vehicle, 25 mg/kg ABP 980, or 25 mg/kg trastuzumab (EU) intravenously (IV) twice weekly for 1 month (8 doses), which resulted in similar exposure. Following 1 month of repeated administration, both ABP 980 and trastuzumab were well tolerated. Consistent with historical studies with trastuzumab, findings in the comparative monkey study were confined to injection-site reactions and

were similar in incidence and severity for ABP 980 and trastuzumab. The toxicokinetic profile of ABP 980 was similar to that of trastuzumab and no unexpected toxicities were observed.

A 14-day Good Laboratory Practice-compliant toxicology study with ABP 980 and trastuzumab (Study 118501) was conducted in male and female rats. The dose regimen was selected to match that used in the comparative monkey study. Ten rats/sex/group were administered 25 mg/kg ABP 980 or 25 mg/kg trastuzumab (EU) IV twice weekly for 14 days. No toxicity was observed and there were no effects on reproductive organs after administration of ABP 980 or trastuzumab.

A tissue cross-reactivity study was performed in order to compare the immunoreactivity of biotinylated ABP 980 and trastuzumab in normal human tissues and blood smears (Study 37628 CRE). No significant differences in staining patterns or locations were recorded and the staining was also consistent with the published data for trastuzumab (European Medicines Agency [EMA] Herceptin [trastuzumab] European Public Assessment Report [EPAR]: Scientific Discussion, 21 October 2005).

Table 2 provides a summary of nonclinical safety findings from ABP 980 nonclinical studies and the reference medicinal product, Herceptin, nonclinical studies (EMA Herceptin [trastuzumab] EPAR: Scientific Discussion, 21 October 2005).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 980 studies		
Toxicity		
• Repeat-dose toxicity		
14-day repeat-dose comparative toxicology study in male and female rats at 25 mg/kg dosed IV twice weekly (Study 118501)	In the 14-day repeat-dose comparative toxicity study in rats with ABP 980 and trastuzumab (EU), no toxicity was observed.	No effects on systemic toxicity were observed.
1-month repeat-dose comparative toxicology study in female cynomolgus monkeys at 25 mg/kg dosed IV twice weekly (Study 37630 TSP)	The repeat-dose toxicokinetic profiles were similar for ABP 980 and trastuzumab (EU). In the 1-month repeat-dose comparative toxicity study, treatment-related indurations or nodules at the injection sites were observed with both ABP 980 and trastuzumab (EU). Slightly higher mean urea and triglyceride levels were observed with both trastuzumab (EU) and ABP 980 as compared to control. No unexpected toxicities were observed with ABP 980 and the toxicokinetic profile was similar for ABP 980 and trastuzumab (EU).	Injection site indurations or nodules were similar after ABP 980 and trastuzumab treatment and no effects on systemic toxicity were observed. These effects are assumed to be relevant for humans.
• Single-dose toxicity, developmental and reproductive toxicity; genotoxicity; carcinogenicity single and repeat-dose toxicity	In line with the EU guidance on biosimilar products (CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues [EMEA/CHMP/BMWP/42832/20 05 Rev 1]) these studies have not been performed for ABP 980.	As a biosimilar medicinal product, the observed effects of Herceptin are expected for ABP 980.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Herceptin studies		
Toxicity		
• Single and repeat-dose toxicity		
Single-dose acute studies by IV bolus administration in mice at 0, 9.4, 47, and 94 mg/kg and in rhesus monkeys at 0, 4.7, 23.5, and 47 mg/kg	Toxicity was not observed following IV bolus administration in mice and rhesus monkeys.	There was no evidence of acute or multiple-dose toxicity in studies of up to 6 months (Herceptin SmPC).
4-week study in rhesus monkeys and 12-week and 26-week studies in cynomolgus monkeys, 1 to 25 mg/kg once or twice weekly	Trastuzumab was well-tolerated and observations were confined to injection-site trauma in the monkey (EMA Herceptin [trastuzumab] EPAR: Scientific Discussion, 21 October 2005).	
• Reproduction toxicity	Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin IV formulation and have revealed no evidence of impaired fertility or harm to the fetus. Placental transfer of trastuzumab during the early (days 20 to 50 of gestation) and late (days 120 to 150 of gestation) fetal development period was observed (Herceptin SmPC).	It is not known whether Herceptin can affect reproductive capacity. Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus (Herceptin SmPC).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Herceptin studies (continued)		
Toxicity (continued)		
• Embryo-fetal and peri-/postnatal toxicity	No maternal toxicity, embryotoxicity, or teratogenicity was observed (EMA Herceptin [trastuzumab] EPAR: Scientific Discussion, 21 October 2005).	In the postmarketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Women who become pregnant should be advised of the possibility of harm to the fetus (Herceptin SmPC).
• Genotoxicity	Genotoxicity has been investigated for Herceptin by in vitro and in vivo studies and the results were negative for all tests (Herceptin SmPC; EMA Herceptin [trastuzumab] EPAR: Scientific Discussion, 21 October 2005).	Herceptin is not genotoxic (Herceptin SmPC).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Herceptin studies (continued)		
Cardiac dysfunction	Preclinical studies of trastuzumab to investigate cardiac dysfunction, primarily LVEF and CHF have been performed and several possible mechanisms have been suggested (De Keulenaer et al, 2010). A feedback loop may exist involving neuregulin and receptor tyrosine-protein kinase ErbB2 (as a co-receptor) as part of a cell survival mechanism; cell survival signaling may be blocked or altered by trastuzumab; downregulation of ErbB2 may prevent cell survival signaling with trastuzumab use; trastuzumab may increase cardiac physiological stress or damage; or trastuzumab may have a direct effect on cardiomyocytes. Recently, it was reported that HER2 signaling plays an important role in the sympathovagal control systems of the heart. Cooperation of neuregulin and the cholinergic system produced potent anti-adrenergic effects, resulting in a decrease in cardiac output and blood pressure in in vitro studies. Thus, this suggests that resting sympathetic tone may be increased in patients treated with trastuzumab and in neuregulin-deficient mice (De Keulenaer et al, 2010). The clinical importance of these findings is not clear.	Cardiac dysfunction has been observed in Herceptin clinical trials. Patients treated with Herceptin are at increased risk for developing CHF (New York Heart Association [NYHA] class 2 to 4) or asymptomatic cardiac dysfunction (Herceptin SmPC).
Intrathecal administration 4-week, repeat-dose study in cynomolgus monkeys, weekly intrathecal administration at doses of 0, 0.3, or 15 mg	Trastuzumab has been administered intrathecally in a small number of spontaneous cases for treatment of central nervous system (CNS) metastases. Thus, intrathecal administration was studied in cynomolgus monkeys. No effects on standard toxicology parameters or neurologic function were reported following trastuzumab administration. The doses administered in the cynomolgus monkeys and cerebral spinal fluid concentrations achieved in this study were greater than those reported in patients after intrathecal administration (Braen et al, 2010).	There is no direct relevance related to the approved indications for Herceptin.

Part II: Module SIII - Clinical Trial Exposure

Estimated cumulative subject exposure in completed Amgen-sponsored clinical studies since the beginning of the development program for ABP 980 is summarized in Table 3 and Table 4. For both studies, the estimates are based on actual exposure data. Cumulative subject exposure from the completed phase 1 and phase 3 clinical trials, with a database lock date of 29 March 2017, are presented by age and race or ethnic group in Table 5 and Table 6, respectively.

Table 3. Total Subject Exposure to ABP 980 or Trastuzumab in Amgen-sponsored Clinical Trials[a] by Indication (Safety Analysis Set)

Indication	ABP 980 n (subj-yrs)	Trastuzumab n (subj-yrs)[b]
Global Phase 1 pharmacokinetic study	50 (4.24)	107 (9.08)
Phase 3 EBC study	535 (488.59)	361 (228.89)
Total	585 (492.83)	468 (237.97)

EBC = early breast cancer; EU = European Union; US = United States; subj-yrs = subject-years
[a] Data from the completed global phase 1 pharmacokinetic Study 20130119 (completed on 15Oct2014) and the phase 3 Study 20120283 (completed on 29Mar2017) are included.
[b] Exposure to trastuzumab includes exposure to both US- and EU-authorized trastuzumab (if applicable to the study).
Source Dataset: adamph1.adex, adamph1.adsl and adamph3.adsl, Program: t-exp-ind.sas, Output: t-exp-ind.rtf, Generated on: 30MAY2017 14:45.

Table 4. Total Subject Exposure to ABP 980 or Trastuzumab by Indication and Duration of Cumulative Exposure in Amgen-sponsored Clinical Trials[a] (Safety Analysis Set)

	ABP 980		Trastuzumab[b]	
Indication	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)
Global Phase 1 pharmacokinetic study	50 (4.24)	-	107 (9.08)	-
Phase 3 EBC study	24 (5.62)	511 (482.97)	192 (49.73)	169 (179.15)
Total	74 (9.86)	511 (482.97)	299 (58.81)	169 (179.15)

EBC = early breast cancer; EU = European Union; US = United States; subj-yrs = subject-years
[a] Data from the completed global phase 1 pharmacokinetic Study 20130119 (completed on 15Oct2014) and the phase 3 Study 20120283 (completed on 29Mar2017) are included.
[b] Exposure to trastuzumab includes exposure to both US- and EU-authorized trastuzumab (if applicable to the study).
Source Dataset: adamph1.adex, adamph1.adsl and adamph3.adsl, Program: t-exp-ind-cum.sas, Output: t-exp-ind-cum.rtf, Generated on: 30MAY2017 14:46.

Table 5. Total Subject Exposure to ABP 980 or Trastuzumab in the Phase 3 EBC Study[a] by Age Group (Safety Analysis Set)

Age Group	ABP 980 n (subj-yrs)	Trastuzumab n (subj-yrs)
< 50 years	206 (191.40)	134 (85.97)
≥ 50 years	329 (297.19)	227 (142.92)
Total	535 (488.59)	361 (228.89)

EBC = early breast cancer; subj-yrs = subject-years
[a] Data from the phase 3 EBC Study 20120283 (completed on 29Mar2017) are included.
Source Dataset: adamph3.adsl, Program: t-exp-ind-age.sas, Output: t-exp-ind-age.rtf, Generated on: 30MAY2017 14:46.

Table 6. Total Subject Exposure to ABP 980 or Trastuzumab in the Phase 3 EBC Study[a] by Race or Ethnic Group (Safety Analysis Set)

	ABP 980 n (subj-yrs)	Trastuzumab n (subj-yrs)
Ethnic		
Hispanic or Latino	47 (42.95)	36 (25.05)
Not Hispanic or Latino	487 (444.92)	324 (203.58)
Not allowed to collect	1 (0.72)	1 (0.25)
Race		
White or Caucasian	489 (445.38)	333 (210.98)
Black or African American	12 (12.01)	4 (1.02)
Asian	3 (2.80)	3 (2.36)
American Indian or Alaska Native	1 (1.07)	-
Other	30 (27.32)	21 (14.53)
Unknown	-	-
Total	535 (488.59)	361 (228.89)

EBC = early breast cancer; subj-yrs = subject-years
[a] Data from the phase 3 EBC Study 20120283 (completed on 29Mar2017) are included.
Source Dataset: adamph3.adsl, Program: t-exp-ind-race.sas, Output: t-exp-ind-race.rtf, Generated on: 30MAY2017 14:47.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

For clinical trials for both ABP 980 and Herceptin, a number of exclusion criteria were applied to increase the homogeneity of the clinical trial sample and to minimize potential confounding factors. Since ABP 980 was developed as a biosimilar for Herceptin, the clinical trial for EBC was designed as a head-to-head study versus the reference medicinal product. Therefore, exclusion criteria were constructed to reflect the current precautions and contraindications for Herceptin. Therefore, Table 7 reflects the important exclusion criteria for ABP 980 as well as for Herceptin.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients	ABP 980 is immunologically similar to the reference medicinal product.	No	In line with the reference medicinal product, Herceptin, hypersensitivity to trastuzumab, murine proteins, or to any of the excipients, is a contraindication in the KANJINTI SmPC.
Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy	ABP 980 is immunologically similar to the reference medicinal product.	No	In line with the reference medicinal product, Herceptin, severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy is a contraindication in the KANJINTI SmPC.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Early breast cancer			
Subjects that have serious cardiac illness or medical condition. The conditions include CHF, history of myocardial infarction, other cardiomyopathy, poorly controlled hypertension, or uncontrolled arrhythmia	In patients receiving therapy with the reference medicinal product, Herceptin, alone or in combination with paclitaxel or docetaxel, particularly following anthracycline containing chemotherapy, heart failure has been observed.	No	In line with the reference medicinal product, Herceptin, language concerning treatment of patients with these pre-existing conditions is currently addressed in Section 4.4 “Special warnings and precautions for use” of the KANJINTI SmPC. Patients treated with KANJINTI are at increased risk for developing CHF (NYHA class 2 to 4) or asymptomatic cardiac dysfunction. Caution should be exercised in treating patients with increased cardiac risk, eg, hypertension, documented coronary artery disease, CHF, LVEF of < 55%, and older age.
In subjects that have low LVEF of < 50% or < 55% (this will depend upon the patient population)	Patients with low LVEF are thought to be at increased risk of cardiac toxicity associated with administration of Herceptin and ABP 980.	No	In line with the reference medicinal product, Herceptin, language concerning LVEF < 55% is currently addressed in Section 4.4, “Special warnings and precautions for use” of the KANJINTI SmPC.
Pregnant and lactating women who are of childbearing potential or it has been < 1 year after menopause (unless surgically sterile) who are unable or unwilling to use adequate contraceptive measures during study treatment	Herceptin and ABP 980 are not recommended during pregnancy.	No	In line with the reference medicinal product, Herceptin, language concerning pregnancy is currently addressed in Section 4.6 Fertility, pregnancy, and lactation of the KANJINTI SmPC. Women of childbearing potential should be advised to use effective contraception during treatment with KANJINTI and for 7 months after treatment has concluded. KANJINTI should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Early breast cancer (continued)			
Pregnant and lactating women who are of childbearing potential or it has been < 1 year after menopause (unless surgically sterile) who are unable or unwilling to use adequate contraceptive measures during study treatment (continued)			Women who become pregnant should be advised of the possibility of harm to the fetus. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breastfeed during KANJINTI therapy and for 7 months after the last dose.
Metastatic breast cancer in addition to main exclusion criteria in early breast cancer			
Subjects that have clinically significant infections	Patients are at increased risk for infectious complications due to myelosuppression potentially due to an inability to tolerate myelosuppressive chemotherapy.	No	In line with the reference medicinal product, risk of infections is addressed in Section 4.8, “Undesirable effects” of the KANJINTI SmPC. However, assessment of the patients health and/or fitness is a routine oncology practice, thus no specific warnings or exclusion is included in the KANJINTI SmPC.
Subjects that have evidence of CNS metastases	It is possible that monoclonal antibodies like the reference medicinal product, Herceptin, and ABP 980 will not cross the blood brain barrier and that there is limited time to benefit from treatment in a trial setting.	No	The reference medicinal product, Herceptin has been shown to control extra-cranial disease but may not prevent disease recurrence. Further, there is no evidence to suggest that the reference medicinal product, Herceptin, is associated with an increased risk of CNS metastases in patients with MBC or EBC. Thus, KANJINTI should not be restricted as an option available to physicians for the treatment of patients with brain metastasis.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Metastatic breast cancer in addition to main exclusion criteria in early breast cancer (continued)			
Subjects that have evidence of CNS metastases (continued)			No active screening is performed in breast cancer patients for CNS metastases in the clinical setting.
Subjects that have a life expectancy of < 3 months	Patients with short life expectancy are usually not included in clinical trials.	No	This concern is only applicable within the clinical setting, and thus is not considered by the MAH to be a significant reason to reduce physician options in treatment of patients with a shortened (< 3 months) life expectancy.
Metastatic gastric cancer			
Subjects with current, significant, or uncontrolled gastrointestinal (GI) bleeding	GI bleeding is often a symptom of disease progression, thus it may be difficult for patients with GI bleeding to comply with study assessments. In addition, it is possible that these patients may not be able to tolerate myelosuppressive chemotherapy. In patients treated with the reference medicinal product, Herceptin, serious adverse events with GI bleeding and gastric perforation have been reported.	No	Assessment of the patients' health and/or fitness is a routine oncology practice, thus no specific warnings or exclusion is included in the KANJINTI SmPC. This concern is not considered by the MAH to be a significant reason to reduce physician options in treatment of patients with active infections with KANJINTI.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Metastatic gastric cancer (continued)			
Subjects with active infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus	Patients are at increased risk for infectious complications due to myelosuppression potentially due to an inability to tolerate myelosuppressive chemotherapy.	No	Assessment of the patients' health and/or fitness is a routine oncology practice, thus no specific warnings or exclusion is included in the KANJINTI SmPC. This concern is not considered by the MAH to be a significant reason to reduce physician options in treatment of patients with active infections with KANJINTI.

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SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development *Programs*

The clinical development program for a biosimilar candidate is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 8. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant women have not been studied in ABP 980 and reference medicinal product, Herceptin, clinical programs.
Breastfeeding women	Breastfeeding women have not been studied in ABP 980 and reference medicinal product, Herceptin, clinical programs.
Patients with relevant comorbidities	
Patients with hepatic impairment	ABP 980 and Herceptin have not been studied in this population.
Patients with renal impairment	ABP 980 and Herceptin have not been studied in this population.
Patients with cardiovascular impairment	Patients with history of myocardial infarction, angina pectoris requiring medical treatment, history of or existing CHF (NYHA class 2 to 4), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with trastuzumab (Herceptin SmPC). Subjects with serious cardiac illness or medical condition or low LVEF of < 50% or < 55% were also excluded from ABP 980 clinical studies.
Immunocompromised patients	Oncology patients are generally considered to be immunocompromised. In the EBC study, 535 subjects were exposed to ABP 980 and 361 subjects were exposed to trastuzumab.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.

Table 8. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Population with relevant different ethnic origin	ABP 980 and Herceptin have been studied in subject populations of a variety of racial backgrounds and ethnicity in clinical studies (see Table 6).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	
Male breast cancer patients	Male breast cancer patients were excluded from the ABP 980 EBC study. Breast cancer in males is a rare disease that accounts for < 1% of all male tumors. However, information about safety and use in male and female patients with MGC (which has a higher incidence in men compared to women) is available from clinical studies with the reference medicinal product, Herceptin, and is available in the KANJINTI SmPC.
Paediatric patients	Paediatric patients have not been studied in ABP 980 clinical program as per the Guidelines for Biosimilars (Regulation [EC] No 1901/2006 [Paediatric Regulation] amended by Regulation [EC] No 1902/2008).
Elderly patients	In line with the reference medicinal product, Herceptin, dedicated pharmacokinetic studies in the elderly have not been carried out.
Patients with respiratory impairment	Patients with severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy are contraindicated for the reference medicinal product, Herceptin, and were excluded from the ABP 980 clinical program.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to estimates of patient-time and patient-counts (when feasible) using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

The cumulative number of patient-years of exposure to KANJINTI (trastuzumab) through commercial distribution is shown in Table 9 below.

Table 9. Estimated Number of Patient-years of Exposure to KANJINTI (trastuzumab), by Region, in the Postmarketing Setting Cumulatively From Launch Through 14 April 2026

Cumulative Number of Patient-years of Exposure[a]					
AU	Canada	EUR	US	Other	Total
3 767	7 431	44 571	105 442	22 027	183 237

AU = Australia; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = Countries, not otherwise specified, where Amgen is the marketing authorization holder; US = United States
Note: Numbers may not add to the total due to rounding.
[a] Cumulatively through 14 April 2026.

Postauthorization Use From Business Partners

Per Daiichi Sankyo distribution, cumulatively through 24 September 2025, there has been an estimated 616 patient-years of exposure to Trastuzumab biosimilar for Intravenous Drip Infusions in Japan.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed. The reference medicinal product, Herceptin, is not associated with any abuse potential.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 10. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Missing Information		
Safety of 75 mg/m^2 Versus 100 mg/m^2 Docetaxel Dose	Safety of 75 mg/m^2 Versus 100 mg/m^2 Docetaxel Dose, previously classified as missing information, is removed from the list of safety concerns	This safety concern is removed to align with the reference medicinal product, Herceptin®.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified risks, important potential risks, and missing information presented in Sections SVII.3.1 and SVII.3.2 for Kanjinti are presented as per the EU RMP of Herceptin®. No new safety concerns were identified in the Kanjinti clinical program.

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 11. Important Identified Risk: Cardiac Dysfunction

Potential mechanisms	The cell survival signaling pathway may be affected by ABP 980 through alteration in a potential feedback loop involving neuregulin and ErbB2 (as a co-receptor) which may promote myocyte survival, by altering or blocking cell survival, or by preventing cell survival by down-regulating ErbB2. ABP 980 may also exacerbate cardiac physiological stress or injury.
Evidence source(s) and strength of evidence	This important identified risk is included as per the EU RMP of the reference medicinal product, Herceptin. Evidence sources: ABP 980 clinical studies and Herceptin SmPC.
Characterization of the risk	
Frequency	**ABP 980 studies:** Study 20120283 (EBC) One of the most common side effects of trastuzumab treatment is cardiotoxicity manifested as heart failure, accompanied by a decrease in LVEF or an asymptomatic decrease in LVEF. As per the protocol, LVEF measurements were performed at baseline and during therapy (post anthracycline and post trastuzumab/paclitaxel) on all patients to monitor cardiac dysfunction. Study treatment was withheld in subjects who had LVEF decreases 10 ejection fraction points from baseline and to below 50% for 3 weeks and if there was no improvement in LVEF, investigational product was discontinued. Cardiac failure events In the neoadjuvant phase of the EBC clinical trial (ABP 980 or trastuzumab given in combination with paclitaxel), subject incidence of adverse events of cardiac failure was 5.5% (20 of 364 subjects) and 2.2% (8 of 361 subjects) in the ABP 980 and trastuzumab treatment group, respectively. During the adjuvant phase, subjects receiving ABP 980 during the neoadjuvant phase remained on ABP 980 (ABP 980/ABP 980); and subjects who received trastuzumab during the neoadjuvant phase received either trastuzumab (trastuzumab/trastuzumab) or ABP 980 (trastuzumab/ABP 980). Subject incidence of cardiac failure in the adjuvant phase was 4.9% (17 of 349 subjects) in the ABP 980/ABP 980 treatment group; 4.7% (8 of 171 subjects) in the trastuzumab/trastuzumab treatment group; and 4.1% (7 of 171 subjects) in the trastuzumab/ABP 980 treatment group. Data are stratified by age and race in Annex 7.

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Footnotes including abbreviations, are defined on the last page of this table.

Table 11. Important Identified Risk: Cardiac Dysfunction

Characterization of the risk (continued)	
Frequency (continued)	Other cardiac events Subject incidence of adverse events of other cardiac events in the neoadjuvant phase was 4.9% (18 of 364 subjects) and 5.5% (20 of 361 subjects) in the ABP 980 and trastuzumab treatment group, respectively. Subject incidence of other cardiac events in the adjuvant phase was 4.3% (15 of 349 subjects) in the ABP 980/ABP 980 treatment group; 4.7% (8 of 171 subjects) in the trastuzumab/trastuzumab treatment group; and 4.7% (8 of 171 subjects) in the trastuzumab/ABP 980 treatment group. Data are stratified by age and race in Annex 7. LVEF decline In the neoadjuvant phase, a total of 0.3% (1 of 350 subjects) and 0.9% (3 of 348 subjects) in the ABP 980 and trastuzumab arms, respectively, experienced LVEF decline by ≥ 10 percentage points compared to baseline and to < 50%. In the adjuvant phase, the incidence of subjects with LVEF decline by ≥ 10 percentage points and to < 50% was similar in the treatment arms (2.9% [10 of 347 subjects], 1.8% [3 of 171 subjects], and 3.6% [6 of 167 subjects] in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980, arms, respectively). Exposure-adjusted incidence rate The exposure-adjusted incidence rate of cardiac failure events (based on a narrow standardized Medical Dictionary for Regulatory Activities query search) in the entire study was 2.22 (8/359.78) subjects/total exposure time [patient-years] in the ABP 980/ABP 980 treatment group, 0.55 (1/182.85 subjects/total exposure time [patient-years]) in the trastuzumab/trastuzumab treatment group, and 1.14 (2/175.57 subjects/total exposure time [patient-years]) in the trastuzumab/ABP 980 treatment group. **Herceptin studies:** In 3 pivotal EBC clinical trials of adjuvant IV Herceptin given in combination with chemotherapy, the incidence of grade 3 or 4 cardiac dysfunction (specifically symptomatic CHF) was 0.3% to 0.4% in patients who were administered Herceptin sequentially after taxane and 2.0% in patients who were administered Herceptin concurrently with a taxane (Herceptin SmPC). When Herceptin was administered after completion of adjuvant chemotherapy NYHA class 3 to 4, heart failure was observed in 0.6% of patients in the 1-year arm after a median follow-up of 12 months. In another study, after a median follow-up of 8 years, the incidence of severe CHF (NYHA class 3 and 4) in the Herceptin 1-year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6% (Herceptin SmPC).

Footnotes including abbreviations, are defined on the last page of this table.

Table 11. Important Identified Risk: Cardiac Dysfunction

Characterization of the risk (continued)	
Frequency (continued)	In the pivotal metastatic trials of IV Herceptin, the incidence of cardiac dysfunction varied between 9% and 12% when it was combined with paclitaxel and 6% to 9% when administered as monotherapy. The incidence rate of cardiac dysfunction in patients receiving Herceptin concurrently with anthracycline/cyclophosphamide was 27%. In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2% in patients receiving Herceptin and docetaxel (Herceptin SmPC).
Severity	The majority of cardiac failure events and other cardiac events in the ABP 980 groups were mild or moderate in severity, which was comparable with the trastuzumab comparator groups. No fatal cardiac failure events or other cardiac events were reported in ABP 980 clinical studies. Data are stratified by age and race in Annex 7.
Reversibility	Cardiac failure events and other cardiac events may resolve with appropriate management. However, fatal outcomes associated with cardiac dysfunction have been reported for Herceptin (Herceptin SmPC).
Long-term outcomes	Long-term outcome data are not available for this risk for KANJINTI, but are expected to be comparable to Herceptin.
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of the cardiac dysfunction. In patients that experience cardiac failure, there may be a significant impact on the quality of life. Fatal outcomes have been reported for Herceptin (Herceptin SmPC).
Risk factors and risk groups	Risk factors include older age (> 50 years of age [Herceptin SmPC]), underlying cardiovascular disease, and type of chemotherapy agent (such as anthracyclines). Hypertension (and antihypertensive drugs), body mass index > 25 kg/m^2, history of coronary artery disease, CHF, LVEF < 55%, LVEF decrease by 10 to 15 points, and paclitaxel treatment before or after adjuvant treatment are also associated with a higher risk for cardiac dysfunction (Herceptin SmPC). Herceptin administered after anthracycline-containing chemotherapy may increase the incidence of symptomatic and asymptomatic cardiac events in the adjuvant setting; and events may be more apparent when taxanes are administered concurrently as opposed to sequentially. Patients in the neoadjuvant setting who are chemotherapy-naïve can receive low-dose anthracycline (ie, maximum cumulative doses of doxorubicin and epirubicin are 180 mg/m^2 and 360 mg/m^2, respectively). However, patients who are treated concurrently with a full-course of low-dose anthracyclines and Herceptin in the neoadjuvant setting should not receive cytotoxic chemotherapy after surgery (Herceptin SmPC).

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Footnotes including abbreviations, are defined on the last page of this table.

Table 11. Important Identified Risk: Cardiac Dysfunction

Preventability	Patients should be evaluated for cardiac function, undergo periodic LVEF monitoring, and any cardiac dysfunction should be closely monitored.
Impact on the risk-benefit balance of the product	The risk of cardiac dysfunction has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product, Herceptin.

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CHF = congestive heart failure; EBC = early breast cancer; EU = European Union; IV = intravenous; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics

Table 12. Important Identified Risk: Administration-Related Reactions (ARRs)

Potential mechanisms	It is possible that ARRs (or reactions to monoclonal antibodies in general) may be due to immediate and delayed hypersensitivity (beta-type reactions) or over-reactions or depression of the immune system such as immunodeficient autoimmune or allergic responses (gamma-type reactions); but other mechanisms may also be involved like targeted release of cytokines (Calogiuri et al, 2009).
Evidence source(s) and strength of evidence	This important identified risk is included per the EU RMP of the reference medicinal product, Herceptin. Evidence sources: ABP 980 clinical studies and Herceptin SmPC.
Characterization of the risk	
Frequency	**ABP 980 studies:** Study 20120283 (EBC) In the neoadjuvant phase of the EBC clinical trial (ABP 980 or trastuzumab given in combination with paclitaxel), subject incidence of adverse events of ARRs was 23.1% (84 of 364 subjects) and 20.2% (73 of 361 subjects) in the ABP 980 and trastuzumab treatment group, respectively. During the adjuvant phase, subjects receiving ABP 980 during the neoadjuvant phase remained on ABP 980 (ABP 980/ABP 980); and subjects who received trastuzumab during the neoadjuvant phase received trastuzumab [trastuzumab/trastuzumab] or ABP 980 [trastuzumab/ABP 980]. Subject incidence of ARRs in the adjuvant phase was 9.2% (32 of 349 subjects) in the ABP 980/ABP 980 treatment group; 9.4% (16 of 171 subjects) in the trastuzumab/trastuzumab treatment group; and 13.5% (23 of 171 subjects) in the trastuzumab/ABP 980 treatment group. Data are stratified by age and race in Annex 7. Exposure-adjusted incidence rate The exposure-adjusted incidence rate of ARRs, specifically infusion reactions, for the entire study was 33.04 (95/287.56 subjects/total exposure time [patient-years]) in the ABP 980/ABP 980 treatment group, 31.27 (46/147.10 subjects/total exposure time [patient-years]) in the trastuzumab/trastuzumab treatment group, and 30.64 (44/143.58 subjects/total exposure time [patient-years]) in the trastuzumab/ABP 980 treatment group. The exposure-adjusted incidence rate of ARRs, specifically hypersensitivity, for the entire study was 9.66 (33/341.52 subjects/total exposure time [patient-years]) in the ABP 980/ABP 980 treatment group, 9.75 (17/174.35 subjects/total exposure time [patient-years]) in the trastuzumab/trastuzumab treatment group, and 8.98 (15/166.95 subjects/total exposure time [patient-years]) in the trastuzumab/ABP 980 treatment group. **Herceptin studies:** In the pivotal trial, the rate of all grade ARRs was 37.2% with the Herceptin IV formulation; severe grade 3 reactions were reported in 2.0% of the patients during the treatment phase; and no severe grade 4 or 5 reactions were observed (Herceptin SmPC).

Footnotes including abbreviations, are defined on the last page of this table.

Table 12. Important Identified Risk: Administration-Related Reactions (ARRs)

Characterization of the risk (continued)	
Severity	The majority of events of ARRs in the ABP 980 groups were mild or moderate in severity, which was comparable with the trastuzumab comparator groups. No fatal events of ARRs were reported in ABP 980 clinical studies. Data are stratified by age and race in Annex 7.
Reversibility	Events of ARRs may resolve with appropriate management. However, fatal outcomes have been reported for Herceptin (Herceptin SmPC).
Long-term outcomes	Long-term outcome data are not available for this risk.
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of the ARR. Fatal outcomes have been reported for Herceptin (Herceptin SmPC).
Risk factors and risk groups	Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal ARR and should not be treated with Herceptin (Herceptin SmPC). Therefore, in line with the reference medicinal product, Herceptin, severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy is a contraindication in the KANJINTI SmPC.
Preventability	Pre-medication may be used to reduce risk of occurrence of these events. Patients should be observed for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Infusion of KANJINTI should be done slowly or temporarily stopped until these symptoms resolve.
Impact on the risk-benefit balance of the product	The risk of administration-related reactions (ARRs) has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product, Herceptin.

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ARR = administration-related reaction; EBC = early breast cancer; EU = European Union; IV = intravenous; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics

Table 13. Important Identified Risk: Oligohydramnios

Potential mechanisms	There may be a direct effect on the function of HER2 receptors in the fetal kidney which may decrease cell proliferation and reduce fetal kidney function in vivo (Bader et al, 2007).
Evidence source(s) and strength of evidence	This important identified risk is included per the EU RMP of the reference medicinal product, Herceptin. Evidence source: Herceptin SmPC.
Characterization of the risk	
Frequency	**ABP 980 studies:** Study 20120283 (EBC) Women of childbearing potential who are pregnant or breastfeeding were excluded from the ABP 980 clinical trial. **Herceptin studies:** The frequency of oligohydramnios with the use of Herceptin is unknown. In the postmarketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin (Herceptin SmPC).
Severity	Not applicable.
Reversibility	Unknown if oligohydramnios is reversible. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable (Herceptin SmPC).
Long-term outcomes	Long-term outcome data are not available for this risk.
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of the oligohydramnios.
Risk factors and risk groups	Females of child-bearing potential who are taking Herceptin, or within 7 months following the last dose of Herceptin, are at risk (modified from Herceptin SmPC). Incidence and risk of developing oligohydramnios may be higher when trastuzumab is used beyond the first trimester and for longer durations during pregnancy (Zagouri et al, 2013).
Preventability	Treatment in pregnant women should only occur when the potential benefits to the pregnant woman outweigh the potential risks. Effective contraception should be used during treatment in women of childbearing potential and for at least 7 months after treatment has concluded.
Impact on the risk-benefit balance of the product	The risk of oligohydramnios has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	The public health impact is not expected to be greater than the reference medicinal product, Herceptin.

EBC = early breast cancer; EU = European Union; HER2 = human epidermal growth factor receptor 2; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics

SVII.3.2 Presentation of the Missing Information

None.

Part II: Module SVIII - Summary of the Safety Concerns

Table 14. Summary of Safety Concerns

Important identified risks	Cardiac dysfunction Administration-related reactions (ARRs) Oligohydramnios
Important potential risks	None
Missing information	None

ARRs = administration-related reactions

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

There are no further routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 15.

Table 15. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible.	All safety concerns	To monitor if there are any batch-specific issues in the postmarketing environment.	Not applicable

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned KANJINTI category 1 to 3 studies.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

The safety information in the KANJINTI SmPC is aligned to the reference medicinal product, Herceptin.

V.1 Routine Risk Minimization Measures

Table 16. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Cardiac dysfunction	Routine risk communication: • SmPC Sections 4.2, 4.4, 4.8, and 5.1 • Package Leaflet (PL) Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to suspend KANJINTI if LVEF percentage drops ≥ 10 points from baseline AND to below 50%; to consider discontinuation of KANJINTI if LVEF has not improved, or has declined further, or if symptomatic CHF has developed; and to refer all such patients for assessment by a cardiologist, is included in SmPC Section 4.2. • Recommendation to perform cardiac assessments at baseline, every 3 months during treatment, and every 6 months following discontinuation of treatment until 24 months from the last administration of KANJINTI (and yearly for up to 5 years in EBC patients who receive anthracycline-containing chemotherapy, or longer if a continuous decrease of LVEF is observed); to perform a careful risk-benefit assessment before deciding to treat with KANJINTI; if possible, to avoid anthracycline-based therapy for up to 7 months after stopping KANJINTI or to monitor cardiac function carefully; to perform more frequent monitoring for patients who develop asymptomatic cardiac dysfunction; to consider discontinuation of KANJINTI in patients with asymptomatic decrease in left ventricular function if no clinical benefit of KANJINTI therapy has been seen; to suspend KANJINTI if LVEF percentage drops ≥ 10 points from baseline AND to below 50%; to consider discontinuation of KANJINTI if LVEF has not improved, or has declined further, or symptomatic CHF has developed; and to refer all such patients for assessment by a cardiologist, is included in SmPC Section 4.4. Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription

Table 16. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Administration-related reactions (ARRs)	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, 4.7, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to observe patients for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms; that interruption or slowing the rate of the infusion may help control such symptoms; and that the infusion may be resumed when symptoms abate, is included in SmPC Section 4.2. • Recommendation that pre-medication may be used to reduce the risk of occurrence of infusion reactions, and that should an infusion reaction occur, the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms, is included in SmPC Section 4.4. Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription
Oligohydramnios	Routine risk communication: • SmPC Sections 4.6 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that if a pregnant woman is treated with KANJINTI, or if a patient becomes pregnant while receiving KANJINTI or within 7 months following the last dose of KANJINTI, close monitoring by a multidisciplinary team is desirable, is included in SmPC Section 4.6. Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription
Important Potential Risks	
None	
Missing Information	
None	

V.2 Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V.1 are sufficient to manage the safety concerns of KANJINTI.

V.3 Summary of Risk Minimization Measures

Table 17. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Cardiac dysfunction	Routine risk minimization measures: • SmPC Section 4.2, where a recommendation for when to suspend or discontinue KANJINTI and to refer patients for assessment by a cardiologist, is given • SmPC Section 4.4, where a recommendation to perform baseline and regular cardiac assessments, to perform a risk-benefit assessment before treatment with KANJINTI, to avoid anthracycline-based therapy for up to 7 months after stopping KANJINTI or to monitor cardiac function carefully, to frequently monitor patients who develop asymptomatic cardiac dysfunction, when to suspend or consider discontinuation of KANJINTI, and to refer patients for assessment by a cardiologist, is given • SmPC Sections 4.8 and 5.1 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Table 17. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Administration-related reactions (ARRs)	Routine risk minimization measures: • SmPC Section 4.2, where a recommendation to observe patients for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for infusion-related symptoms, that interruption or slowing the rate of the infusion may help control symptoms; and that the infusion may be resumed when symptoms abate, is given • SmPC Section 4.3 • SmPC Section 4.4, where a recommendation that pre-medication may be used to reduce the risk of occurrence of infusion reactions, and that should an infusion reaction occur, the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms, is given • SmPC Sections 4.7 and 4.8 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Table 17. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Oligohydramnios	Routine risk minimization measures: • SmPC Section 4.6, where a recommendation that if a pregnant woman is treated with KANJINTI, or if a patient becomes pregnant while receiving KANJINTI or within 7 months following the last dose of KANJINTI, close monitoring by a multidisciplinary team is desirable, is given • SmPC Section 4.8 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Important Potential Risks		
None		
Missing Information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for KANJINTI is presented below.

Summary of Risk Management Plan for KANJINTI® (trastuzumab)

This is a summary of the risk management plan (RMP) for KANJINTI. The RMP details important risks of KANJINTI, how these risks can be minimized, and how more information will be obtained about KANJINTI's risks and uncertainties (missing information).

KANJINTI's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how KANJINTI should be used.

This summary of the RMP for KANJINTI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of KANJINTI's RMP.

I. The Medicine and What it is Used for

KANJINTI is authorized for the treatment of early breast cancer, metastatic breast cancer, and metastatic gastric cancer (see SmPC for the full indication). It contains trastuzumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of KANJINTI's benefits can be found in KANJINTI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/kanjinti

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of KANJINTI, together with measures to minimize such risks and the proposed studies for learning more about KANJINTI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

Important risks of KANJINTI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of KANJINTI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Cardiac dysfunction Administration-related reactions (ARRs) Oligohydramnios
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Important identified risk: Cardiac dysfunction	
Evidence for linking the risk to the medicine	This important identified risk is included per the European Union (EU) RMP of the reference medicinal product, Herceptin. Evidence sources: ABP 980 clinical studies and Herceptin SmPC.
Risk factors and risk groups	Risk factors include older age (> 50 years of age [Herceptin SmPC]), underlying cardiovascular disease, and type of chemotherapy agent (such as anthracyclines). Hypertension (and antihypertensive drugs), body mass index > 25 kg/m^2, history of coronary artery disease, congestive heart failure (CHF), left ventricular ejection fraction (LVEF) < 55%, LVEF decrease by 10 to 15 points, and paclitaxel treatment before or after adjuvant treatment are also associated with a higher risk for cardiac dysfunction (Herceptin SmPC). Herceptin administered after anthracycline-containing chemotherapy may increase the incidence of symptomatic and asymptomatic cardiac events in the adjuvant setting; and events may be more apparent when taxanes are administered concurrently as opposed to sequentially. Patients in the neoadjuvant setting who are chemotherapy-naïve can receive low-dose anthracycline (ie, maximum cumulative doses of doxorubicin and epirubicin are 180 mg/m^2 and 360 mg/m^2, respectively). However, patients who are treated concurrently with a full-course of low-dose anthracyclines and Herceptin in the neoadjuvant setting should not receive cytotoxic chemotherapy after surgery (Herceptin SmPC).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, where a recommendation for when to suspend or discontinue KANJINTI and to refer patients for assessment by a cardiologist, is given • SmPC Section 4.4, where a recommendation to perform baseline and regular cardiac assessments, to perform a risk-benefit assessment before treatment with KANJINTI, to avoid anthracycline-based therapy for up to 7 months after stopping KANJINTI or to monitor cardiac function carefully, to frequently monitor patients who develop asymptomatic cardiac dysfunction, when to suspend or consider discontinuation of KANJINTI, and to refer patients for assessment by a cardiologist, is given • SmPC Sections 4.8 and 5.1 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important identified risk: Administration-related reactions (ARRs)	
Evidence for linking the risk to the medicine	This important identified risk is included per the EU RMP of the reference medicinal product, Herceptin. Evidence sources: ABP 980 clinical studies and Herceptin SmPC.
Risk factors and risk groups	Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal ARR and should not be treated with Herceptin (Herceptin SmPC). Therefore, in line with the reference medicinal product, Herceptin, severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy is a contraindication in the KANJINTI SmPC.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, where a recommendation to observe patients for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for infusion-related symptoms, that interruption or slowing the rate of the infusion may help control symptoms; and that the infusion may be resumed when symptoms abate, is given • SmPC Section 4.3 • SmPC Section 4.4, where a recommendation that pre-medication may be used to reduce the risk of occurrence of infusion reactions, and that should an infusion reaction occur, the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms, is given • SmPC Sections 4.7 and 4.8 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important identified risk: Oligohydramnios	
Evidence for linking the risk to the medicine	This important identified risk is included per the EU RMP of the reference medicinal product, Herceptin. Evidence source: Herceptin SmPC.
Risk factors and risk groups	Females of child-bearing potential who are taking Herceptin, or within 7 months following the last dose of Herceptin, are at risk (modified from Herceptin SmPC). Incidence and risk of developing oligohydramnios may be higher when trastuzumab is used beyond the first trimester and for longer durations during pregnancy (Zagouri et al, *Breast Cancer Res Treat*, 2013;137[2]:349-357).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6, where a recommendation that if a pregnant woman is treated with KANJINTI, or if a patient becomes pregnant while receiving KANJINTI or within 7 months following the last dose of KANJINTI, close monitoring by a multidisciplinary team is desirable, is given • SmPC Section 4.8 • PL Sections 2 and 4 • Legal status: Restricted medical prescription Additional risk minimization measures: • None

Important Potential risk:
None

Missing information:
None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of KANJINTI.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for KANJINTI.

PART VII: ANNEXES

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Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not Applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.