22 March 2018
EMA/CHMP/261937/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

KANJINTI

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/004361/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

4-PL	4-parameter logistic
ABP 980	Biosimilar of trastuzumab
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AEX	Anion exchange
ATO	Amgen Thousand Oaks
AUCinf	Area under the serum concentration time curve from time 0 to infinity
AUClast	Area under the serum concentration time curve from time 0 to time of last quantifiable concentration
AUC0-168h	Area under the serum concentration-time curve during a 168-hour dosing interval
CEX-HPLC	Cation exchange - high pressure liquid chromatography
CDC	Complement-dependent cytotoxicity
Cmax	Maximum serum concentration
CHO	Chinese hamster ovary
cIEF	Capillary isoelectric focusing
CPV	continued process verification
CQA	critical quality attribute
CSR	Clinical study report
CV	Coefficient of variation
DCIS	ductal carcinoma in situ
EBC	Early breast cancer
EC50	Effective concentration yielding a 50% response
ECD	Extracellular domain
ECG	Electrocardiogram
ECLA	Electrochemiluminescent immunoassay
EFS	Event free survival
ELISA	Enzyme linked immunosorbent assay
Fab	fragment antigen binding
FBS	fetal bovine serum
Fc fragment,	crystallisable region of monoclonal antibody
FcγRs	Fc gamma receptors
FcRn	Fc neonatal receptor
EoI	End of infusion
EOI	Events of interest
EU	European Union
FA	Fucose analogue
Fc	Fragment crystallisable region of immunoglobulin
FDA	Food and Drug Administration
FMEA	Failure Modes Effect Analysis
GCP	Good Clinical Practice
GLP	Good laboratory practice
HER2	Human epidermal growth factor receptor 2
HC	Heavy chains
HCP	Host cell protein
HMW	High molecular weight
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G1
IPCs	In-process controls
ITT	Intent to treat
IV	Intravenous(ly)
LAL	Limulus amebocyte lysate
LC	Light chains
LER	low endotoxin recovery
LIVCA	limit of in vitro cell age
LLOQ	lower limit of quantitation
LMW	low molecular weight

LOD	limit of detection
LOQ	limit of quantitation
LVEF	Left ventricular ejection fraction
MCB	Master Cell Bank
MedDRA	Medical Dictionary of Regulatory Activities
MSD	Merck Sharp & Dohme
nrCE-SDS	Non-reduced capillary electrophoresis-sodium dodecyl sulfate
NRI	Nonresponder imputation
OS	Overall survival
PACMP	Post approval change management protocol
PBMC	Peripheral blood mononuclear cells
pCR	Pathologic complete response
PK	Pharmacokinetic
PP	Per protocol
PQRA	product quality risk assessment
PR	Progesterone receptor
rCE-SDS	Reduced capillary electrophoresis-sodium dodecyl sulfate
RD	Risk difference
RR	Risk ratio
RTRT	Real-time release testing
SE-UHPLC	Size exclusion-ultra-high pressure liquid chromatography
SmPC	Summary of Product Characteristics
SOC	System organ class
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V., BREDA submitted on 1 March 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for KANJINTI, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2015. The applicant applied for the following indication:

KANJINTI is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

Breast cancer

Metastatic breast cancer

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 two 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.

Early breast cancer

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) (see section 5.1).

- 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 tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Kanjinti should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

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 tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/00/145/001

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/00/145/001

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:

- Community
- Community Marketing authorisation number: EU/1/00/145/001

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP in 17 February 2011, 16 February 2012, 21 June 2012, December 2012 and 19 June 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

The application was received by the EMA on	1 March 2017
The procedure started on	23 March 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 June 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 June 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 June 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 September 2017

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 October 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2017
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	9 November 2017
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 January 2018
The outstanding issues were partially addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 January 2018
Upon agreement with CHMP, the applicant submitted additional data on	2 February 2018
The Rapporteurs circulated an updated Joint Assessment Report on the additional data to the List of Outstanding Issues to all CHMP members on	9 February 2018
The CHMP agreed on a new list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 February 2018
The outstanding issues were addressed by the applicant on	26 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	7 March 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to KANJINTI on	22 March 2018

2. Scientific discussion

2.1. Problem statement

This centralised marketing authorisation application concerns the Biotech medicinal product Kanjinti. It is an abridged application for a biosimilar under Article 10 (4) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

About the product

Kanjinti has been developed as a similar biological medicinal product to the innovator product Herceptin (trastuzumab), which was approved in the European Union (EU) in August 2000 (EMEA/H/C/000278).

Kanjinti (also referred as ABP 980) is supplied in 2 presentations containing 150 mg or 420 mg per single-use vials.

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20%-30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) or chromogenic in situ hybridisation (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8% to 34.0% for IHC and 7.1% to 42.6% for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. HER2 overexpression was found in a number of disease states, including metastatic breast cancers, early breast cancer and metastatic gastric cancer (MGC). The extracellular domain of the receptor (ECD) can be shed into the blood stream and measured in serum samples (see Herceptin SmPC section 5.1).

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling 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 tumour 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 (see Herceptin SmPC section 5.1).

Type of Application and aspects on development

The marketing authorisation application of Kanjinti is an abridged application for similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The applicant received Scientific Advice from the CHMP in February 2011, February 2012, March 2012, December 2012 and June 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

The development programme was according to the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005, Rev1.

2.2. Quality aspects

2.2.1. Introduction

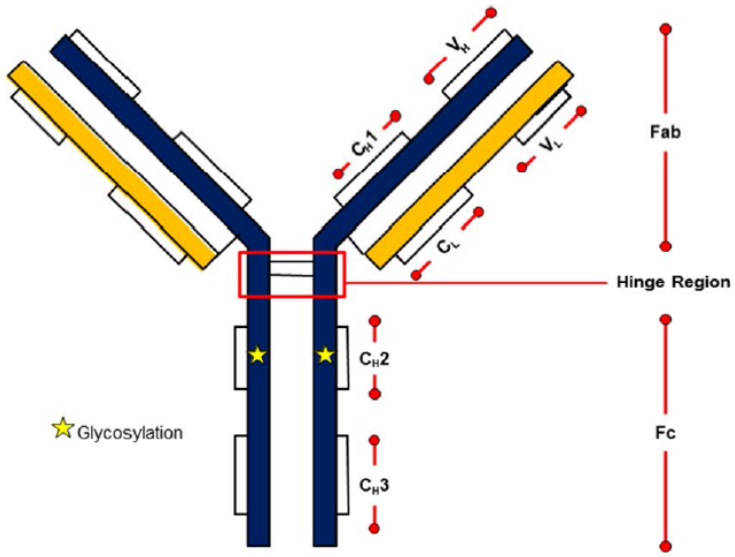
The finished product Kanjinti (ABP 980), also referred as drug product (DP) by the applicant, is a powder for concentrate for solution for infusion containing 150 mg or 420 mg trastuzumab as active substance. Other ingredients are: histidine monohydrochloride, histidine, trehalose dihydrate and polysorbate 20. The product is available in clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film and an aluminum seal with flip-off dust cover. ABP 980 has been developed as a similar biological medicinal product to the reference medicinal product Herceptin (trastuzumab). Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.2.2. Active Substance

General Information

The active substance of Kanjinti (ABP 980), trastuzumab, is a recombinant humanised monoclonal antibody of the immunoglobulin G1 (IgG1) subclass directed against the human epidermal growth factor receptor 2 (HER2) receptor. ABP 980 is produced from a mammalian Chinese hamster ovarian (CHO) cell line. ABP 980 consists of 2 heavy chains (HC) of the lgG1 subclass and 2 light chains (LC) of the kappa subclass. ABP 980 contains 32 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each HC contains 449 amino acids with 4 intrachain disulfide bonds. Each LC contains 214 amino acids with 2 intrachain disulfide bonds. The amino acid sequence of ABP 980 is based on that of the reference product Herceptin, with the exception that ABP 980 sequence was designed without the HC C-terminal lysine. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn^{300}. The theoretical molecular mass of the fully assembled main glycoform containing 1 A2G0F moiety per HC is 148,219 Da.

Figure 1. Schematic representation of trastuzumab



Heavy chains are shown in blue and light chains are shown in orange.
V_H is the variable domain of the heavy chain.
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain.
V_L is the variable domain of the light chain.
C_L is the constant domain of the light chain.
Fab is the fragment antigen-binding region.
Fc is the fragment crystallizable region.

Manufacture, characterisation and process controls

ABP 980 active substance is manufactured in accordance with current good manufacturing practices (cGMP) at Patheon Biologics B.V., Groningen, The Netherlands.

Description of manufacturing process and process controls

The trastuzumab active substance manufacturing process has been adequately described. The main steps of the manufacturing process are fermentation, recovery and purification. The ABP 980 antibody is expressed in a transfected CHO cell line. The process begins with the thawing of a working cell bank (WCB) vial. A single

production lot is initiated from a single vial thaw. The purification of ABP 980 comprises chromatography steps and two orthogonal dedicated virus clearance steps

The container closure system for active substance is a bag. The bag material component complies with Ph.Eur. 3.1.7.

Control of Materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

A two-tier cell bank system, consisting of a Master Cell Bank (MCB) and WCB was generated. MCB and WCB were characterised according to ICH requirements. The proposed reduced testing of the WCB has been adequately justied. The adventitious agents assays test results indicate that the cell bank is sterile and free of detectable mycoplasma and viruses. All newly prepared WCBs will also be manufactured in accordance with cGMP guideline and qualified, complying with ICH Q5D and Q5A (R1). During routine manufacturing, the cell culture age is controlled to less than limit of in vitro cell age (LIVCA). This is supported by several assays demonstrating genetic stability of the production cell line and that the LIVCA cells are free of adventitious viruses.

Control of critical steps and intermediates

Performance indicators are used to evaluate in-process performance. Performance indicators are designated as in-process controls (IPCs) for routine manufacture. Limits for IPCs are categorised as rejection, action, or control limits. An adequate justification for IPC limits is provided. A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the trastuzumab manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process Validation

The trastuzumab active substance manufacturing process has been validated adequately. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces trastuzumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Small scale studies (chemical hold times) were carried-out to define hold times for the in-process pools and most of these hold times have been validated at commercial scale.

Active substance is shipped using qualified shipping containers.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program. Several changes have been introduced during the development of the manufacturing process. Analytical comparability of the active substance obtained from the different processes and scales has been demonstrated in comparability studies. Additional characterisation tests assessing the primary structure, glycosylation, charge variants, and biological function were carried out; stability under accelerated and stress

conditions. Although minor differences were observed, it could be concluded that material from commercial scale is comparable to the pre-clinical and clinical material used during development.

The Applicant followed an enhanced development approach using existing knowledge on the reference product, ABP 980 and other monoclonal antibodies, process development and manufacturing experience, risk assessment tools, and process characterisation studies to define an integrated control strategy as outlined in ICH Q11. A comprehensive set of product quality attributes of trastuzumab was assessed for their potential impact on efficacy and safety and critical quality attributes (CQA) were identified. The impact of the active substance and finished product manufacturing steps on CQA was evaluated and investigated in univariate and/or multivariate process characterisation studies using qualified small-scale models of the respective process steps.

Process characterisation studies were conducted using qualified small-scale models that are representative of the commercial-scale process, by executing a series of studies including univariate, multivariate, and process challenge experiments. Upon completion of the process characterisation studies, production bioreactor process parameters were classified based on their effects on performance indicators.

The integrated control strategy incorporates a number of control elements including process parameters, in-process controls, release specifications, and periodic testing controls (e.g., validation, comparability, stability) of the active substance and finished product. The integrated control strategy reflects knowledge of product quality attributes and their potential to impact patient safety and product efficacy, as well as an understanding of how these attributes are controlled during manufacturing.

Characterisation

The trastuzumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. The biological characterisation included binding (HER2, Fc gamma receptor type IIIa[V] FcγRIIIa[V], and Fc neonatal receptor (FcRn)) and functional (proliferation inhibition, antibody-dependent cellular cytotoxicity (ADCC)) activity covering Fab and Fc related functions of ABP 980. Product- and process-related impurities were identified and adequately addressed. Process-related impurities are present at low levels and are well controlled by the active substance manufacturing process. A risk-based assessment was conducted for raw materials used in the process to identify components requiring evaluation of process clearance. All tested reagents were cleared below the assay limit of quantitation (LOQ) by the process. The results indicated that the reagent clearance capability of the process substantially exceeds the clearance requirement. In summary, the characterisation is considered appropriate for this type of molecule.

Specification

The specification tests include appearance (visual), identity, purity, adventitious agents, potency, quantity and general tests. The test for purity was amended, the acceptance criteria for potency were tightened and additional acceptance criteria were updated. The updated set of specifications is considered adequate.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines; suitability of compendial methods addressing safety aspects (bioburden, endotoxin, mycoplasma) has been verified.

The method for the determination of biological activity is an anti-proliferation assay, which performs well with regard to accuracy, repeatability precision, and robustness.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Primary ABP 980 reference standard and the working reference standard were established for release. Both materials were qualified and the suitability for use was demonstrated. The proposed qualification procedure for future reference standards is acceptable.

Stability

An expiry period is proposed for active substance stored at the recommended storage conditions. The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

Real time, real condition stability data on commercial batches of active substance from the commercial manufacturing process stored in a container representative of the one proposed for commercial manufacture for up to 36 months and for up to 6 months under accelerated conditions at 5 ºC were provided. Long term stability data derived from studies at recommended storage condition for 2 primary batches are available for 36 months and for one primary batch for 18 months. Appearance (including colour and clarity), purity, potency, quantity and pH were tested during stability, this is acceptable. There are no trends during the long term conditions.

Results on stress conditions at 25 ºC were also provide and are supportive of the proposed storage conditions.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

A Post Approval Change Management Protocol is being included which outlines future shelf life extensions of the active substance. The implementation of the results will be submitted as Type IB variation.

Comparability exercise for Active Substance

The ABP 980 active substance manufacturing process development occurred in 4 distinct phases. Process changes were made to accommodate the increase in process scale and to improve robustness for commercial production. Analytical comparability evaluations were performed to demonstrate comparability of ABP 980 active substance manufactured during development.. The results demonstrate that active substances produced at all 4 distinct phases can be considered comparable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product (also referred to as DP) is supplied as a sterile, white to pale yellow, preservative free lyophilised powder for concentrate for solution for infusion containing trastuzumab as active substance L-histidine hydrochloride, L-histidine, α,α-trehalose dihydrate, and polysorbate 20. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

ABP 980 is supplied in 2 presentations containing 150 mg or 420 mg per single-use vials.

The finished product is intended for reconstitution with 7.2 mL (150 mg) or 20 mL (420 mg) of sterile water for injections. Upon reconstitution, each vial contains approximately 21 mg/mL ABP 980, the reconstituted product is intended for dilution in saline (0.9% sodium chloride) for intravenous administration. No formula overages are included. The higher nominal amount of ABP 980 of 156 mg per 150 mg vial and 440 mg per 420 mg vial, respectively, has been justified.

As the 420 mg vial presentation is not authorised in Europe, the Summary of Product Characteristics (SmPC) states that the 420 mg vial will only be for single-use.

Amgen developed ABP 980 drug product to have the same formulation, route of administration, dosage form, and strength as the reference product Herceptin (trastuzumab). The small quantitative differences in the excipient content are considered acceptable. Formulation development studies demonstrated that ABP 980 is physically and chemically stable after lyophilisation in the proposed formulation. The finished product formulation is identical to the formulation of the active substance and is not modified during the finished product manufacturing. The intended commercial formulation is the same as that used during clinical studies and both presentations were used in clinical studies.

The finished product is stored in 20 mL (for the 150 mg strength) or 50 mL (for the 420 mg strength) clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film and an aluminium seal with flip-off dust cover. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Manufacture

EU batch release is performed by Amgen Europe B.V., Breda, Netherlands.

Process characterisation was conducted by executing experiments to determine the effect of varying select process parameter set points on relevant product quality and performance indicators. Process development took place at different manufacturing sites as described under the comparability exercise. Minor modifications were implemented to accommodate an increase in process scale and facility fit. Identical raw materials and container closure components were used for the clinical and commercial processes. Overall, comparability could be demonstrated for all sites.
The different manufacturing steps are sufficiently described. The provided control strategy for the DP manufacturing process is also acceptable: the classification of input and output parameters is justified and supported by adequately defined limits/ranges supported by data generated during process design studies.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Product specification

The specification include tests for the lyophilised product (appearance, moisture content and reconstitution time) and tests for the reconstituted product: appearance, colour, , identity, purity and impurities , potency , quantity, osmolality, pH , subvisible particles, adventitious agents.

Specifications for finished product release are set in accordance with Ph. Eur. Requirements and ICH Q6B. Appearance of the reconstituted drug product, although not in accordance with the Ph. Eur. Monograph monoclonal antibodies for human use (2031), is considered justified. The potency assay acceptance criteria were tightened during the procedure
Analytical methods
The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data, of the finished product, generated using the commercial methods, were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The same reference standard is used for testing the active substance and finished product.

Stability of the product

Based on available stability data, the 30 months shelf-life when stored at the recommended storage temperature of 2°C to 8°C (referred to as 5°C), as stated in the SmPC, are acceptable.

Real time/real condition stability data, and 6 months under accelerated conditions at 25 ºC / 60% RH and stress conditions 40ºC / 75% RH according to the ICH guidelines were provided.

The stability specification includes all the stability indicating tests of the release specification. The results observed in the accelerated and stress studies are supported by forced degradation studies. Kanjinti was shown to be sensitive to light exposure and temperature cycling. Lyophilised finished product samples subjected to ICH and clinical lighting conditions in secondary packaging showed no change in product quality relative to control samples, demonstrating that the secondary packing protects the ABP 980 drug product from photodegradation

After reconstitution with sterile water for injections, the reconstituted solution is physically and chemically stable for 48 hours at 2°C - 8°C. Additionally, solutions of Kanjinti for intravenous infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C, as demonstrated by the compatibility studies, stored for up to 48 hours.

A post approval Change Management Protocol – Finished Product Shelf Life is being included which outlines future shelf life extensions and the mechanism to submit real-time data. The PACMP is acceptable and the results will be submitted via Type IB variation.

Comparability exercise for Finished Medicinal Drug Product

The initial 150 mg drug product development and clinical batches were manufactured at a clinical manufacturing site. Subsequently, the process was transferred from to an alternate clinical manufacturing site. For commercial manufacturing, the 150 mg and 420 mg manufacturing processes were transferred to a commercial manufacturing site. Overall the data set indicates that the drug product manufactured at commercial manufacturing site is comparable to drug product manufactured at clinical manufacturing sites.

Adventitious agents

No animal or human derived materials are used in the manufacturing process of ABP 980. The TSE risk is considered negligible. Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been demonstrated. Cell banks were tested for the absence of adventitious viruses in accordance with applicable guidelines. The unprocessed harvest is routinely tested for viral contaminants. Effective and robust dedicated virus clearance stepsare integrated into the manufacturing process and the chromatography steps contribute to virus reduction. Virus clearance by these steps has been adequately validated in accordance with ICH Q5A and CPMP/ BWP/268/95. In summary, the implemented measures ensure a high safety margin with respect to adventitious agents.

GMO

N/A

Biosimilarity

Amgen used EU sourced Herceptin as the comparator arm in the nonclinical and clinical program. Thus, analytical similarity assessment is performed between ABP 980 and EU sourced Herceptin. A total of 33 Herceptin batches including all lots used in the clinical trials, were tested in the analytical similarity assessment. The ABP 980 lots evaluated as part of analytical similarity assessment included those used in the clinical trials and the process validation lots, manufactured at intended commercial site, scale and process. For certain assays, subsets of batches were used, which was justified.

The comprehensive analytical similarity assessment included comparative evaluations of biological activities, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, thermal stability and degradation studies, general properties, and process-related impurities. Data were evaluated against pre-defined similarity assessment criteria. A multi-tiered approach was used to define similarity. For attributes where significant differences may pose a risk to efficacy, safety, or immunogenicity, a quality range was used. For the quality range approach, similarity was demonstrated if > 90% of the individual values satisfied the limits.

As process-related impurities do not have to be comparable, but need to be eliminated to acceptable levels, sufficient process capability for removal was demonstrated by spiking studies and process validation.

Regarding the primary structure the results demonstrate that ABP 980 has a similar intact molecular mass compared to Herceptin, similar levels of the reduced and deglycosylated LC and HC masses, the same amino acid sequence, similar disulphide structure and similar levels of free sulfhydryl.

Profiles of the particle and aggregate content of ABP 980 and Herceptin were assessed using a combination of test methods. ABP 980 has similar or lower levels of subvisible particles as compared to Herceptin.

Product-related substances and impurities of ABP 980 and Herceptin were assessed using a combination of methods that evaluate size and charge variants. Slightly lower amounts of SE-UHPLC main peak are observed for ABP 980. An increase of HMW species is observed at the same time. The predominant HMW species have been characterised as dimers. It is agreed that the overall levels of HMW are low and it is unlikely that this minor quantitative difference does impact biological activity and/or safety.

Two side-by-side experiments were included for profile comparison. The results demonstrate that ABP 980 has a similar glycan map profile: the ABP 980 lots are within the quality range for afucosylation, for high mannose, galactosylation, afucosylated galactosylation, and sialylation. Nevertheless a cluster of batches of the reference product seem to exhibit lower levels of afucosylation, galactosylation, and afucosylated galactosylation, all three impacting ADCC activity and potentially clinical efficacy. As requested, the applicant recalculated the quality ranges by excluding that cluster and updated the specification accordingly.

Differences are observed for acidic and main peaks by CEX-HPLC. These modifications are not considered to impact biological activity as demonstrated by the characterisation of the acidic peak fractions with regard to potency and ADCC activity. It is therefore agreed that the differences are unlikely to be clinically meaningful. Thermal forced degradation rates obtained for ABP 980 and Herceptin are similar for SE-UHPLC, rCE-SDS, nrCE-SDS, CEX-HPLC, and potency.

The biological activities were evaluated by a comprehensive set of functional assays and binding studies addressing both Fab and Fc-functions of the molecule.

No significant differences were observed for assays addressing inhibition of HER2 signaling such as Proliferation Inhibition Bioassays in BT-474 and NCI-N87 cells, HER2 Binding by ELISA, Inhibition of AKT Phosphorylation.

No meaningful differences are observed in FcRn and FcγR binding, except for the FcγRIIIa Binding. Although it is agreed that all of the ABP 980 lots are within the quality range for relative FcγRIIIa (158F) binding, the same cluster of batches of the reference product which exhibited lower levels of afucosylation, seem to exhibit lower binding activity. Lower binding activities to the FcγRIIIa receptors are not unexpected due to the differences in afucosylation.

ADCC activity was measured both by engineered NK92 huFcγRIIIa (158V) and isolated PBMC cells as effector cells and SKBR3 HER2-expressing cells as target cells. With both tests, ABP 980 and Herceptin have comparable ADCC activity. The data confirm that the relative ADCC activity of all ABP 980 lots is entirely within the Min/Max range of the reference product. In line with the results for afucosylation and FcγRIIIa binding it is noted that the results indicate a cluster of batches of the reference product exhibiting lower ADCC activity. In addition results obtained for the reference product lots display higher variability whereas the results measured for the Kanjinti lots are within a very narrow range at the upper range of the reference product. Given the correlation between levels of afucosylation, FcγRIII binding and ADCC it is not surprising that the same cluster of batches of the reference product which exhibited lower levels of afucosylation and lower FcγRIII binding also have lower ADCC activity.

The data provided, including the results on FcγRIIa binding, illustrate that ABP 980 has similar ADCP activity as compared to Herceptin. Although ABP 980 has higher average relative C1q binding as compared to Herceptin,

this difference is not considered to be clinically meaningful since there is no complement-dependent cytotoxicity (CDC) exhibited by either product as demonstrated in CDC assays with rituximab as control. Furthermore CDC activity was not reported as mechanism of action for trastuzumab

Overall it can be concluded that from a quality point of view, ABP 980 can be considered as highly similar to Herceptin. In addition the data obtained for ABP 980 also show that the results for all relevant quality attributes are within very narrow ranges, suggesting that the manufacturing process is robust, consistent and well controlled.

A tabular summary of the analytical similarity assessment is provided in Table 5, Table 6, Table 7 and Table 8 below.

Table 1. ABP 980 vs Trastuzumab Analytical Similarity Assessment Results for Functional Activity Assays

Method	Relevant Activity	Key Findings
Fab-mediated Activities		
Ligand-independent proliferation inhibition bioassay in BT-474 cells	HER2	Similar inhibition
HER2 binding	HER2	Similar binding
HER2 binding kinetics	HER2	Similar binding kinetics
Inhibition of AKT phosphorylation	HER2	Similar inhibition
Inhibition of proliferation in NCI-N87 cells	HER2	Similar inhibition
Inhibition of proliferation-synergy with chemotherapeutic in NCI-N87 cells	HER2	Similar inhibition
Lack of proliferation inhibition in non-amplified HER2 cells	HER2	Similar lack of inhibition
Fc-mediated Characterisation		
FcRn binding	FcR	Similar binding
FcγRIa binding	FcR	Similar binding
FcγRIIa (131H) binding	FcR	Similar binding
FcγRIIb binding	FcR	Similar binding
FcγRIIIa (158V) binding	FcR	Similar binding
FcγRIIIa (158F) binding	FcR	Similar binding
FcγRIIIb binding	FcR	Similar binding
FcγR binding on primary macrophages	FcR	Similar binding
C1q binding	C1q	Slightly higher relative binding
Fab- and Fc-mediated Characterisation		
ADCC	HER2 and FcR	Similar ADCC activity
ADCP	HER2 and FcR	Similar ADCP activity
Lack of ADCC activity in HER2 negative cells	HER2 and FcR	Similar lack of ADCC activity
Lack of CDC	HER2 and C1q	Similar lack of CDC activity

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Abbreviations defined on last page of this table

Table 2. ABP 980 vs Trastuzumab Analytical Similarity Assessment Results for Structural and Purity Characteristics

Category	Analytical Testing and Parameter	Key Findings
Primary Structure	Intact molecular mass: molecular weight	Similar molecular weight
	Intact molecular mass: profile	Similar profile
	Reduced and deglycosylated molecular masses of HC and LC: molecular weight	Similar molecular weight
	Reduced and deglycosylated molecular masses of HC and LC: profile	Similar profile
	Reduced peptide map: amino acid sequence	Similar amino acid sequence
	Reduced peptide map: profile	Similar profile
	Non-reduced peptide map: disulfide structure	Similar disulfide structure
	Non-reduced peptide map: profile	Similar profile
	Ellman's assay: free thiol	Similar levels of free sulfhydryl
	Glycan map: % afucosylation	Similar afucosylation
	Glycan map: % high mannose	Similar high mannose
	Glycan map: % galactosylation	Similar galactosylation
	Glycan map: % afucosylated galactosylation	Similar afucosylated galactosylation
	Glycan map: % sialylation	Similar sialylation
	Glycan map: profile	Similar profile
	cIEF: isoelectric point	Similar isoelectric point
	cIEF: profile	Similar profile
	Extinction coefficient	Similar extinction coefficient
	Identity by ELISA	Same identity
Higher Order Structure	FTIR: spectral similarity	Similar FTIR spectra
	FTIR: profile	Similar profile
	Near UV CD: spectral similarity	Similar near UV CD spectra
	Near UV CD: profile	Similar profile
	DSC: T_{m1}	Similar T_{m1}
	DSC: T_{m2}	Similar T_{m2}
	DSC: profile	Similar profile

Abbreviations defined on last page of this table

Table 3. ABP 980 vs Trastuzumab Analytical Similarity Assessment Results for Structural and Purity Characteristics

Category	Analytical Testing and Parameter	Key Findings
Particles and Aggregates	MFI: ≥ 5 μm particles	Similar particle levels
	MFI: ≥ 5 μm non-spherical particles	Similar non-spherical particle levels
	HIAC: ≥ 2 μm particles ≥ 5 μm particles ≥ 10 μm particles ≥ 25 μm particles	Similar particle levels
	FFF: submicron particles	Similar submicron particle levels
	DLS: submicron particles	Similar submicron particle levels
	AUC-SV: monomer	Similar monomer
	AUC-SV: profile	Similar profile
	SE-HPLC-SLS: molar mass	Similar molar mass
	SE-HPLC-SLS: profile	Similar profile
Product-related Substances and Impurities	SE-UHPLC: profile	Similar profile
	SE-UHPLC: HMW	Minor quantitative difference in HMW, which primarily consists of dimer species
	SE-UHPLC: main peak	
	rCE-SDS: profile	Similar profile
	rCE-SDS: HC+LC	Minor quantitative difference in NGHC
	rCE-SDS: NGHC	
	rCE-SDS: LMW + MMW	
	nrCE-SDS: profile	Similar profile
	nrCE-SDS: main peak	Minor quantitative difference in partially reduced species
	nrCE-SDS: pre-peaks	
	CEX-HPLC: profile	Similar profile
	CEX-HPLC: acidic peaks	Differences in the levels acidic and main peaks; however, all critical quality attributes at similar levels
	CEX-HPLC: main peak	
	CEX-HPLC: basic peaks	
Thermal Stability and Forced Degradation	Forced degradation	Similar forced degradation profile

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Abbreviations defined on last page of this table

Table 4 Table 6. ABP 980 vs Trastuzumab Analytical Similarity Assessment Results for Structural and Purity Characteristics

Category	Analytical Testing and Parameter	Key Findings
General Properties	Protein content	Similar protein content
	Reconstituted protein concentration	Similar reconstituted protein concentration
	Reconstitution time	Similar reconstitution time

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AUC-SV = analytical ultracentrifugation sedimentation velocity; CEX-HPLC = cation exchange high performance liquid chromatography; cIEF = capillary isoelectric focusing; DLS = dynamic light scattering; DSC = differential scanning calorimetry; ELISA = enzyme linked immunosorbent assay; FFF = field flow fractionation; FTIR = fourier transform infrared spectroscopy; HC = heavy chain; HCP = host cell protein; HIAC = high accuracy light obscuration particle counting; HMW = high molecular weight; LC = light chain; LC-MS = liquid chromatography mass spectrometry; LMW = low molecular weight; MFI = micro flow imaging; MMW = mid molecular weight; NGHC = non-glycosylated heavy chain; nrCE-SDS = non reduced capillary electrophoresis - sodium dodecyl sulfate; qPCR = quantitative polymerase chain reaction; rCE-SDS = reduced capillary electrophoresis - sodium dodecyl sulfate; SE-UHPLC = size exclusion ultra-high performance liquid chromatography; SE-HPLC-SLS = size exclusion high performance liquid chromatography with light scattering detection; UV CD = ultraviolet circular dichroism

Discussion on chemical, pharmaceutical and biological aspects

Module 3 of the dossier for ABP 980 is of good quality and the information provided is sufficiently detailed.

Similarity between ABP 980 and the reference product, EU-Herceptin, has been addressed in an extensive comparability exercise. The similarity between ABP 980 and EU-Herceptin can be confirmed. Furthermore the data show that the ranges obtained for ABP 980 are very narrow suggesting that the manufacturing process is robust, consistent and well controlled.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.4. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

The biological activities pertaining to the primary mechanisms of action and other known biological activities, including the absence of specific functions expected for ABP 980 and trastuzumab, were evaluated by a comprehensive set of functional assays and binding studies. It is agreed that all of the ABP 980 lots are within

the quality range for relative FcγRIIIa (158F) Binding. Nevertheless the same cluster of batches of the reference product which exhibited lower levels of afucosylation, seem to exhibit lower binding activity. Lower binding activities to the FcγRIIIa receptors are not unexpected due to the differences in afucosylation. As already discussed above, this correlation between levels of afucosylation, FcγRIII binding and ADCC fits well to the cluster of batches of the reference product which exhibited lower levels of afucosylation, and lower FcγRIII binding also seem to have lower ADCC activity.

The results of the nonclinical program demonstrate a similarity between ABP 980 and trastuzumab with respect to inhibition of tumour growth in BT-474 and NCI-N87 xenograft models. In the NCI-N87 xenograft model at a dose of 3mg/kg the T/C ratio for Biosimilar/Herceptin is 81.6% suggesting a stronger tumour inhibition by the biosimilar.

2.3.2. Pharmacokinetics

The PK of ABP 980 was assessed in a GLP-compliant, 1-month multiple-dose toxicology study in cynomolgus monkey. Validation results show that the method described for the determination of Herceptin and ABP 980 in Cynomolgus monkey serum has adequate precision, accuracy and selectivity. Based on t1/2, AUC0-inf, AUC0-96h and AUC0-168h values, trastuzumab exposure was similar after injection of Herceptin or FTMB (ratios ranged between 0.94 and 1.15 on day 1 and between 1.08 and 1.15 in week 4).

2.3.3. Toxicology

The toxicology program with ABP 980 and trastuzumab includes a comparative 1-month repeat-dose monkey toxicology study, a 14-day repeat-dose rat toxicology study, and two tissue cross-reactivity studies with frozen human tissues. In line with guidance on biosimilars, single dose toxicity, genotoxicity, carcinogenicity, and developmental and reproductive toxicity studies are not warranted.

In the GLP compliant study in cynomolgus monkeys the test item FTMB is equivalent to ABP 980. Six female cynomolgus monkeys were treated iv twice every week for a period of 4 weeks at the dose-level of 25 mg/kg. No unscheduled mortalities occurred and no signs of systemic toxicity were observed. Local reactions were observed in both trastuzumab-treated groups, but with a higher incidence and duration in animals treated with FTMB. The difference is not considered significant. Body weight was not affected in any group. There were no treatment-related findings in electrocardiography, blood pressure, ophthalmology, haematology and urinalysis. At blood biochemistry similar slightly higher mean urea and triglyceride levels were observed in groups treated with Herceptin and FTMB compared to placebo. There were no significant differences in the organ weights, macroscopic or microscopic changes between the Herceptin and the FTMB groups. There were no organ weight changes related to the administration of Herceptin or FTMB. There was a trend towards increased lymphoid stimulation in the popliteal lymph nodes draining the injection sites in the Herceptin and FTMB groups. There were no significant effects at the injection sites after injections of Herceptin or FTMB. Based on PK values, trastuzumab exposure can be considered similar after injection of Herceptin or FTMB. Overall the toxicology data indicate that ABP 980 and Herceptin can be considered comparable.

2.3.4. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, trastuzumab is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

The applicant used a stepwise approach in order to demonstrate that ABP 980 is comparable to Herceptin with respect to PD/PK and toxicity. Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity and on local tolerance are not required for non-clinical testing of biosimilars. In line with the "3R" policy and the guidance given in the CHMP guidelines and on biotechnology and biosimilar products the company is discouraged to performing the in vivo repeat-dose toxicology study in Cynomolgus monkeys given also the limited number of animals used in this study, which limits statistical evaluation.

2.3.6. Conclusion on the non-clinical aspects

The overall data on PD/PK and toxicology indicate that ABP 980 can be considered similar to the reference product Herceptin.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3.31. Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report/ Location
Healthy Subject PK and Initial Tolerability Study Reports (Module 5.3.3.1)								
PK similarity	20130119	PK similarity of ABP 980 relative to trastuzumab (US) and to trastuzumab (EU); PK similarity of trastuzumab (US) relative to trastuzumab (EU); safety, tolerability, and immunogenicity	Randomized, single-blind, single-dose, 3-arm, parallel-group study	ABP 980 trastuzumab (US) trastuzumab (EU) 6 mg/kg IV infusion Single dose	157 (50 ABP 980, 52 trastuzumab [US], 55 trastuzumab [EU])	Healthy male subjects	Single dose	Complete; full CSR/ Module 5.3.3.1 20130119
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)								
Clinical similarity	20120283	Efficacy, safety, and immunogenicity of ABP 980 vs trastuzumab (EU)	Randomized, multicenter, double-blind, active-controlled study	ABP 980 trastuzumab (EU) Initial dose 8 mg/kg IV followed by maintenance doses of 6 mg/kg IV every 3 weeks	725 (364 ABP 980, 361 trastuzumab)	HER2+ early breast cancer	15 months (including run-in ctx)	Concluded; Primary analysis CSR/ Module 5.3.5.1 20120283

CSR = clinical study report; ctx = chemotherapy; EU = European Union; HER2+ = human epidermal growth factor receptor 2-positive; IV = intravenous; PK = pharmacokinetic; US = United States.

2.4.2. Pharmacokinetics

The clinical pharmacokinetics program comprised a PK similarity study conducted in healthy subjects (Study 20130119) using a single 6-mg/kg IV dose, and the collection of PK data during the clinical similarity study in subjects with HER2+ EBC (Study 20120283) where ABP 980 and trastuzumab (EU) were administered at a single loading dose of 8 mg/kg IV, followed by maintenance doses of 6 mg/kg IV every 3 weeks for up to 1 year.

A single ECL assay (electrochemiluminescence), based on the technology from MSD (Meso Scale Discovery) in microtiter plates, was designed to quantify ABP 980 and trastuzumab (US and EU) in human serum. A PK method qualification study was performed using independent standard curves of ABP 980 and US- or EU-sourced Herceptin. Full validation results of the single calibrator (ABP 980) method subsequently used for determination of trastuzumab concentration in clinical samples met the criteria of the guideline for bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

For Study 20130119, a total of 3059 samples were analyzed in 162 analytical runs and 159 (98%) runs met the method acceptance criteria.

For Study 20120283, a total of 5969 samples were analyzed in 251 analytical runs and 228 (90.8%) runs met the method acceptance criteria.

For Study 20130119 and Study 20120283, samples were evaluated for binding ADAs using a 2-tiered immunoassay that consisted of a screening assay and a confirmatory assay. A validated ECL bridging immunoassay was used to detect antibodies capable of binding ABP 980, trastuzumab (US), or trastuzumab (EU). All samples positive for binding ADAs were assessed for neutralizing antibodies capable of binding to ABP 980, trastuzumab (US), or trastuzumab (EU) using a target binding assay.

The objective of Study 20130119 was the demonstration of PK similarity in healthy male subjects following a single 6-mg/kg IV dose, of ABP 980 relative to trastuzumab (US) and trastuzumab (EU), and trastuzumab (US) relative to trastuzumab (EU). A total of n= 50 in the ABP 980 group and n=46 in the EU-Herceptin group were evaluable for PK including subgroups of ca. 20% Japanese subjects. PK equivalence was assessed by AUCinf and Cmax (primary endpoints) calculated from noncompartmental analysis. The 90% CIs for the ratios of geometric means for the parameters Cmax, AUCinf, and AUClast (secondary endpoint) were fully contained within the standard bioequivalence criteria of 0.80 to 1.25. GM. Ratios and 90% CIs comparing ABP 980 and EU-sourced HERCEPTIN (PK parameter population) were: AUCinf: 1.00 [0.95, 1.06]; AUClast: 1.00 [0.95, 1.06]; Cmax: 0.99 [0.95, 1.03].

In the clinical similarity study conducted in women with HER2+ EBC (Study 20120283), the dose and frequency of dosing were chosen in consideration of the current trastuzumab prescribing information. Investigational product was administered for a total of 4 cycles at a single loading dose of 8 mg/kg IV, followed by maintenance doses of 6 mg/kg IV infusion every 3 weeks (neoadjuvant phase). Following surgery, subjects entered the adjuvant phase and received investigational product (ABP 980 or trastuzumab) every 3 weeks for up to 1 year. Pre-infusion trough concentrations of ABP 980 and trastuzumab (EU) were measured in all randomised subjects (n=725) from visit 5 (baseline) through visit 9 (neoadjuvant treatment phase), and post-surgery at visit 10 (start of adjuvant phase), 14, 18 and at the end of the study visit (EOS). To further characterise the PK of ABP 980 compared with trastuzumab, a subset of 267 subjects (135 subjects in the ABP 980 group and 132 subjects in the trastuzumab group) also had an additional post-infusion serum sample collected after the fourth cycle of investigational product in the neoadjuvant phase (visit 8).

When analyzed by treatment received in the neoadjuvant phase for subjects in the PK analysis population (363 subjects in the ABP 980 group and 361 subjects in the trastuzumab group), results showed that pre-infusion

trough concentrations were similar between ABP 980 and EU-Herceptin at all visits during the neoadjuvant phase. Geometric mean trough serum concentrations increased at each visit in each arm of the neoadjuvant phase, reaching 44.1 µg/mL and 44.8 µg/mL at visit 9 (pre-surgery, post dose 4) for ABP 980 and trastuzumab, respectively. Also steady state trough levels measured during the adjuvant phase were similar (e.g. visit 14, pre-dose 6 after surgery, geometric mean Ctrough: 53.5 vs. 52.8 µg/mL, respectively). For the subset of subjects who had additional post-infusion serum samples collected after the fourth cycle infusion in the neoadjuvant phase, results showed that post-infusion levels of ABP 980 and trastuzumab were comparable (geometric mean EoI: 160.8 and 154.9 µg/mL, respectively).

In addition, a population PK analysis using a published population PK model (Quartino et al, 2016) and the observed data from Study 20120283 was performed to assess the consistency of the PK of ABP 980 with the PK of trastuzumab reported in the literature. The 2-compartment model structure with linear and nonlinear elimination, including covariate effects was deemed adequate to describe the observed concentration-time data for both ABP 980 and trastuzumab from Study 20120283. The type of treatment was not a significant predictor of key PK parameters. The estimates for all fixed and random effects parameters were highly consistent with reported PK parameters reported in literature.

2.4.3. Pharmacodynamics

No pharmacodynamic data were included in the program as there are no specific, surrogate pharmacodynamic markers available that are considered relevant to predicting clinical outcomes for trastuzumab.

2.4.4. Discussion on clinical pharmacology

Performance and results of the PK method qualification study are considered appropriate to demonstrate analytical comparability between ABP 980 and trastuzumab (US and EU). The subsequent use of a single calibrator (ABP 980) during validation and clinical sample analysis is thus considered justified.

Results of study 20130119 demonstrate PK equivalence in healthy male subjects between ABP 980 and EU-sourced Herceptin. The geometric mean exposure levels of ABP 980 and EU-Herceptin (Cmax: 135.9 and 136.9 µg/mL; AUCinf: 34061 and 33947 µg*h/mL, respectively) were consistent with levels reported in the literature after single dose administration of 6 mg/kg Herceptin in healthy subjects (Wynne et al. 2012; Yin et al. 2014). The study population (n= 157) comprised 31 Japanese subjects. Appropriate subgroup analyses (Non-Japanese vs. Japanese) were performed by the Company. The 90% CIs for all comparisons (AUCinf, Cmax and AUClast) were within the bioequivalence criteria of 0.80 to 1.25. The overall study design and statistical methods for study 20130119 are considered acceptable.

Comparison of Ctrough and EoI levels during the neoadjuvant and adjuvant phase of study 20120283 supports PK similarity of ABP 980 and EU-Herceptin in female patients with HER2+ EBC. Steady-state seems to have been reached by the time-point of Visit 14. As no supplementary PK sampling was done between Visit 10 and 14, no definite conclusion on the time point of reaching steady state can be drawn from this study. However, the range of trough levels and accumulation over time observed were as expected for Herceptin.

ABP 980 and Herceptin treatment arms comprised 363 and 361 subjects, respectively. Baseline values are available for only 353 and 347 patients, respectively. N=34 subjects (N=17 per arm, i.e. 5%) had quantifiable baseline trastuzumab levels. Sample collection after start of infusion or pre-exposure to trastuzumab was excluded as possible causes. The reason for this observation is unknown. Since trough concentration profiles for

subjects with quantifiable baseline values were consistent with those observed for other subjects, and the fraction of these patients was similar and not more than 5% in both treatment groups, this is accepted.

Population PK analysis using a published population PK model for trastuzumab and the observed data from Study 20120283 further supported that PK of ABP 980 is highly consistent with the trastuzumab PK reported in the literature.

2.4.5. Conclusions on clinical pharmacology

PK equivalence between ABP 980 and EU-Herceptin is considered as proven.

2.5. Clinical efficacy

2.5.1. Main study

The pivotal efficacy trial was a randomised, double blind, active controlled clinical similarity study in adult female subjects with HER2+ EBC designed to compare the safety, efficacy, PK, and immunogenicity of ABP 980 with trastuzumab. Study 20120283 included a run in chemotherapy phase (epirubicin and cyclophosphamide), a neoadjuvant phase (ABP980 or trastuzumab + paclitaxel) followed by surgery and an adjuvant phase (ABP980 or trastuzumab). Randomisation was stratified according to T stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Subjects who initially received trastuzumab (EU) during the neoadjuvant phase were randomised to either continue receiving trastuzumab or switch to ABP 980 (single transition) during the adjuvant phase. Subjects who initially received ABP 980 during the neoadjuvant phase continued to receive ABP 980 during the adjuvant phase.

Study Participants

Key inclusion criteria

- women ≥ 18 years of age with histologically confirmed invasive breast cancer with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and who were planning for surgical resection of breast tumour and SLND or ALND and neoadjuvant chemotherapy
- HER2-positive disease defined as 3+ overexpression by immunohistochemistry or HER2 amplification by fluorescence in situ hybridisation with known ER and PR hormone receptor status at study entry
- left ventricular ejection fraction (LVEF) of ≥ 55% by 2D echocardiogram
- measurable disease (assessment method used in order of priority: ultrasound, mammography, magnetic resonance imaging, or physical examination) in the breast after diagnostic biopsy, defined as longest diameter ≥ 2.0 cm
- Inclusion Criteria for Randomisation: had LVEF of ≥ 55% by 2D echocardiogram and completed all 4 cycles of run-in chemotherapy

Key exclusion criteria

- Presence of bilateral breast cancer or known metastases
- receiving prior treatment including chemotherapy
- biologic therapy
- radiation or surgery for primary breast cancer

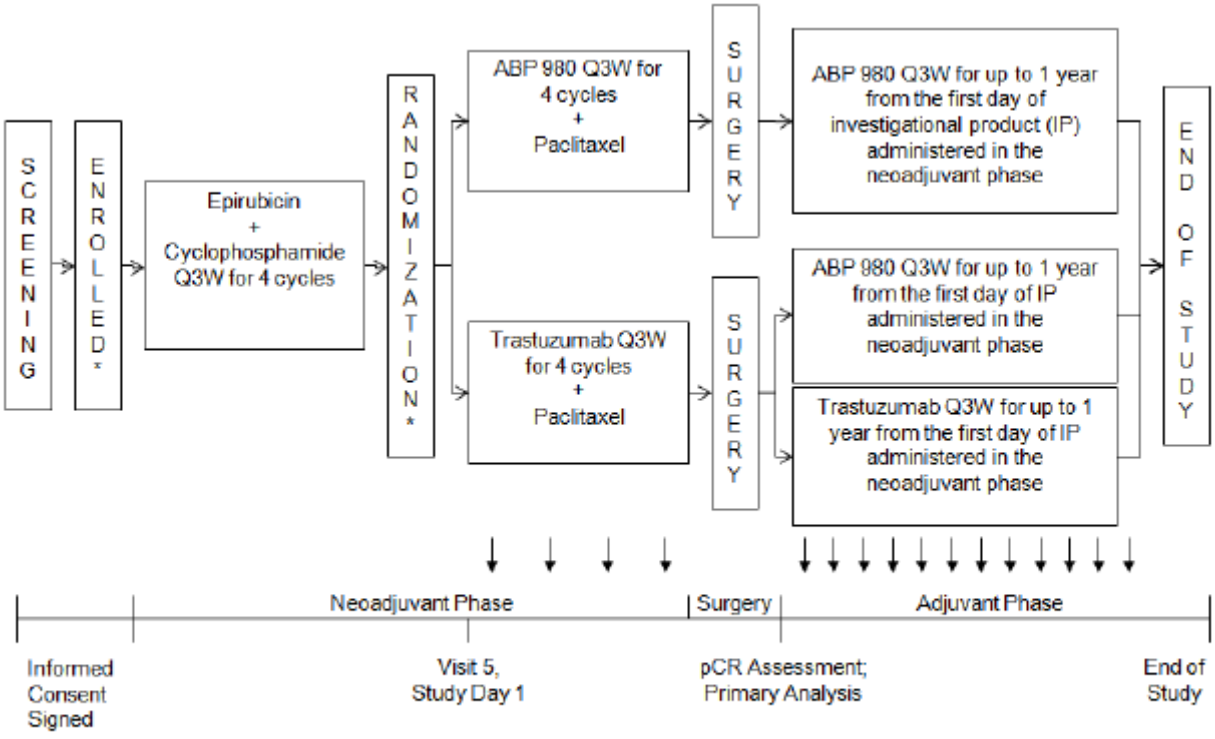
concomitant active malignancy or a history of malignancy in the past 5 years, except treated basal cell carcinoma of the skin or carcinoma in situ of the cervix.

Treatments

Run-in Chemotherapy: Run-in chemotherapy consisted of epirubicin, 90 mg/m2, and cyclophosphamide, 600 mg/m2, Q3W for 4 cycles.

Neoadjuvant Therapy: Paclitaxel was given at a dose of 175 mg/m2 Q3W for 4 cycles (or 80 mg/m2 QW for 12 cycles, if local standard of care). Investigational product (ABP 980 or trastuzumab) was administered at an initial dose of 8 mg/kg over a 90-minute IV infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles.

Adjuvant Therapy: After surgery, subjects received investigational product (ABP 980 or trastuzumab) at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.



Q3W = every 3 weeks
* 827 subjects enrolled and 725 subjects randomized

Outcomes / endpoints

Co-primary efficacy endpoints

- risk difference of the incidence of pCR in breast tissue and axillary lymph nodes
- risk ratio of the incidence of pCR in breast tissue and axillary lymph nodes

Note: pCR was defined as the absence of invasive tumour cells in the breast tissue and in axillary lymph nodes, regardless of residual DCIS.

Secondary efficacy endpoints

- risk difference of pCR in breast tissue
- risk ratio of pCR in breast tissue
- risk difference of pCR in breast tissue and axillary lymph nodes and absence of DCIS
- risk ratio of pCR in breast tissue and axillary lymph nodes and absence of DCIS

Note: pCR in breast was defined as the absence of invasive tumour cells in the breast tissue, regardless of residual DCIS and pCR without DCIS was defined as the absence of invasive tumour cells in the breast tissue and in axillary lymph node(s) and absence of DCIS.

Primary and secondary endpoint assessment was conducted locally and centrally.

Statistical methods

The primary efficacy analysis was performed on the pCR evaluable set (all randomised subjects that underwent surgery and had an evaluable pCR assessment; analysed according to actual treatment received), 3) and a sensitivity analysis was conducted on the ITT set (all randomised subjects) with non-responder imputation for patients without pCR assessment.

The primary comparison of ABP 980 to trastuzumab (both in combination with standard of care neoadjuvant cancer treatment), was assessed using the co-primary efficacy endpoints, RD and RR of pCR in breast and axillary lymph nodes. A sequential testing method was implemented where equivalence between ABP 980 and trastuzumab was first assessed on the RD using a two-sided 90% confidence interval with a fixed equivalence margin of ± 13%. The confidence interval was derived using a generalised linear model adjusted for stratification factors. If successful, equivalence between ABP 980 and trastuzumab was next assessed for the RR using a two-sided 90% confidence interval with a fixed equivalence margin of (0.7586, 1/0.7586). For the risk difference a binary model with identity link was used and the log link was used for the relative risk.

Analyses on other efficacy endpoints are regarded as descriptive. For continuous outcomes, the mean difference between ABP 980 and trastuzumab and its 2-sided 90% CI were estimated using analysis of covariance (ANCOVA) model adjusted for stratification factors and other relevant covariates, and binary outcomes were analysed in the same way as the co-primary endpoints.

Results

Conduct of the study

The number of patients with important protocol deviations is overall comparable between the treatment groups.

Baseline data

In the pCR evaluable population, the majority of subjects were white and not Hispanic/Latino (91.7% and 90.4%, respectively). The mean age (SD) was 52.6 (11.0) years; the age range was from 26 to 85 years. The majority of subjects had axilla lymph node involvement and had tumours that were estrogen receptor (ER) positive and/or progesterone receptor (PR) positive at baseline (75.0% and 73.9%, respectively). The mean (SD) time of disease duration was 4.2 (1.9) months. Demographic and baseline disease characteristics were generally comparable between the 2 treatment groups, with small numerical differences in some of the subgroups.

Numbers analysed

906 patients were screened. Of those 725 received at least one dose of IP in the neoadjuvant phase. The primary efficacy analysis was performed on the pCR evaluable population, which included a total of 696 subjects (358 in the ABP 980 treatment group and 338 in the trastuzumab treatment group). 691 patients entered the adjuvant phase.

9 subjects who already completed screening and run-in chemotherapy were manually randomised to the trastuzumab treatment arm due to a delay in manufacturing of ABP 980. These patients were not included in the pCR summaries or efficacy analyses (ITT population).

Outcomes and estimation

Co-primary endpoints

The co-primary endpoints of the study were Risk Difference (RD) and Risk Ratio (RR) of pCR in breast tissue and axillary lymph nodes regardless of DCIS. According to local laboratory evaluation in the pCR evaluable population 172 patients (48.0%) in the ABP 980 arm achieved a pCR whereas in the trastuzumab arm the number of patients with pCR was 137 (40.5%). Results for pCR by central laboratory evaluation were comparable to these results: ABP 980 pCR = 162 patients (47.8%); trastuzumab pCR = 138 patients (41.8%).

The RD (ABP 980/trastuzumab) was 7.3 %with a 2 sided 95% CI of (0.0, 14.6). While the lower limit of the confidence interval was within the pre-specified equivalence margin of ±13%, thereby ruling out non-inferiority, the upper limit of the confidence interval does not fall within the equivalence margin. The same applies to the risk ratio (RR=1.1877) with a 2 sided 95% CI of (1.0054, 1.4031). As a sequential testing strategy was employed, and the analysis had to be stopped in the case of not succeeding equivalence in RD, the results of the RR of pCR was only presented descriptively, and also for RR of pCR the upper border of the predefined margin (0.7585;1.3182) was crossed.

Sensitivity analyses based on central laboratory evaluation (conducted by independent blinded pathologists) and additional factors are presented in the below table. For the primary analysis set (pCR evaluable population)

the upper limit of the 95% CI only barely crosses the upper equivalence margin (5.8%, /-1.7/13.2%) while results from the PP and the ITT using NRI are preserved in the predefined equivalence margins (PP: 4.1%, -3.5/11.6% and ITT w. NRI 5.1%, -2.0/12.3%).

Table 6. Sensitivity Analyses: Risk Difference of Pathologic Complete Response in Breast Tissue and Axillary Lymph Nodes

	pCR[a]				
Analysis	ABP 980 n/N (%)	Trastuzumab n/N (%)	RD (%)	95% CI	90% CI
Assessed by local laboratory					
PP population[b]	166/351 (47.3)	134/328 (40.9)	6.4	(-1.0, 13.8)	(0.2, 12.6)
ITT population using NRI[b]	172/364 (47.3)	137/352 (38.9)	8.1	(0.9, 15.3)	(2.0, 14.1)
ITT population using NRI: adjusted for correct stratification factors[c]	172/364 (47.3)	137/352 (38.9)	8.2	(1.0, 15.4)	(2.2, 14.2)
pCR evaluable population: adjusted for correct stratification factors[c]	172/358 (48.0)	137/338 (40.5)	7.4	(0.1, 14.7)	(1.3, 13.6)
pCR evaluable population: additional model covariates[d]	172/358 (48.0)	137/338 (40.5)	7.3	(0.0, 14.6)	(1.1, 13.4)
Assessed by central laboratory					
pCR evaluable population[b]	162/339 (47.8)	138/330 (41.8)	5.8	(-1.7, 13.2)	(-0.5, 12.0)
PP population[b]	156/333 (46.8)	137/321 (42.7)	4.1	(-3.5, 11.6)	(-2.3, 10.4)
ITT population using NRI[b]	162/364 (44.5)	138/352 (39.2)	5.1	(-2.0, 12.3)	(-0.9, 11.1)

Table 3.3.5.2 (Summary of Pathologic Complete Response (Study 20120283 pCR Evaluable Population) (cut-off 05 May 2016)

Variable	ABP 980 (N = 358)	Trastuzumab (N = 338)
pCR[a], n (%)		
Yes	172 (48.0)	137 (40.5)
No	186 (52.0)	201 (59.5)
RD (ABP 980 - trastuzumab)[b] (%)	7.3	
95% CI for RD[b]	(0.0, 14.6)	
RR (ABP 980/trastuzumab)[b]	1.1877	
95% CI for RR[b]	(1.0054, 1.4031)	

CSR = clinical study report; pCR = pathologic complete response; RD = risk difference; RR = risk ratio
Note: RD margin = (-13%, 13%); RR margin = (0.7586, 1.3182). For the primary efficacy analysis, pCR evaluation was based on a local laboratory evaluation of tumour samples.
[a] pCR was defined as the absence of invasive tumour cells in the breast tissue and axillary lymph node(s) regardless of residual ductal carcinoma in situ.
[b] Point estimates and CIs were estimated using a generalised linear model adjusted for the randomisation stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.
Source: Modified from Table 14-4.1.1 of the Study 20120283 CSR.

Secondary endpoints

The secondary endpoints were RR and RD in breast tissue only and in breast and axillary lymph nodes in the absence of DCIS.

In breast tissue only the RD of pCR was 6.0% with a 2 sided 95% CI of (-1.3%, 13.4%); the RR of pCR was 1.1463 with a 2-sided 95% CI of (0.9835, 1.3360).

The RD of pCR in breast tissue only in the pCR evaluable population based on a local laboratory evaluation of the tumour samples was 6.0% with a 2 sided 95% CI of (-1.3%, 13.4%); the RR of pCR was 1.1463 with a 2-sided 95% CI of (0.9835, 1.3360). Except for one value (RD in breast tissue only in the PP population) all upper limits of the confidence intervals for RR and RD were above the predefined equivalence margin of the primary analysis.

Table 10. Summary of Pathologic Complete Response in Breast Tissue Only (Study 20120283 pCR Evaluable Population)

	Local Laboratory Evaluation		Central Laboratory Evaluation	
Variable	ABP 980 (N = 358)	Trastuzumab (N = 338)	ABP 980 (N = 343)	Trastuzumab (N = 330)
pCR in breast tissue only[a], n (%)				
Yes	183 (51.1)	152 (45.0)	176 (51.3)	156 (47.3)
RD (ABP 980 - trastuzumab)[b] (%)	6.0		4.1	
90% CI for RD[b]	(-0.2, 12.2)		(-2.1, 10.4)	
95% CI for RD[b]	(-1.3, 13.4)		(-3.3, 11.5)	
RR (ABP 980/trastuzumab)[b]	1.1463		1.1019	
90% CI for RR[b]	(1.0080, 1.3035)		(0.9723, 1.2488)	
95% CI for RR[b]	(0.9835, 1.3360)		(0.9492, 1.2791)	

CSR = clinical study report; pCR = pathologic complete response; RD = risk difference; RR = risk ratio.
[a] pCR was defined as the absence of invasive tumor cells in the breast tissue regardless of residual ductal carcinoma in situ.
[b] Point estimates and CIs were estimated using a generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.
Source: Modified from Table 14-4.3.1 and Table 14-4.3.6 of the Study 20120283 CSR.

Analysis by ADCC activity (NK92 assay)

In order to investigate potential reasons why the upper border of the predefined margin was crossed, the Applicant provided analyses excluding patients who received trastuzumab lots with ADCC activity ≤ 60% and to investigate the impact of ADCC on efficacy via inclusion as covariate in the primary analysis model (see tables with data cut-off 26 Mar 2017 below).

Table 3.3.5.3. Risk Difference of Pathologic Complete Response (ABP 980 Versus Trastuzumab, Excluding Subjects Receiving Trastuzumab Lots with Low ADCC [≤ 60%]) (cut-off: 26 Mar 2017)

	pCR				
Analysis	ABP 980 n/N (%)	Trastuzumab Without Low ADCC Batches[a] n/N (%)	RD (%)	95% CI	90% CI
Primary endpoint: pCR in breast tissue and axillary lymph nodes[b]					
Assessed by local laboratory					
pCR evaluable population[c]	172/358 (48.0)	130/321 (40.5)	7.3	-0.2, 14.7	1.0, 13.5
PP population[c]	166/351 (47.3)	127/311 (40.8)	6.3	-1.2, 13.8	0.0, 12.6
Assessed by central laboratory					
pCR evaluable population[c]	162/339 (47.8)	130/313 (41.5)	5.9	-1.6, 13.5	-0.4, 12.3
PP population[c]	156/333 (46.8)	129/304 (42.4)	4.2	-3.5, 11.8	-2.3, 10.6

Table 3.3.5.4. Risk Ratio of Pathologic Complete Response (ABP 980 Versus Trastuzumab, Excluding Subjects Receiving Trastuzumab Lots with Low ADCC [≤ 60%]) (cut-off: 26 Mar 2017)

Analysis	ABP 980 n/N (%)	pCR Trastuzumab Without Low ADCC Batches[a] n/N (%)	RR	95% CI	90% CI
Primary endpoint: pCR in breast tissue and axillary lymph nodes[b]					
Assessed by local laboratory					
pCR evaluable population[c]	172/358 (48.0)	130/321 (40.5)	1.1879	1.0028, 1.4073	1.0304, 1.3695
PP population[c]	166/351 (47.3)	127/311 (40.8)	1.1610	0.9776, 1.3788	1.0050, 1.3412
Assessed by central laboratory					
pCR evaluable population[c]	162/339 (47.8)	130/313 (41.5)	1.1465	0.9678, 1.3583	0.9945, 1.3218
PP population[c]	156/333 (46.8)	129/304 (42.4)	1.1010	0.9281, 1.3062	0.9539, 1.2708

The applicant provided additional analyses on non-product-related factors. Compared with the stratification factors included in the primary efficacy analysis, the stratification factor of T-stage (< T4 versus T4) was replaced with the full scale of T-stage classification, and histological grade in addition to age were added as baseline covariates. Results of this analysis showed that the RD of pCR was reduced from 7.3% observed in the primary analysis to 6.5% (90% CI: 0.4%, 12.6%; 95% CI: -0.8%, 13.8%). Additionally, the analysis based on central pathology review shows the 95% CI for RD of pCR (-2.4%, 12.4%) is within the pre-specified margin.

In a supplementary analysis all subjects with average ADCC level per cycle ≤ 83% were set to missing. Three analyses were subsequently conducted: A complete case analysis (excluding all subjects with average ADCC ≤ 83%), multiple imputation for the missing ADCC levels and bootstrap resampling to replace the missing ADCC levels. All corresponding 95% confidence intervals were contained within the pre-specified equivalence margin. However, the choice of the cut off (exclusion of ADCC ≤ 83%) was not justified.

Table 13-2. Summary of Risk Difference of Pathologic Complete Response Accounting for Subjects Receiving at Least 1 Cycle of ABP 980 or Trastuzumab with an Average ADCC Level ≤ 83% (Study 20120283 pCR Evaluable Population)

	pCR[a] Rate (%)		RD		
Analysis (N for ABP 980; N for trastuzumab)	ABP 980	Trastuzumab	Estimate	90% CI	95% CI
Removal of subgroup[b] (232; 267)	46.1%	43.1%	2.9%	(-4.4%, 10.2%)	(-5.8%, 11.6%)
Multiple imputation (model based)[c] (358; 338)	45.9%	43.0%	2.8%	(-4.5%, 10.1%)	(-5.9%, 11.5%)
Simulation (bootstrap resampling)[d] (358; 338)	46.1%	43.0%	3.0%	(-3.4%, 8.9%)	(-4.7%, 10.0%)

Multivariable models were estimated as part of the responses to the D180 LoOI, adjusting for ADCC and non-product-related factors (ie, nodal status, hormone receptor status, planned paclitaxel dosing schedule, geographic region, full spectrum of tumour stage, histological grade, and age). In the model without interaction effect for ADCC and treatment, the adjusted treatment effect (RD) was 6.8% (95% CI: -0.5%, 14.1%), i.e., the pre-specified margin of (-13%, 13%) was not met. A model with interaction for ADCC and treatment was also provided but was considered seriously flawed and not considered further.

Table 3.3.5.5. Risk Difference of Pathologic Complete Response (ABP 980 Versus Trastuzumab, Excluding Subjects Receiving Trastuzumab Lots with Low ADCC [≤ 60%]) in breast tissue only(cut-off: 26 Mar 2017)

Analysis	pCR ABP 980 n/N (%)	pCR Trastuzumab Without Low ADCC Batches* n/N (%)	RD (%)	95% CI	90% CI
Secondary endpoint: pCR in breast tissue only[d]					
Assessed by local laboratory					
pCR evaluable population[c]	183/358 (51.1)	144/321 (44.9)	6.1	-1.4, 13.5	-0.2, 12.3
PP population[c]	177/351 (50.4)	141/311 (45.3)	5.0	-2.6, 12.5	-1.4, 11.3
Assessed by central laboratory					
pCR evaluable population[c]	176/343 (51.3)	148/313 (47.3)	3.9	-3.6, 11.5	-2.4, 10.3
PP population[c]	169/336 (50.3)	147/304 (48.4)	1.9	-5.8, 9.5	-4.6, 8.3

Table 3.3.5.6. Risk Ratio of Pathologic Complete Response (ABP 980 Versus Trastuzumab, Excluding Subjects Receiving Trastuzumab Lots with Low ADCC [≤ 60%]) in breast tissue only (cut-off: 26 Mar 2017)

Analysis	pCR ABP 980 n/N (%)	pCR Trastuzumab Without Low ADCC Batches* n/N (%)	RR	95% CI	90% CI
Secondary endpoint: pCR in breast tissue only[d]					
Assessed by local laboratory					
pCR evaluable population[c]	183/358 (51.1)	144/321 (44.9)	1.1482	0.9823, 1.3421	1.0073, 1.3089
PP population[c]	177/351 (50.4)	141/311 (45.3)	1.1198	0.9561, 1.3114	0.9807, 1.2786
Assessed by central laboratory					
pCR evaluable population[c]	176/343 (51.3)	148/313 (47.3)	1.0981	0.9432, 1.2784	0.9665, 1.2475
PP population[c]	169/336 (50.3)	147/304 (48.4)	1.0513	0.9018, 1.2256	0.9243, 1.1958

Analysis based on ADCC-PBMC assay

The applicant provided additional data on ADCC for trastuzumab and ABP 980 clinical lots using a PBMC (peripheral blood mononuclear cells) assay. This analysis identified a lower ADCC cut-point of ≤ 65% (as compared to the NK92 assay in the previous analysis), differentiating 71 subjects with low ADCC in the trastuzumab reference product arm, and provides an analysis based on a more physiologically relevant assay, since the PBMC ADCC assay uses donors that are heterozygous for FcγRIIIa (158V/F), as compared to the high affinity variant [FcγRIIIa (158V)] used in the NK92 assay. FcγRIIIa (158F) carriers were recently shown to more potently mediate ADCC as compared to FcγRIIIa (158V/V) carriers in breast cancer patients (Boero et al, 2015), therefore supporting that PBMC ADCC assay is more physiologically relevant as both genetic variants are represented.

The analytical similarity data demonstrate the following:

• mean ADCC by PBMC of all trastuzumab (EU) lots is 83%

• mean ADCC by PBMC of pre-shift trastuzumab (EU) lots is 93%, and mean of ADCC post-shift trastuzumab (EU) lots is 63%

• mean ADCC by PBMC of all ABP 980 lots is 99%

71 subjects in the trastuzumab treatment group (pCR evaluable population) were exposed to at least one treatment that included a trastuzumab lot having ADCC levels ≤ 65% in the neoadjuvant phase of the clinical similarity study. The analysis was performed on the pCR evaluable population using both local and central laboratory evaluations of the tumour samples.

Table 2. Summary of Pathologic Complete Response, Adjusting for Subjects Exposed to Trastuzumab with ADCC Activity Levels ≤ 65%, Quantified Using PBMC Assay (Study 20120283)

	pCR[a]			RD[d]		
Analysis	ABP 980 n/N (%)	Trastuzumab: Excluding Subjects Exposed to Trastuzumab with ADCC Activity Levels ≤ 65%[b] n/N (%)	Trastuzumab: Subjects Exposed to Trastuzumab with ADCC Activity Levels ≤ 65%[c] n/N (%)	Estimate	90% CI	95% CI
Assessed by local laboratory						
pCR evaluable population	172/358 (48.0)	116/267 (43.4)	21/71 (29.6)	4.4%	(-2.1%, 11.0%)	(-3.4%, 12.3%)
Assessed by central laboratory						
pCR evaluable population	162/339 (47.8)	114/259 (44.0)	24/71 (33.8)	3.5%	(-3.2%, 10.2%)	(-4.5%, 11.5%)

ADCC = antibody-dependent cell-mediated cytotoxicity; DCIS = ductal carcinoma in situ; PBMC = peripheral blood mononuclear cell; pCR = pathologic complete response; RD = risk difference;
Note: RD margin = (-13%, 13%)
[a] pCR was defined as the absence of invasive tumor cells in the breast tissue and axillary lymph node(s) regardless of residual DCIS.
[b] Including subjects who did not take trastuzumab from batches with low PBMC ADCC (≤ 65%).
[c] Including subjects who took any trastuzumab from batches with low PBMC ADCC (≤ 65%).
[d] Risk difference between ABP 980 and trastuzumab without low PBMC ADCC batches. Point estimates and CIs were estimated using a generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.
Source: Modified from Table 14-4.ap.20.1 and Table 14-4.ap.20.3 in Module 5.3.5.1 – Day 180 Follow-up: Study 20120283 - Post-hoc Analysis Tables.

Demographic and baseline data of the 71 Herceptin-treated patients exposed to at least one treatment with a trastuzumab lot having ADCC levels ≤ 65% are presented below.

Table 1. Demographic and Study Baseline Characteristics by Neoadjuvant Treatment (pCR Evaluable Population)

Variable	ABP 980 (N = 358)	Trastuzumab Without Low PBMC ADCC <= 65 (N = 267)	Trastuzumab With Low PBMC ADCC <= 65 (N = 71)	Trastuzumab With Low PBMC ADCC <= 65 Lot E100581-0002L005 (N = 54)
Race [n (%)]				
White	325 (90.8)	242 (90.6)	71 (100.0)	54 (100.0)
Black or African American	10 (2.8)	2 (0.7)	0 (0.0)	0 (0.0)
Asian	2 (0.6)	2 (0.7)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	20 (5.6)	21 (7.9)	0 (0.0)	0 (0.0)
Ethnicity [n (%)]				
Hispanic or Latino	31 (8.7)	35 (13.1)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	327 (91.3)	231 (86.5)	71 (100.0)	54 (100.0)
Not allowed to collect	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Age (Years)				
n	358	267	71	54
Mean (std)	52.7 (10.74)	52.6 (11.31)	52.0 (11.51)	51.3 (10.89)
Median	53.0	53.0	53.0	52.5
Q1, Q3	46.0, 60.0	44.0, 61.0	42.0, 60.0	42.0, 58.0
Min, Max	28, 85	26, 79	31, 79	31, 74

Variable	ABP 980 (N = 358)	Trastuzumab Without Low PBMC ADCC <= 65 (N = 267)	Trastuzumab With Low PBMC ADCC <= 65 (N = 71)	Trastuzumab With Low PBMC ADCC <= 65 Lot E100581-0002L005 (N = 54)
Age Group [n (%)]				
<50 years	139 (38.8)	102 (38.2)	25 (35.2)	19 (35.2)
>=50 years	219 (61.2)	165 (61.8)	46 (64.8)	35 (64.8)
Weight (kg)				
n	358	267	71	54
Mean (std)	72.52 (14.902)	73.28 (13.902)	69.88 (13.552)	70.41 (11.791)
Median	70.55	71.00	68.00	70.50
Q1, Q3	61.60, 81.00	63.00, 81.20	59.00, 78.00	63.00, 77.00
Min, Max	40.1, 120.0	47.0, 118.0	45.0, 108.0	48.0, 108.0
Height (cm)				
n	358	267	71	54
Mean (std)	162.32 (6.699)	161.98 (6.852)	163.24 (7.008)	164.40 (6.477)
Median	162.00	162.00	163.00	163.50
Q1, Q3	158.00, 166.00	158.00, 166.00	160.00, 167.00	160.00, 167.00
Min, Max	140.0, 180.5	145.0, 182.0	147.0, 183.0	150.0, 183.0
BMI (kg/m^2)				
n	358	267	71	54
Mean (std)	27.54 (5.544)	27.98 (5.296)	26.27 (5.097)	26.12 (4.507)
Median	26.90	27.29	25.28	25.73
Q1, Q3	23.83, 30.49	23.88, 31.24	22.27, 29.67	23.03, 28.60
Min, Max	16.7, 46.7	18.2, 50.4	16.6, 40.5	16.6, 37.8

Variable	ABP 980 (N = 358)	Trastuzumab Without Low PBMC ADCC <= 65 (N = 267)	Trastuzumab With Low PBMC ADCC <= 65 (N = 71)	Trastuzumab With Low PBMC ADCC <= 65 Lot E100581-0002L005 (N = 54)
Node classification [n (%)]				
N0	86 (24.0)	69 (25.8)	19 (26.8)	14 (25.9)
N1	176 (49.2)	112 (41.9)	32 (45.1)	22 (40.7)
N2	64 (17.9)	57 (21.3)	11 (15.5)	9 (16.7)
N3	32 (8.9)	29 (10.9)	9 (12.7)	9 (16.7)
Hormone receptor status [n (%)]				
ER+ and/or PR+	263 (73.5)	197 (73.8)	54 (76.1)	42 (77.8)
ER- and PR-	95 (26.5)	70 (26.2)	17 (23.9)	12 (22.2)
Histologic grading [n (%)]				
Grade 1	8 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	171 (47.8)	137 (51.3)	27 (38.0)	21 (38.9)
Grade 3	119 (33.2)	92 (34.5)	29 (40.8)	22 (40.7)
Unknown	60 (16.8)	38 (14.2)	15 (21.1)	11 (20.4)
Disease Duration (months)				
n	358	267	71	54
Mean (std)	4.28 (2.474)	4.02 (0.916)	3.97 (0.654)	3.97 (0.710)
Median	3.85	3.80	3.90	3.85
Q1, Q3	3.50, 4.40	3.50, 4.30	3.50, 4.30	3.50, 4.10
Min, Max	3.0, 38.7	2.9, 11.0	3.2, 7.7	3.2, 7.7

Variable	ABP 980 (N = 358)	Trastuzumab Without Low PBMC ADCC <= 65 (N = 267)	Trastuzumab With Low PBMC ADCC <= 65 (N = 71)	Trastuzumab With Low PBMC ADCC <= 65 Lot E100581-0002L005 (N = 54)
Paclitaxel dosing schedule [n (%)]				
Q3W	252 (70.4)	191 (71.5)	57 (80.3)	47 (87.0)
QW	106 (29.6)	76 (28.5)	14 (19.7)	7 (13.0)
Geographic region [n (%)]				
Eastern Europe	267 (74.6)	194 (72.7)	65 (91.5)	52 (96.3)
Western Europe	42 (11.7)	34 (12.7)	6 (8.5)	2 (3.7)
Other	49 (13.7)	39 (14.6)	0 (0.0)	0 (0.0)
Age Group [n (%)]				
< 40 years	42 (11.7)	35 (13.1)	14 (19.7)	12 (22.2)
>= 40 years	316 (88.3)	232 (86.9)	57 (80.3)	42 (77.8)
Node classification [n (%)]				
N0	86 (24.0)	69 (25.8)	19 (26.8)	14 (25.9)
N1 or N2 or N3	272 (76.0)	198 (74.2)	52 (73.2)	40 (74.1)
Histologic grading [n (%)]				
Grade 1 or Grade 2	179 (50.0)	137 (51.3)	27 (38.0)	21 (38.9)
Grade 3	119 (33.2)	92 (34.5)	29 (40.8)	22 (40.7)
Unknown	60 (16.8)	38 (14.2)	15 (21.1)	11 (20.4)

Ancillary analyses

Several subgroup analyses have been conducted by the Applicant to give an estimate whether comparable results in similarity assessment are achieved across various groups compared to the whole dataset. These results provide an impression, are however hard to interpret, since numbers of patients are overall too small and variability too large to allow for confirmatory assessment. A higher pCR activity for KANJINTI seemed more pronounced in Hormone receptor negative patients, patients with tumour stage 4, and patients older than 50. These results should however, as indicated above, be interpreted with caution and not be regarded as confirmatory.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial 20120283

Title: A RANDOMISED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING THE EFFICACY AND SAFETY OF ABP 980 COMPARED WITH TRASTUZUMAB IN SUBJECTS WITH HER2 POSITIVE EARLY BREAST CANCER		
Study identifier	20120283	
Design	randomised, multicenter, double-blind, active-controlled Phase 3 study	
	Duration of main phase (neoadjuvant): Duration of Run-in phase: Duration of Extension phase (adjuvant):	4 Cycles (12 weeks) 4 Cycles (12 weeks) Up to 1 year
Hypothesis	Equivalence	

Treatments groups	ABP980 (Kanjinti)		Neoadjuvant: ABP980 + Paclitaxel ABP980: initial dose 8mg/kg IV, subsequent 6mg/kg IV Q3W for 3 Cycles Paclitaxel: Q3W for 4 Cycles (or QW for 12 cycles) N= 364 Adjuvant: ABP980 6 mg/kg IV Q3W up to 1 year N= 349
	Trastuzumab EU (Herceptin)		Neoadjuvant: Trastuzumab + Paclitaxel Trastuzumab: initial dose 8mg/kg IV, subsequent 6mg/kg IV Q3W for 3 Cycles Paclitaxel: 175 mg/m² Q3W for 4 Cycles (or QW for 12 cycles) N= 361 Adjuvant: Trastuzumab 6 mg/kg IV Q3W up to 1 year N=171 **OR** ABP980 6 mg/kg IV Q3W up to 1 year N=171
Endpoints and definitions	Co-Primary endpoint	pCR (regardless of DCIS)	pCR in breast and axillary tissue regardless of DCIS
	Secondary endpoint	pCR (breast only)	pCR in breast tissue only
	Secondary endpoint	pCR (no DCIS)	pCR in breast and axilla tissue in the absence of DCIS
Database lock	05 May 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	pCR evaluable population		
Descriptive statistics and estimate variability	Treatment group	ABP980	Trastuzumab
	Number of subject	358	338
	pCR (regardless of DCIS) (n; %)	172 (48.0)	137 (40.5)
	pCR (breast) (n; %)	183 (51.1)	152 (45.0)

	pCR (no DCIS) (n; %)	135 (37.7)	100 (29.6)
Effect estimate per comparison	Primary endpoint: pCR (regardless of DCIS)	**Comparison groups**	**ABP980 - Trastuzumab**
		RD	7.3
		95% CI	(0.0, 14.6)
		Comparison groups	**ABP980 / Trastuzumab**
		RR	1.1877
		95% CI	(1.0054, 1.4031)
	Secondary endpoint: pCR (breast only)	**Comparison groups**	**ABP980 - Trastuzumab**
		RD	6.0
		95% CI	(-1.3, 13.4)
		Comparison groups	**ABP980 / Trastuzumab**
		RR	1.1463
		95% CI	(0.9835, 1.3360)
	Secondary endpoint: pCR (no DCIS)	**Comparison groups**	**ABP980 - Trastuzumab**
		RD	8.0
		95% CI	(1.0, 15.0)
		Comparison groups	**ABP980 / Trastuzumab**
		RR	1.2746
		95% CI	(1.0316, 1.5748)
Notes	Pre-defined equivalence margins were for RD ±13% and for RR (0.7586, 1.3182). The SAP only foresaw 90% confidence intervals to evaluate equivalence, i.e., the presented analyses are supportive only. Prespecified sensitivity analyses were performed based on a local and a central laboratory evaluation of tumour samples on the PP population and the intent-to-treat (ITT) population using nonresponder imputation.		

2.5.2. Discussion on clinical efficacy

Development of the biosimilar candidate ABP 980 (trastuzumab) in terms of clinical efficacy is based on a single pivotal phase III clinical trial in patients with early HER2-positive breast cancer.

Design and conduct of clinical studies

Study 20120283 was a randomised, double blind, active controlled clinical similarity study in adult female subjects with HER2+ EBC with 3 phases which included a run-in chemotherapy phase (4 cycles of epirubicin and cyclophosphamide Q3W) followed by 4 cycles of neoadjuvant treatment (Q3W) with paclitaxel plus either ABP980 or trastuzumab. After surgery patients treated with the reference product were 1:1 randomised to either continue with Herceptin or switch to ABP 980. Treatment was received up to 1 year. The focus of the adjuvant phase was particularly to gain long-term data for safety and immunogenicity. For this procedure, the focus in the adjuvant phase was put on the ABP 980 and the trastuzumab only group, since switching and interchangeability is outside the remit of this MA procedure. At time of data cut-off all patients have completed the neoadjuvant phase. Hence data for the primary and secondary endpoints are complete. 221 patients are still ongoing in the adjuvant setting.

The chosen trial design has been discussed in a CHMP scientific advice. The clinical setting, as well as the indications were deemed acceptable. Risk difference and risk ratio of pCR was agreed upon as sensitive surrogate endpoint. Solely, the definition of pCR and whether DCIS should be included was issue of discussion. The Applicant chose the definition of pCR rate in breast and axillary nodes regardless of DCIS as primary endpoint. This was accepted by CHMP owing to the fact that the secondary endpoints included the same endpoint but in the absence of DCIS.

Primary and secondary endpoint assessment was conducted locally and centrally and did not reveal major deviations.

As discussed in the EMA scientific advice (EMEA/H/SA/2033/1/FU/3/2012/II), calculation of a 13% equivalence margin of RD in pCR rate was based on the NOAH study, where a difference in pCR rate between chemo + trastuzumab vs chemo alone of 19% could be observed. The validity of the margin "relies on the 'constancy' assumption being valid (that results of the NOAH study are applicable to the setting of this prospective study) and this assumption should be addressed in any MAA". The statistical rationale for the equivalence margin was mainly based on interactions with regulatory agencies and chosen for pragmatic reasons.

Overall, the demographic and baseline characteristics were relatively balanced between the treatment groups.

Nine subjects who already completed screening and run-in chemotherapy were manually randomised to the trastuzumab treatment arm due to a delay in manufacturing of ABP 980. These patients were not included in the pCR summaries or efficacy analyses (ITT population).

Discontinuation of subjects during the neoadjuvant phase (without surgery) was rare (6 vs 14 subjects with ABP 980 and Trastuzumab, respectively) with slightly more subjects withdrawing consent in the reference treatment arm (5 vs 2), but regarding the low discontinuation rate this is considered negligible. 96.4% vs. 90.9% of subjects were included in the PP population for pCR evaluation. Fourteen subjects (1.9%) discontinued study after surgery and before entering the adjuvant phase (N=9; 2.5% with ABP 980 and N=5; 1.4% with Trastuzumab), again observed imbalances were not considered meaningful. The most common type of deviation was misstratification in IXRS (61 subjects [8.4%]). Nearly 70% of the misstratification concerned the Nodal status, further categories were tumour classification (~20%) and paclitaxel dosing schedule (~10%).

It seems however plausible that the misstratifications regarding nodal status and probably tumour classification could not be anticipated at time of randomisation and only became apparent after surgery.

Efficacy data and additional analyses

The proportion of patients achieving pCR in the ABP980 group was 47.3%. For the pCR evaluable population the RD (ABP 980/trastuzumab) was 7.3 % with a 2 sided 95% CI of (0.0, 14.6). While the lower limit of the confidence interval was within the pre-specified equivalence margin of ±13%, thereby ruling out non-inferiority, the upper limit of the confidence interval does not fall within the equivalence margin. The same applies to the risk ratio (RR=1.1877) with a 2 sided 95% CI of (1.0054, 1.4031) as well as to the secondary endpoints (except for RD in breast tissue only in the PP population).

The applicant provided sensitivity analysis based on central laboratory evaluation, which was conducted by independent blinded pathologists, as opposed to the predefined local evaluation. In principle this can be considered justifiable, however, this was not the predefined primary analysis. A certain number of patients were excluded from the central evaluation, with a bigger gap being observed in the ABP 980 arm (19 in ABP 980, 8 In EU Herceptin) due to inadequate pCR samples. The applicant was asked to provide detailed reasons for this

exclusion. Regarding the observed results for centrally analysed samples, it was concluded that inter-pathologist variability (local 123 sites, central: 2 reader paradigm) rather than the evaluation of different slides contributed to the more similar results for centrally analysed samples and that the discordance between local and central laboratories did not have a meaningful impact on the study results.

Shifts in ADCC activity that have been observed for some Herceptin lots used in study 20120283 could have contributed to the reasons why the primary endpoint in study 20120283 was not met. Since ADCC is one of the known mechanisms of action affecting trastuzumab efficacy, the higher variability in ADCC activity in the Herceptin lots could have contributed to a wider CI that slightly exceeded the upper equivalence margin. In general, a downward shift in ADCC-related attributes was observed in some Herceptin lots. A concurrent downward shift in afucosylation, afucosylated galactosylation, and galactosylation was observed in the same lots that also demonstrated lower FcγRIIIa binding, which is expected based on the structure-function relationship. Therefore additional analyses for ADCC activity measured by PBMCs as effector cells were conducted.

Taking all data, ADCC activity, glycan structure and expiration date into account, a cut- off value of 65% for the further analyses was considered justified. 71 subjects were identified which received the trastuzumab reference product with lower ADCC activity if applying the cut point of 65%. The risk difference of pCR between the treatment groups was reduced to 4.4% when excluding subjects exposed to at least one trastuzumab with ADCC activity levels ≤65%.

In addition, small imbalances in baseline characteristics were observed between subjects in the 2 treatment arms regarding the histological grade of tumours (more subjects with lower grade tumours were randomised to ABP 980) and tumour stage (within the < T4 stratum, more subjects had T1 or T2 tumours in the ABP 980 group). Initially performed subgroup analyses, including T-stage (< T4 vs T4) did not reveal any influence. However, when adding histological grade as stratification factor and using the full T-staging instead of T-stage <T4 vs T4, the observed RD between trastuzumab and ABP 980 was reduced. By additionally using central laboratory assessments, the RD could be further reduced and the primary endpoint was met as the 95% confidence interval for RD was entirely contained within the pre-specified margin of (-13%, 13%).

Event free survival and overall survival data were similar between the treatment groups although it has to be noted that data were immature at time of submission.

Taking the provided analyses regarding the clinical efficacy into account, and considering the totality of the data, the residual uncertainty does not question the biosimilarity between Kanjinti and Herceptin.

2.5.3. Conclusions on the clinical efficacy

In view of the totality of the evidence similarity between Kanjinti and Herceptin in terms of efficacy is considered sufficiently established.

Regarding extrapolation of all indications approved for the reference product Herceptin, scientific evidence are indicating that the mechanism of action of trastuzumab is similar in different target conditions in both early and metastatic breast cancer (HER2-positive), as well as HER2-positive gastric cancer. Hence, extrapolation to the non-studied oncology indications is considered acceptable.

2.6. Clinical safety

Safety data are derived from 2 ABP 980 clinical studies:

One single-dose clinical pharmacology study:

- Study 20130119, a pharmacokinetic (PK) similarity study in healthy subjects with subgroup analyses of Japanese and non-Japanese subjects

One active-controlled clinical similarity study:

- Study 20120283, a randomised, double-blind, study of ABP 980 compared with trastuzumab in adult female subjects with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC) (data cut-off 05 May 2016)

For both studies, the safety analyses were performed on the safety analysis set that included all subjects who received any amount of investigational product. Safety findings presented in this marketing application include safety data for a total of 882 subjects: 585 subjects who received ABP 980 and 468 who received trastuzumab.

With the responses to the D120 List of Questions the Applicant submitted updated safety, immunogenicity and PK data with a data cut-off on 29 Mar 2017.

Patient exposure

	Number of Subjects Receiving any Amount of IP			
Study Type Study Number	ABP 980 Only	Trastuzumab Only	Trastuzumab/ ABP 980	Total
PK Similarity Study in Healthy Subjects				
Study 20130119	50	107[a]	NA	157
Controlled Clinical Study in Patients				
Study 20120283	364	190	171	725
All Clinical Studies				
Total	414	297	171	882

Study 20120283

In the neoadjuvant phase all 725 subjects who were randomised received at least 1 dose of investigational product (364 and 361 subjects in the ABP 980 and trastuzumab arms, respectively). In general, the total exposure was similar in the 2 treatment arms during the neoadjuvant phase, with 357 (98.1%) and 352 subjects (97.5%) in the ABP 980 and trastuzumab arms, respectively, receiving 4 doses of investigational product, and a median average weight-based dose administered of 6.50 mg/kg in both arms. The mean (SD) cumulative total dose of investigational product administered in the neoadjuvant phase was 1872.4 (404.1) mg for subjects in the ABP 980 group and 1874.6 (380.1) mg for subjects in the trastuzumab group. For subjects receiving paclitaxel every 3 weeks, the mean (SD) cumulative total dose was 685.8 (65.2) mg/m2 for subjects in the ABP 980 group and 678.7 (83.0) mg/m2 for subjects in the trastuzumab group.

At the time of data cut-off a total of 691 subjects had received at least 1 dose of investigational product in the adjuvant phase: 349 in the ABP 980/ABP 980 group, 171 in the trastuzumab/trastuzumab group, and 171 in the trastuzumab/ABP 980 group. As of the data cut-off, the number of doses administered ranged from 1 dose to 13 doses. The mean (SD) cumulative total dose of investigational product administered in the adjuvant phase

was 5165.3 (1334.8) mg for subjects in the ABP 980/ABP 980 group, 5259.2 (1208.9) mg for subjects in the trastuzumab/trastuzumab group, and 5286.5 (1371.3) mg for subjects in the trastuzumab/ABP 980 group.

Study 20130119

Subjects received investigational product as a single IV dose of 6 mg/kg; a total of 50, 52, and 55 subjects were exposed to a single dose of 6 mg/kg IV ABP 980, trastuzumab (US), and trastuzumab (EU), respectively.

Adverse events

Study 20130119

79.0% of subjects overall reported at least 1 adverse event. Most adverse events were assessed as grade 1 or grade 2 in severity. There were no grade 4 or grade 5 events and no deaths. A total of 6 serious adverse events were reported for 2 subjects (1.3%). Adverse events leading to investigational product discontinuation were reported for 1 subject (0.6%).

Adverse events reported for more than 5% of subjects in any treatment group were headache, upper respiratory tract infection, chills, pyrexia, myalgia, nausea, epistaxis, arthralgia, and lethargy. Treatment emergent adverse events that were grade ≥ 3 occurred in 1 subject (secondary to a motor bike accident) in the trastuzumab (US) treatment group and 1 subject (events of infusion related reaction and headache; probably related to study drug) in the trastuzumab (EU) treatment group.

Study 20120283

Neoadjuvant phase

79.9% of subjects overall reported at least 1 treatment emergent adverse event, the incidence (292 [80.2%] and 287 [79.5%] in the ABP 980 and trastuzumab arms, respectively) and severity (54 (14.8%) and 51 subjects (14.1%) experienced CTCAE grade ≥ 3 adverse events) were similar between the ABP 980 and trastuzumab treatment groups. The subject incidence of any EOI in the ABP 980 and trastuzumab treatment groups was 43.1% and 40.7%, respectively. Treatment emergent adverse events were fatal in the neoadjuvant phase for 1 subject in the ABP 980 group and 0 subjects in the trastuzumab group.

Treatment emergent adverse events were most frequently reported from the nervous system disorders and musculoskeletal and connective tissue disorders system organ class (SOC). The largest difference (> 5%) between the treatment groups has been observed in the SOC „Respiratory, thoracic and mediastinal disorders" (ABP 980:10.4% [n=38] vs. trastuzumab: 4.7% [n=17]). The majority of these events were Grade 1 and grade 2 with epistaxis (only grade 1) being the most frequent PT. Events of arthralgia and asthenia were the treatment emergent adverse events reported most frequently (17.3% and 15.2% in the ABP 980 and trastuzumab groups, respectively, for arthralgia; and 14.8% and 16.3%, respectively, for asthenia). The proportion of subjects who experienced grade ≥ 3 treatment emergent adverse events in either treatment group was similar (14.8% in the ABP 980 group and 14.1% in the trastuzumab group). The most common grade ≥ 3 treatment emergent adverse event was neutropenia.

120 patients experienced 280 IP-related adverse events: 60 patients [n=16.5%] with 116 events in the ABP group and 60 patients [n=16.6%] with 164 events in the trastuzumab group.

Adjuvant phase

Most subjects experienced at least 1 treatment emergent adverse event at the time of data cutoff (26 Mar 2017), the incidence was comparable across the ABP 980/ABP 980 (61.6%) and trastuzumab/ABP 980 group (63.2%) whereas in the trastuzumab only group a lower number of AEs was reported (56.1%). The number of serious adverse events, adverse events of interest and adverse events leading to discontinuation were higher in the ABP 980 only group compared to the other groups. Treatment emergent adverse events were fatal in the adjuvant phase for 1 subject in the trastuzumab/ABP 980 group and 0 subjects in the ABP 980/ABP 980 and trastuzumab/trastuzumab groups.

Treatment emergent adverse events were most frequently reported from the injury, poisoning, and procedural complications SOC. There was ≥5% difference between one or more of the treatment groups in the SOCs of Infections and Infestations (15.5% for ABP 980/ABP 980, 9,9% for trastuzumab/trastuzumab, and 13.5% for trastuzumab/ABP 980), Nervous System Disorders (13.5%, 7.0%, and 8.8%, respectively), and Gastrointestinal Disorders (10.9%, 4.1%, and 6.4%, respectively). Events of radiation skin injury and neutropenia were the treatment emergent adverse events reported most frequently (10.6%, 9.9% and 9.4% in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 groups, respectively, for radiation skin injury; and 7.2%, 5.8%, and 3.5%, respectively, for neutropenia). The proportion of subjects who experienced grade ≥3 treatment emergent adverse events in the 3 treatment groups was 8.6%, 6.4%, and 7.6%, respectively. The most common grade ≥3 treatment emergent adverse events were hypertension, neutropenia and gamma glutamyltransferase increased.

109 patients experienced 252 IP-related adverse events: 59 patients [n=16.9%] with 137 events in the ABP only group, 24 patients [n=14.0%] with 54 events in the trastuzumab only group and 26 patients [n=15.9%] with 61 events in the trastuzumab/ABP 980 group.

Table 3.3.8.1 Overall Summary of Treatment-emergent Adverse Events – Neoadjuvant and Adjuvant Phases
(Study 20120283 Safety Analysis Population) (cut-off: 05 May 2016)

	Neoadjuvant Phase		Adjuvant Phase		
Adverse Event Category	ABP 980 N = 364 n (%)	Trastuzumab N = 361 n (%)	ABP 980/ ABP 980 N = 349 n (%)	Trastuzumab/ Trastuzumab N = 171 n (%)	Trastuzumab/ ABP 980 N = 171 n (%)
Any adverse event	292 (80.2)	287 (79.5)	201 (57.6)	89 (52.0)	98 (57.3)
Any grade ≥ 3 adverse event	54 (14.8)	51 (14.1)	27 (7.7)	10 (5.8)	10 (5.8)
Any fatal adverse event	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Any serious adverse event	18 (4.9)	5 (1.4)	14 (4.0)	4 (2.3)	4 (2.3)
Any EOI	157 (43.1)	147 (40.7)	102 (29.2)	39 (22.8)	45 (26.3)
Any adverse event leading to discontinuation of IP	3 (0.8)	2 (0.6)	7 (2.0)	1 (0.6)	2 (1.2)

Any adverse event leading to discontinuation of paclitaxel	8 (2.2)	15 (4.2)	NA	NA	NA
Any adverse event leading to study discontinuation	4 (1.1)	2 (0.6)	6 (1.7)	0 (0.0)	2 (1.2)
Any adverse event leading to dose delay of IP	19 (5.2)	23 (6.4)	14 (4.0)	5 (2.9)	7 (4.1)
Any adverse event leading to dose delay of paclitaxel	45 (12.4)	40 (11.1)	NA	NA	NA
Any adverse event leading to dose change of paclitaxel	21 (5.8)	23 (6.4)	NA	NA	NA

CSR = clinical study report; EOI = event of interest; IP = investigational product; NA = not applicable.
Note: Only treatment-emergent AEs are summarised. For each category, subjects are included only once, even if they experienced multiple events in that category. Only subjects who received at least 1 dose of IP in the adjuvant phase are included in the population for this summary.
Source: Modified from Table 14-6.1.1, Table 14-6.1.2, Table 14-6.12.1.1, Table 14-6.12.1.2 in Study 20120283 CSR

Table 3.3.8.2 Overall Summary Adverse Events – Adjuvant Phase (Safety Analysis Population) (cut-off: 26 Mar 2017)

Adverse Event Category	ABP 980/ ABP 980 (N = 349) n (%)	Trastuzumab/ Trastuzumab (N = 171) n (%)	Trastuzumab/ ABP 980 (N = 171) n (%)
Any treatment-emergent adverse event	215 (61.6)	96 (56.1)	108 (63.2)
Any grade ≥ 3 treatment-emergent adverse event	30 (8.6)	11 (6.4)	13 (7.6)
Any fatal treatment-emergent adverse event	0 (0.0)	0 (0.0)	1 (0.6)
Any serious treatment-emergent adverse event	18 (5.2)	6 (3.5)	6 (3.5)
Any treatment-emergent adverse event of interest	114 (32.7)	43 (25.1)	51 (29.8)
Any treatment-emergent adverse event leading to discontinuation of IP	7 (2.0)	3 (1.8)	4 (2.3)
Any treatment-emergent adverse event leading to discontinuation from study	7 (2.0)	2 (1.2)	2 (1.2)
Any treatment-emergent adverse event leading to dose delay of IP	16 (4.6)	6 (3.5)	8 (4.7)

IP = investigational product
Note: Only treatment-emergent adverse events were summarized. For each category, subjects were included only once, even if they experienced multiple events in that category.
Source: Table 14-6.1.2 and Table 14-6.12.1.2

Data were presented on the three SOCs considered to most significantly impact the overall adverse events: nervous system disorders, gastrointestinal disorders and infections and infestations.

Nervous System Disorders

In review of adverse events by Nervous System Disorder SOC, the most commonly reported adverse events by preferred term (PT) causing the numerical imbalance in the overall rate were headache, dizziness, and peripheral neuropathy. Each of these PTs were classified as CTCAE Grade 1 or 2. With respect to relatedness, headache was reported as related for 1.1% for ABP 980 vs 0.6% for trastuzumab, dizziness was reported as related for 0.3% for ABP 980 and 0 for trastuzumab, and peripheral neuropathy was reported as related for 0.6% for ABP 980 vs 0 for trastuzumab. The subject incidence reported for each of these events was below the historical trastuzumab data reported in the Herceptin SmPC. Adverse events of headache, dizziness, and peripheral neuropathy are listed as very common (≥ 1/10) or common (≥ 1/100 to < 1/10) undesirable effects of trastuzumab (Herceptin Summary of Product Characteristics, April 2017). Additionally, neuropathy (including peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and hypoesthesia) is an adverse reaction associated with the use of paclitaxel, known to have a late time to onset; therefore, the events of neuropathy observed in the adjuvant phase could have been manifestations of a neurologic process that started during or following the neoadjuvant phase.

Gastrointestinal Disorders

In review of adverse events by Gastrointestinal Disorder SOC, the most commonly reported adverse events by preferred term in this SOC causing the numerical imbalance in the overall rate were nausea, diarrhea, and abdominal pain. Each of these PTs were classified as CTCAE Grade 1 or 2. With respect to relatedness to IP, only nausea was considered related (0.9% for ABP 980 vs 0.6% for trastuzumab) and none of the events within diarrhea or abdominal pain AEs were considered related to treatment. Adverse events of nausea, diarrhea, and abdominal pain are listed as very common (≥ 1/10) undesirable effects of trastuzumab (Herceptin Summary of Product Characteristics, April 2017). The subject incidence reported for each of these events was below the historical trastuzumab data reported in the Herceptin® SmPC.

Infections and Infestations

In review of adverse events by Infections and Infestations SOC, the most commonly reported adverse event by preferred term in this SOC causing the numerical imbalance in the overall rate were upper respiratory tract infection, nasopharyngitis, and influenza. Each of these PTs were classified as CTCAE Grade 1 or 2. With respect to relatedness to IP, none of the events were considered related to treatment. Adverse events of upper respiratory tract infection, nasopharyngitis, and influenza are listed as very common (≥ 1/10) undesirable effects of trastuzumab (Herceptin Summary of Product Characteristics, April 2017). The subject incidence reported for each of these events was below the historical trastuzumab data reported in the Herceptin SmPC.

Safety data based on ADCC

The applicant provided additional safety data from the adjuvant phase separate for trastuzumab with and without low ADCC batches by NK92 ADCC assay and PBMC assay, respectively. The number of subjects in the Safety Analysis Population exposed to the low ADCC lots within each phase of the clinical study is provided below:

ADCC by NK92 assay (≤ 60%);

•Neoadjuvant phase – 18 subjects

•Adjuvant phase – 60 subjects

ADCC by PBMC assay (≤ 65%);

•Neoadjuvant phase – 82 subjects

•Adjuvant phase – 66 subjects

Exclusion of subjects based on ADCC NK92 assay

A total of 60 subjects have received four low ADCC lots, as determined by the NK92 assay, within the adjuvant phase of the clinical similarity study. Please refer to Table 2 for the treatment-emergent adverse events (TEAEs) summary table on the requested analyses based on exclusion of these subjects. Please also note that all of the above-referenced four lots had the expiry date after August 2018, considered "post-shift" batches. The incidence of any TEAEs in the ABP 980 group was 61.6%, compared to 60.4% in the trastuzumab arm excluding subjects who have received the low ADCC lots. When comparing within the trastuzumab arms, the incidence within the sub-group of subjects never exposed to low ADCC lots was 60.4% vs 48.3% for subjects exposed to low ADCC lots, suggesting the possibility that subjects receiving trastuzumab with lower ADCC may have reduced the overall adverse event rate experienced in that treatment group. Subsequent assessment of safety data by ADCC exposure at a more granular level for specific adverse events is challenged by the low overall rates within each category.

Table. Summary of Treatment-Emergent Adverse Events by Treatment and NK92 ADCC - Adjuvant Phase (Safety Analysis Population)

Adverse Event Category	ABP 980/ABP 980 (N = 349) n (%)	Trastuzumab/ Trastuzumab Without Low NK92 ADCC Batches[a] (N = 111) n (%)	Trastuzumab/ Trastuzumab With Low NK92 ADCC Batches[b] (N = 60) n (%)
Any treatment-emergent adverse event	215 (61.6)	67 (60.4)	29 (48.3)
Any grade >= 3 treatment-emergent adverse event	30 (8.6)	8 (7.2)	3 (5.0)
Any serious treatment-emergent adverse event	18 (5.2)	4 (3.6)	2 (3.3)
Infusion reactions	28 (8.0)	10 (9.0)	4 (6.7)
Neutropenia	38 (10.9)	11 (9.9)	5 (8.3)
Infections and Infestations	54 (15.5)	7 (6.3)	10 (16.7)
Hypersensitivity	11 (3.2)	5 (4.5)	2 (3.3)
Cardiac failure	2 (0.6)	1 (0.9)	0 (0.0)
Pulmonary toxicity	4 (1.1)	1 (0.9)	1 (1.7)

Note: Adverse events are coded using MedDRA version 19.0. Only treatment-emergent adverse events are summarized. For each category, subjects are included only once, even if they experienced multiple events in that category.
[a] Including subjects who did not take trastuzumab from batches with low NK92 ADCC (<= 60%) during adjuvant phase.
[b] Including subjects who took any trastuzumab from batches with low NK92 ADCC (<= 60%) during adjuvant phase.

Source Dataset: Table 14-6.af.14.1.7 in Module 5.3.5.1 - Study 20120283 - Post-hoc Analysis Tables - Day 180 Request from Rapporteur

Exclusion of Subjects Based on ADCC PBMC Assay

Please refer to Table 3 for safety analyses excluding 66 subjects who have received low ADCC lots during the adjuvant phase, as determined by the PBMC assay. When comparing any TEAEs in the ABP 980 group (61.6%) to the trastuzumab group excluding the subjects exposed to low ADCC lots (58.1%), no meaningful difference is observed. When assessing the potential impact of low ADCC on safety within the trastuzumab group, the rate of TEAEs for subjects who have never received low ADCC lots is 58.1% vs 53.0% for subjects who have received

low ADCC lots. This analysis is consistent with the above exclusion based on the NK92 ADCC assay, suggesting the possibility of a correlation between ADCC exposure and the incidence of adverse events.

Adjuvant Phase (Safety Analysis Population)

Adverse Event Category	ABP 980/ABP 980 (N = 349) n (%)	Trastuzumab/ Trastuzumab Without Low PBMC ADCC Batches[a] (N = 105) n (%)	Trastuzumab/ Trastuzumab With Low PBMC ADCC Batches[b] (N = 66) n (%)
Any treatment-emergent adverse event	215 (61.6)	61 (58.1)	35 (53.0)
Any grade >= 3 treatment-emergent adverse event	30 (8.6)	6 (5.7)	5 (7.6)
Any serious treatment-emergent adverse event	18 (5.2)	3 (2.9)	3 (4.5)
Infusion reactions	28 (8.0)	7 (6.7)	7 (10.6)
Neutropenia	38 (10.9)	11 (10.5)	5 (7.6)
Infections and Infestations	54 (15.5)	7 (6.7)	10 (15.2)
Hypersensitivity	11 (3.2)	3 (2.9)	4 (6.1)
Cardiac failure	2 (0.6)	1 (1.0)	0 (0.0)
Pulmonary toxicity	4 (1.1)	1 (1.0)	1 (1.5)

Note: Adverse events are coded using MedDRA version 19.0. Only treatment-emergent adverse events are summarized. For each category, subjects are included only once, even if they experienced multiple events in that category.
[a] Including subjects who did not take trastuzumab from batches with low PBMC ADCC (<= 65%) during adjuvant phase.
[b] Including subjects who took any trastuzumab from batches with low PBMC ADCC (<= 65%) during adjuvant phase.

Source: Table 14-6.af.24.1.2 in Module 5.3.5.1 - Study 20120283 - Post-hoc Analysis Tables - Day 180 Request from Rapporteur

Exclusion of Subjects Based on Expiry

A total of four trastuzumab lots were identified with expiration date after August 2018, which are the same 4 lots identified based on low ADCC lots, as determined by the ADCC NK92 assay. Overall, 60 subjects received the post-August 2018 lots within the adjuvant phase of the clinical study. Please refer to Table 2 for the safety analysis excluding these subjects.

Serious adverse event / deaths / other significant events

Study 20130119

A total of 6 serious adverse events were reported in 2 subjects (events of tibia fracture, ligament injury, and joint dislocation [all secondary to a motor bike accident]; and deep vein thrombosis, and pulmonary embolism [following surgery for external fixation] in 1 subject in the trastuzumab [US] treatment group; and 1 event of infusion related reaction in 1 subject in the trastuzumab [EU] treatment group). No fatal treatment-emergent adverse events occurred.

Study 20120283

SAEs in neoadjuvant phase

Serious adverse events occurred in 4.9% of subjects (18 subjects) in the ABP 980 treatment group and 1.4% of subjects (5 subjects) in the trastuzumab treatment group. The most frequently reported SOCs were Infections and Infestations; Injury, Poisoning and Procedural Complications; and Blood and Lymphatic System Disorders. Febrile neutropenia was the preferred term reported most frequently (3 subjects in the ABP 980 group and 0

subjects in the trastuzumab group) followed by pneumonia which was reported as grade 3 in 1 subject and grade 5 in 1 subject; all other serious events by preferred term were reported in single subjects in either treatment group. The incidence of treatment related serious adverse events due to investigational product was balanced between the 2 treatment groups (0.8% of subjects [3 subjects] and 0.6% of subjects [2 subjects] in the ABP 980 and trastuzumab groups, respectively).

SAEs in adjuvant Phase

Serious adverse events occurred in 5.2% of subjects (18 subjects) in the ABP 980/ABP 980 group, 3.5% of subjects (6 subjects) in the trastuzumab/trastuzumab group, and 3.5% of subjects (6 subjects) in the trastuzumab/ABP 980 group. All events were reported in a single subject in a single treatment group with the exception of radiation pneumonitis, which was reported in 1 subject each in the trastuzumab/trastuzumab and trastuzumab/ABP 980 groups, and pneumonia, which was reported in 2 subjects in the trastuzumab/trastuzumab group. By relatedness, only a single subject in the trastuzumab/ABP 980 treatment group experienced a serious adverse event possibly related to investigational product (ventricular extrasystoles).

Deaths

6 subjects died on study, including 2 subjects who died from treatment emergent adverse events (ie, events that occurred within 30 days after the last dose of investigational product) and 3 subjects who died from events that occurred more than 30 days after the last dose of investigational product.

Three deaths were reported in the ***neoadjuvant*** phase:

- pneumonia (ABP 980)
- Metastases to the brain (two events in the trastuzumab group)

Three deaths were reported in the ***adjuvant phase*** both in the trastuzumab/ABP 980:

- septic shock (patient with ECOG 3 in wheelchair and respiratory failure prior to Grade 5 event)
- pneumocystis jirovecii pneumonia (tested positive for HIV)
- Metastases to bone, liver, lungs and adrenal glands

None of these deaths were considered related to the investigational medicinal product.

Adverse events of interest

Study 20120283

EOIs were defined as noteworthy events for a particular product or class of products that a sponsor may wish to monitor carefully. The prespecified EOIs were derived based on the mechanism of action and clinical data available in product labelling for trastuzumab. The prespecified EOIs for this study included: cardiac failure, neutropenia, infusion reaction, hypersensitivity, pulmonary toxicity, and infections and infestations. The incidence of EOIs was also summarised in patient years of exposure (the exposure adjusted incidence rate per 100 patient years) and by drug exposure over the entire study.

Neoadjuvant phase

In the neoadjuvant phase a slightly higher percentage of patients in ABP 980 group experienced an "all grade EOI" (43.1% and 40.7% for ABP 980 and trastuzumab, respectively). A similar situation can be seen in case of Infusion reaction (21.7% versus 18.8% for ABP 980 and trastuzumab, respectively) and for neutropenia (19.0% versus 15.8% for ABP 980 and trastuzumab, respectively). The most frequently reported EOIs grade ≥ 3 were neutropenia (5.8% and 5.8% of subjects in the ABP 980 and trastuzumab groups, respectively), infusion reaction (1.9% and 1.9% of subjects, respectively), and infections and infestations (1.9% and 0.6% of subjects, respectively).

Table 3.3.8.2 Overall Summary of Treatment-emergent Adverse Events of Interest - Neoadjuvant Phase (Study 20120283 Safety Analysis Population)

	ABP 980 (N = 364)		Trastuzumab (N = 361)	
Event of Interest	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)
Any EOI	31 (8.5)	157 (43.1)	29 (8.0)	147 (40.7)
Infusion reactions	7 (1.9)	79 (21.7)	7 (1.9)	68 (18.8)
Neutropenia	21 (5.8)	69 (19.0)	21 (5.8)	57 (15.8)
Infections and infestations	7 (1.9)	51 (14.0)	2 (0.6)	53 (14.7)
Hypersensitivity	2 (0.5)	25 (6.9)	2 (0.6)	19 (5.3)
Cardiac failure	0 (0.0)	6 (1.6)	0 (0.0)	1 (0.3)
Pulmonary toxicity	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)

Adjuvant Phase

In the adjuvant phase the overall difference in incidence of all grade EOIs is higher between ABP 980/ABP980 and trastuzumab/trastuzumab: 32.7% versus 25.1%, respectively. Additionally the incidence rate of infections and infestations is higher for ABP 980 arm (15.5% versus 9.9%, ABP 980 and trastuzumab/trastuzumab, respectively). The most frequently reported EOIs grade ≥ 3 were infections and infestations (1.1%, 1.2%, and 1.2% of subjects in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 groups, respectively), neutropenia (0.9%, 1.2%, and 0.6% of subjects, respectively), and infusion reactions (0.6%, 1.2%, and 1.8% of subjects, respectively).

Exposure-adjusted incidence rates

The overall summary of exposure-adjusted incidence rates for EOIs indicate that EOIs (any EOI and especially Infusion reaction and Infections and infestations) show a slightly higher trend towards a higher incidence rate in APB 980 group as in trastuzumab.

Table 3.3.8.3.. Summary of Exposure-adjusted Incidence Rates for Treatment-emergent Adverse Events of Interest– Entire Study (Safety Analysis Population)

	ABP 980/ABP 980 (N = 364)		Trastuzumab/Trastuzumab (N = 190)		Trastuzumab/ABP 980 (N = 171)		Ratio of EAIR (90% CI)	
Preferred Term	Subjects/Total Exposure Time (patient-years)	Incidence Rate	Subjects/Total Exposure Time (patient-years)	Incidence Rate	Subjects/Total Exposure Time (patient-years)	Incidence Rate	ABP 980/ABP 980 vs Trastuzumab/ Trastuzumab	Trastuzumab/ABP 980 vs Trastuzumab/ Trastuzumab
Any EOI	202/205.71	98.20	94/109.89	85.54	93/101.24	91.86	1.15 (0.93, 1.41)	1.07 (0.84, 1.37)
Infusion reactions	95/287.56	33.04	46/147.10	31.27	44/143.58	30.64	1.06 (0.79, 1.42)	0.98 (0.69, 1.39)
Neutropenia	91/293.89	30.96	37/156.91	23.58	36/146.08	24.64	1.31 (0.95, 1.81)	1.05 (0.71, 1.54)
Infections and Infestations	92/307.58	29.91	41/155.02	26.45	44/146.10	30.12	1.13 (0.83, 1.54)	1.14 (0.80, 1.63)
Hypersensitivity	33/341.52	9.66	17/174.35	9.75	15/166.95	8.98	0.99 (0.61, 1.62)	0.92 (0.51, 1.65)
Cardiac failure	8/359.78	2.22	1/182.85	0.55	2/175.57	1.14	4.07 (0.71, 23.27)	2.08 (0.28, 15.62)
Pulmonary toxicity	5/363.77	1.37	2/183.01	1.09	2/176.01	1.14	1.26 (0.32, 4.98)	1.04 (0.20, 5.39)

CI = confidence interval; EAIR = exposure-adjusted incidence rate; EOI = event of interest
[a] The exposure-adjusted incidence rate (EAIR) per 100 patient-years was the number of subjects who experienced an event divided by the total subject exposure time multiplied by 100.
Source: Table 14-6.13.2.3

Events of interest

- Infusion Reaction EOIs

Neoadjuvant phase: 79 [21.7%] subjects and 68 [18.8%] subjects in the ABP 980 and trastuzumab groups, respectively experienced an infusion reaction. Overall, 18 (4.9%) subjects in the ABP 980 group and 10 (2.8%) subjects in the trastuzumab group had EOIs that occurred on the day of or the day after the first day of treatment with investigational product. The frequency of investigational product-related infusion reaction EOIs was 13 [3.6%] subjects and 12 [3.3%] subjects] in the ABP 980 and trastuzumab groups, respectively

Adjuvant phase: Infusion reaction EOIs were serious for 1 (0.6%) subject in the trastuzumab/ABP 980 group (grade 4 respiratory failure). One subject (0.6%) in the trastuzumab/ABP 980 group experienced an infusion reaction EOI that was grade 4 (serious event of respiratory failure). There were no grade 5 infusion reaction EOIs. The frequency of investigational product-related infusion reaction EOIs was 10 [2.9%] subjects, 4 [2.3%] subjects, and 2 [1.2%] subjects in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 groups, respectively.

- Hypersensitivity EOIs

Neoadjuvant phase: Hypersensitivity EOIs were grade 3 for 2 (0.5%) subjects in the ABP 980 group (rash and hypersensitivity) and 2 (0.6%) subjects in the trastuzumab group (rash and drug hypersensitivity). There were no grade 4 or grade 5 hypersensitivity EOIs. With respect to the grade 3 hypersensitivity EOIs, all were assessed as related to paclitaxel and not related to investigational product. The frequency of investigational product-related hypersensitivity EOIs was 6 [1.6%] subjects and 3 [0.8%] subjects in the ABP 980 and trastuzumab groups, respectively.

Adjuvant phase: No hypersensitivity EOIs were serious and all were grade 1 or 2. The frequency of investigational product-related hypersensitivity EOIs was 4 [1.1%] subjects, 2 (1.2%), and 0 (0.0%) in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 groups, respectively.

- Neutropenia EOIs

During the neoadjuvant phase, neutropenia EOIs were grade 4 for 5 (1.4%) subjects in the ABP 980 group and 6 (1.7%) subjects in the trastuzumab group. During the adjuvant phase, neutropenia EOIs were grade 4 for 1 (0.3%) subject in the ABP 980/ABP 980 group and 0 subjects in the trastuzumab/trastuzumab and trastuzumab/ABP 980 groups. There were no grade 5 neutropenia EOIs. (Cut-off 05 May 2016)

- Infections and Infestations EOIs

Neoadjuvvant phase: Infections and infestations EOIs were serious for 6 (1.6%) subjects in the ABP 980 group and 1 (0.3%) subject in the trastuzumab groups. Infections and infestations EOIs were grade 5 for 1 (0.3%) subject in the ABP 980 group (pneumonia) and 0 subjects in the trastuzumab group.

Adjuvant phase: 15.5% (n=54), 9.9% (n=17) and 13.5% (n=23) patients experienced infections and infestations EOI in the ABP980 only, trastuzumab only and in the trastuzumab/ABP980 group, respectively. Infections and infestations EOIs were grade 5 for 1 (0.6%) subject in the trastuzumab/ABP 980 group (septic shock) and for 0 subjects in the ABP 980/ABP 980 and trastuzumab/trastuzumab groups.

- Cardiac Failure EOIs

Neoadjuvant phase: All 7 subjects with cardiac failure EOIs were older than 50 years of age. Of the 6 subjects with cardiac failure EOIs in the ABP 980 treatment group, 3 subjects had relevant ongoing medical history of cardiac disease that may have contributed to cardiac failure EOIs. The subject in the trastuzumab group with a cardiac failure EOI also had relevant ongoing medical history of cardiac disease that may have contributed to the cardiac failure EOI. All 7 subjects underwent surgery and either completed all planned doses of investigational product or were ongoing in the study at the time of the data cutoff. There were no relevant LVEF findings following the cardiac failure EOIs for 6 of the 7 subjects, indicating resolution or no worsening of the cardiac failure EOIs. No cardiac failure EOIs were serious and all were grade 1 or 2.

Adjuvant phase: During the adjuvant phase, 2 (0.6%), 1 (0.6%), and 1 subjects (0.6%) in the ABP 980/ ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980, respectively, had at least 1 cardiac failure event. One subject in the trastuzumab/ABP 980 arm had a cardiac failure event of grade 3, and all others were grade 1 or 2. Only 1 subject (0.6%) in the trastuzumab/trastuzumab arm (Subject 28364008004) had a cardiac failure event that was coincident with LVEF decline by ≥ 10 percentage points compared to baseline and to < 50%.

- Pulmonary toxicity EOIs

Neoadjuvant phase: No pulmonary toxicity EOIs were serious and all were grade 1 or 2.

Adjuvant phase: During the adjuvant phase, 4 (1.1%), 2 (1.2%), and 1 subjects (0.6%) in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 arms, respectively, had at least 1 pulmonary toxicity event. The events were radiation pneumonitis (2 [0.6%] (Grade 1 and 2), 1 [0.6%] (Grade 3), and 1 subjects [0.6%] (Grade 3), respectively), pneumonitis (1 subject [0.3%] in the ABP 980/ABP 980 arm (Grade 1), pulmonary fibrosis (1 subject [0.3%] in the ABP 980/ABP 980 arm (Grade 2)), and interstitial lung disease (1 subject [0.6%] in the trastuzumab/trastuzumab arm (Grade 2)).

Immunological events

The immunogenicity of ABP 980 and trastuzumab was assessed in both clinical trials by measuring the ADA levels using a validated 2-tiered approach that included a screening assay and a confirmatory assay.

Study 20120283

In study 20120283 the blood samples were collected prior to dosing on day 1, at scheduled time points during the study, and at the end of the study.

Neoadjuvant phase

A total of 723 subjects (363 in the ABP 980 treatment group and 360 in the trastuzumab treatment group) had at least one on-study ADA result. Three (0.9%) subjects in the trastuzumab group tested positive for

pre-existing binding ADAs at baseline, and no subjects in either group tested positive for neutralizing ADAs. Postbaseline, 2 (0.6%) subjects in each treatment group (ABP 980 and trastuzumab) with negative or no result at baseline tested positive for binding ADAs; for both of the subjects in the ABP 980 group, the results were transient (ie, negative results at the subject's last time point tested within the study period). No subjects in either treatment group developed neutralizing ADAs during the neoadjuvant phase.

Adjuvant phase

Seven (1.0%) subjects (2 [0.6%] in the ABP 980/ABP 980 treatment group, 2 [1.2%] in the trastuzumab/trastuzumab treatment group, and 3 [1.8%] in the trastuzumab/ABP 980 treatment group) tested positive for pre-existing binding ADAs before the first investigational product dose in the adjuvant phase, and no subjects in any group tested positive for neutralizing ADAs. One subject (0.7%) in the trastuzumab/ABP 980 treatment group developed binding ADAs during the adjuvant phase (ie, subject was binding ADA positive during the adjuvant phase with a negative or no result before the adjuvant phase), but the result was transient (ie, the ADA result was negative at the subject's last time point tested within the study period). No subjects developed neutralizing ADAs.

Study 20130119

In the study 21030119 (PK similarity) blood samples were collected prior to dosing and at the end of the study. There were no pre-existing binding ADAs detected in the baseline samples, and no subjects had a positive binding ADA test at the end of the study.

On study Event free Survival

On study EFS is based on a total of 37 events. The percentage of subjects with disease progression, recurrence, or death was 5.5% in the ABP 980/ABP 980 treatment group, 5.8% in the trastuzumab/trastuzumab treatment group, and 3.5% in the trastuzumab/ABP 980 treatment group. The median EFS (months) had not been reached for any treatment group at the time of the primary analysis. The estimated hazard ratio from a stratified Cox proportional hazards regression model was 0.9969 (90% CI: 0.5340, 1.8612) for ABP 980/ABP 980 versus trastuzumab/trastuzumab and 0.5414 (90% CI: 0.2207, 1.3282) for trastuzumab/ABP 980 versus trastuzumab/trastuzumab.

Overall Survival

Overall, 6 subjects (0.8%) died on study, 1 (0.3%), 2 (1.1%), and 3 (1.8%) in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 treatment groups, respectively. Of these, 2 were considered treatment emergent adverse events, because they occurred within 30 days after the last dose of investigational product.

Laboratory findings

There was no notable difference between the treatment groups with regards to hematology and chemistry laboratory parameters. There were no clinically relevant median changes from baseline in pulse rate, systolic blood pressure, diastolic blood pressure, and weight overall, or based on treatment received in the neoadjuvant phase or treatment received in the neoadjuvant/adjuvant phases.

Discontinuation due to adverse events

Study 20130119

1 subject (trastuzumab [EU]) discontinued investigational product prior to receiving the entire infusion due to adverse events of headache, infusion related reaction, abdominal discomfort, nausea, and chills. The events were reported as resolved at later timepoints on the same day as initial occurrence.

Study 20120283

Neoadjuvant phase

The incidence of treatment-emergent adverse events leading to discontinuation of investigational product was 0.8% (3 subjects) in the ABP 980 treatment group and 0.6% (2 subjects) in the trastuzumab treatment group; the incidence of treatment-emergent adverse events leading to discontinuation of paclitaxel was 2.2% (8 subjects) and 4.2% (15 subjects), respectively. All adverse events leading to discontinuation of investigational product occurred in single subjects in either treatment group. In the ABP 980 and trastuzumab treatment groups, events of peripheral sensory neuropathy (0.5% and 0.3%, respectively), peripheral neuropathy (0.3% and 0.8%, respectively), and toxic neuropathy (0.0% and 0.6%, respectively) were among the most commonly occurring adverse events leading to discontinuation of paclitaxel.

Adjuvant Phase

The incidence of treatment emergent adverse events leading to discontinuation of investigational product was 2.0% (7 subjects) in the ABP 980/ABP 980 treatment group, 1.8% (3 subjects) in the trastuzumab/trastuzumab treatment group, and 2.3% (4 subjects) in the trastuzumab/ABP 980 treatment group. The only adverse event leading to discontinuation of investigational product in more than a single subject in any treatment group was metastases to the central nervous system occurring in 2 subjects in the ABP 980/ABP 980 treatment group and 1 subject in the trastuzumab/trastuzumab group.

2.6.1. Discussion on clinical safety

Safety data are derived from two clinical studies: the completed phase 1 study in healthy subjects (20130119) and the ongoing phase 3 study in patients with early breast cancer (20120283).

Study 20130119

A total of 105 patients (ABP 980: 50 patients; trastuzumab (EU): 55 patients) were included in the safety dataset. Overall, the safety findings were comparable between the ABP 980 group and the trastuzumab (EU) group. However, the reported incidence rate of “any adverse event” was slightly lower in the reference product (EU) arm as in ABP 980 (78.2% versus 84.2 %, respectively). This difference is mainly driven by differences in two kind of AEs, namely myalgia and arthralgia (myalgia was listed for 16 % subjects in ABP 980 arm and for 1.5% in trastuzumab EU arm /arthralgia occurred in 10.0% and 1.8%, respectively).

Study 20120283

A total of 725 patients (ABP 980: 364 patients; trastuzumab: 361 patients) received at least one dose of investigational product and were thus included in the safety population.

The majority of patients received 4 doses of IP treatment (ABP 980: 357 patients (98.1%), trastuzumab: 352 patients (97.5%)) as well as the Q3W schedule of paclitaxel (ABP 980: 70.3%; trastuzumab: 71.5%). Overall,

parameters such as cumulative dose administered, relative dose intensity and number of subjects with dose delay were comparable between the treatment groups for both IP and paclitaxel, respectively.

Neoadjuvant Phase

During the neoadjuvant phase most subjects (292 [80.2%] and 287 [79.5%] in the ABP 980 and trastuzumab arms, respectively) experienced treatment-emergent adverse events (TEAE), and 54 (14.8%) and 51 subjects (14.1%) experienced CTCAE grade ≥ 3 adverse events. The number of IP-related TEAEs, TEAES leading to IP discontinuation and IP-related SAEs was comparable between the treatment groups. The largest difference between the treatment groups has been observed in the SOC „Respiratory, thoracic and mediastinal disorders" (ABP980:10.4% [n=38] vs. trastuzumab: 4.7% [n=17]). The most frequently reported TEAEs were arthralgia, asthenia, neutropenia, peripheral neuropathy and anaemia.

A slightly higher incidence of serious adverse events (4.9% [n=18] vs. 1.4% [n=5]) and events of interest (43.1% [n=157] vs 40.7% [n=147]) was reported in the ABP980 group. A similar situation can be seen in case of infusion reaction (21.7% versus 18.8% for ABP 980 and trastuzumab, respectively) and for neutropenia (19.0% versus 15.8% for ABP 980 and trastuzumab, respectively). Cardiac failure EOI were only Grade 1 and 2 and half of the patients in the ABP 980 group had a history of cardiac disease.

In the ABP 980 group experienced more serious adverse events and more SAEs Grade 3 and 4 compared to the trastuzumab group (4.9% [n=18] vs. 1.4% [N=5]). Among these the infection and infestation was the most common SOC with pneumonia as the predominant PT.

A total of 5 deaths occurred in study 20120283: 2 events of metastases to the brain and 1 event each of pneumonia, septic shock and pneumocystis jirovecii pneumonia. Three of these events occurred in the neoadjuvant phase: pneumonia (ABP 980), both events of metastases to the brain (both trastuzumab). None of these were considered related to the IP.

The incidence of antidrug antibodies was low for both treatment groups (ABP 980: 0.6% [n=2]; trastuzumab: 1.4% [n=5]). The majority of patients had a post-baseline result. No neutralizing antibodies were detected during the neoadjuvant phase.

Adjuvant Phase

In the adjuvant setting the overall number of adverse events was comparable between the ABP 980 only group (61.6%) and the trastuzumab/ABP 980 group (63.2%) whereas in the trastuzumab only group a lower number of AEs was reported (56.1%).

Treatment emergent adverse events were most frequently reported from the injury, poisoning, and procedural complications SOC. There was ≥ 5% difference between one or more of the treatment groups in the SOCs of Infections and Infestations (15.5% for ABP 980/ABP 980, 9,9% for trastuzumab/trastuzumab, and 13.5% for trastuzumab/ABP 980), Nervous System Disorders (13.5%, 7.0%, and 8.8%, respectively), and Gastrointestinal Disorders (10.9%, 4.1%, and 6.4%, respectively). Events of radiation skin injury and neutropenia were the treatment emergent adverse events reported most frequently (10.6%, 9.9% and 9.4% in the ABP 980/ABP 980, trastuzumab/trastuzumab, and trastuzumab/ABP 980 groups, respectively, for radiation skin injury; and 7.2%, 5.8%, and 3.5%, respectively, for neutropenia). The proportion of subjects who experienced grade ≥ 3 treatment emergent adverse events in the 3 treatment groups was 8.6%, 6.4%, and 7.6%, respectively. The most common grade ≥ 3 treatment emergent adverse events were hypertension, neutropenia and gamma glutamyltransferase increased.

The number of patients experiencing an AE that led to discontinuation of investigational product was comparable between the treatment groups whereas the number of patients with AEs leading to study discontinuation was slightly higher in the ABP 980 only group compared to the trastuzumab only group and the trastuzumab/ABP 980 group.

IP-related AEs occurred slightly more often in the ABP 980 only group 59 patients [n=16.9%] with 137 events in the ABP only group compared to the trastuzumab only group (24 patients [n=14.0%] with 54 events) and the trastuzumab/ABP 980 group 26 patients [n=15.9%] with 61 events). There appears to be no clear pattern. Neutropenia, leukopenia and anemia were the most frequently overserved PTs.

The incidence of EOI was higher in the ABP 980 only group (32.7%) compared to the trastuzumab only group (25.1%) and the trastuzumab/ABP 980 group (29.8%). This finding is confirmed by exposure-adjusted incidence rates of EOI per 100 patients-years. Of note in this category (SOC), the incidence rate of infections and infestations is higher for the ABP 980/ABP 980 arm (15.5% versus 9.9% in the trastuzumab/trastuzumab arm, respectively). In addition the observed trend towards higher incidence of infections and infestations has also been reported in study 20130119 (PK in HV).

The incidence of ≥ Grade 3 EOI was similar between the treatment groups.

The number of SAEs (5.2%, 3.5%, and 3.5% subjects in the ABP 980 only, trastuzumab only and trastuzumab /ABP 980 group, respectively) and grade 3 SAEs in the adjuvant phase is slightly increased in the ABP 980 only group compared to the trastuzumab only group and the trastuzumab/ABP 980 group. One grade 5 SAE was reported in one subject in the trastuzumab/ABP 980 group (septic shock) which was also classified as EOI.

A total of 6 deaths occurred in study 20120283 - two of those during the adjuvant phase in the trastuzumab/ABP 980 group: septic shock pneumocystis jirovecii pneumonia.

0.6%, 1.2% and 1.8% of patients were binding antibody positive in the ABP 980 only group, the trastuzumab only group and the trastuzumab/ABP 980 group, respectively. 1 patient with negative or no results before the adjuvant phase was transient binding antibody positive during the adjuvant phase (trastuzumab/ABP 980 group). No neutralizing antibodies were detected during the adjuvant phase. In general the immunogenicity of trastuzumab is low. The level of post-baseline immunogenicity is still unexpectedly low (ADA incidence for originator studies ranges around 7-8%).

Data on event-free survival (EFS) and overall survival (OS) are still too immature to draw any conclusions.

Three SOCs were considered to most significantly impact the overall adverse events: nervous system disorders, gastrointestinal disorders and infections and infestations. For all SOCs the reported subject incidences were below the historical trastuzumab data reported in the Herceptin SmPC. For infections and infestations no related events were reported. For GI disorders 0.9% events for ABP 980 vs 0.6% for trastuzumab were considered related to the IP (all of which were nausea). For the SOC Nervous system disorders the Applicant the incidences of related AEs were slightly higher in the ABP 980 arm, however the overall incidences are very low: headache 1.1% vs 0.6%, dizziness 0.3% vs. 0%, peripheral neuropathy 0.6% vs 0% (ABP 980 vs. trastuzumab).

The observed differences in these SOCs were driven by Grade 1 and 2 AEs. This is however only partly relevant to this submission as Kanjinti is developed as a biosimilar medicinal product whose primary focus should be on the similarity to the originator preferably with a direct comparison in the pivotal clinical trial.

It is acknowledged that the overall safety profile and AE incidences observed in the ABP 980 arm are comparable to the historical profile and data reported in the SmPC. The observed differences in the safety profile of ABP 980 could be owed to the known variability of the originator together with chance findings in the pivotal study.

Safety based on ADCC

Another additional analysis provided safety data from the adjuvant phase separate for trastuzumab with and without low ADCC batches by NK92 ADCC assay and PBMC assay, respectively. Although small numerical differences were noted according to the data sets analysed, such differences were not considered to be clinically significant.

2.6.2. Conclusions on the clinical safety

Although small numerical differences were noted between Kanjinti and Herceptin according to the data sets analysed, such differences were not considered to be clinically significant. Overall the observed safety profiles of ABP 980 and trastuzumab are consistent with the historical safety profile of trastuzumab.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Cardiac dysfunction
	Administration-related reactions (ARRs)
	Hematotoxicity
	Oligohydramnios
	Pulmonary disorder
Important potential risks	Infections
	Medication errors (eg, reduced efficacy due to SC administration of IV formulation, incorrect dosing leading to adverse events)
Missing information	Treatment of male breast cancer patients
	Safety of 75 mg/m^2 versus 100 mg/m^2 docetaxel dose

Pharmacovigilance plan

No additional pharmacovigilance activities are requested. Routine pharmacovigilance activities are considered sufficient to monitor the safety concerns.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risk		
Cardiac dysfunction	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties Relevant text is provided in the following sections of the KANJINTI PIL: • Section 2, What you need to know before you are given KANJINTI • Section 4, Possible side effects	None
Administration-related reactions (ARR)	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.2, Posology and method of administration • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.7, Effects on ability to drive and use machines • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the KANJINTI PIL: • Section 2, What you need to know before you are given KANJINTI • Section 4, Possible side effects	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risk (continued)		
Hematotoxicity	Relevant text is provided in the following sections of the KANJINTI SmPC:	None

	• Section 4.8, Undesirable effects Relevant text is provided in the following sections of the KANJINTI PIL: • Section 4, Possible side effects	

Oligohydramnios	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the KANJINTI PIL: • Section 2, What you need to know before you are given KANJINTI • Section 4, Possible side effects	None
Pulmonary disorder	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the KANJINTI PIL: • Section 2, What you need to know before you are given KANJINTI • Section 4, Possible side effects	None
Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Potential Risk		
Infections	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the KANJINTI PIL: • Section 4, Possible side effects	None
Medication errors (eg, reduced efficacy due to SC administration of IV formulation; increased adverse events due to	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.2, Posology and method of administration	None

incorrect dose, method, or route of administration)	• Section 6.6, Special precautions for disposal and other handling Relevant text is provided in the following sections of the KANJINTI PIL: • Section 3, How KANJINTI is given	
Missing Information		
Treatment of male breast cancer patients	Relevant text is provided in the following sections of the KANJINTI SmPC: • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the KANJINTI PIL: None	None
Safety of 75 mg/m2 versus 100 mg/m2 docetaxel dose	None	None

No additional risk minimisation measures are requested. Routine risk minimisation measures are considered sufficient to mitigate the safety concerns.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. New Active Substance

The CHMP, based on the available data, considers that trastuzumab is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. *Trastuzumab* is contained

in the marketing authorisation of *Herceptin* which was authorised in the Union on 28 August 2000.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kanjinti (trastuzumab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Kanjinti (ABP 980) has been developed by Amgen Europe B.V. as a similar biological medicinal product to Herceptin for intravenous (IV) use which was approved in the European Union (EU) in August 2000 (EMEA/H/C/000278).

The therapeutic indications, dosage and route of administration proposed for ABP 980 are identical to those approved for Herceptin for IV use in HER2 positive metastatic breast cancer, early breast cancer and metastatic gastric cancer.

3.1.2. Main clinical studies

A comprehensive analytical similarity assessment was conducted, which included comparative evaluations of biological activities, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, thermal stability and degradation studies, general properties, and process-related impurities. Data were evaluated against pre-defined similarity assessment criteria. A multi-tiered approach was used to define similarity. The biological activities were evaluated by a comprehensive set of functional assays and binding studies addressing both Fab and Fc-functions of the molecule.

The efficacy and activity of KANJINTI as compared to trastuzumab has been evaluated in three preclinical xenograft tumour models overexpressing HER2. KANJINTI and trastuzumab (EU) were effective in inhibiting tumour growth in the tested setup, consistent with the known trastuzumab MOA.

The clinical evidence supporting the similarity of ABP 980 to the reference product, trastuzumab, includes a 3 arm, single dose PK similarity study in healthy male subjects comparing ABP 980 to trastuzumab (US) and trastuzumab (EU) (Study 20130119); and a randomised, double blind, active controlled clinical similarity study comparing efficacy, safety, PK, and immunogenicity of ABP 980 to trastuzumab (EU) in female subjects with EBC (Study 20120283).

3.2. Favourable effects

Regarding the primary structure the results demonstrate that ABP 980 has a similar intact molecular mass compared to trastuzumab (EU), similar levels of the reduced and deglycosylated LC and HC masses, the same amino acid sequence, similar disulphide structure and similar levels of free sulfhydryl. No significant differences were observed for assays addressing inhibition of HER2 signalling such as Proliferation Inhibition Bioassays in BT-474 and NCI-N87 cells, HER2 Binding by ELISA, Inhibition of AKT Phosphorylation. No meaningful differences are observed in FcRn and FcγR binding. The ADCC activity of all ABP980 lots was within the quality range calculated from ADCC activity of trastuzumab (EU).

The overall data on PD/PK and toxicology indicate that ABP 980 can be considered similar to the reference product Herceptin. The results of the nonclinical program demonstrate similarity between ABP 980 and trastuzumab with respect to inhibition of tumour growth in BT-474 and NCI-N87 xenograft models. The TK of ABP 980 was assessed in a GLP-compliant, 1-month multiple-dose toxicology study in cynomolgus monkey. Based on t1/2, AUC0-inf, AUC0-96h and AUC0-168h values, trastuzumab exposure was similar after injection of Herceptin or FTMB (ratios ranged between 0.94 and 1.15 on day 1 and between 1.08 and 1.15 in week 4). No unscheduled mortalities occurred and no signs of systemic toxicity were observed. Local reactions were observed in both trastuzumab-treated groups, but with a higher incidence and duration in animals treated with FTMB. Body weight was not affected in any group. There were no treatment-related findings in electrocardiography, blood pressure, ophthalmology, hematology and urinalysis. At blood biochemistry similar slightly higher mean urea and triglyceride levels were observed in groups treated with Herceptin and FTMB compared to placebo. There were no significant differences in the organ weights, macroscopic or microscopic changes between the Herceptin and the FTMB groups. There were no organ weight changes related to the administration of Herceptin or FTMB. There was a trend towards increased lymphoid stimulation in the popliteal lymph nodes draining the injection sites in the Herceptin and FTMB groups. There were no significant effects at the injection sites after injections of Herceptin or FTMB. Overall the toxicology data indicate that ABP980 and Herceptin can be considered comparable.

Based on the efficacy results of the phase III study Kanjinti was concluded to be equivalent to Herceptin. Results for other efficacy endpoints (EFS and OS) are still immature but do not suggest significant differences at the one year time point. The observed difference in pCR was considered at least in part confounded by a small shift in ADCC activity in a number of the Herceptin batches used in the pivotal trial. Overall it is doubtful that a small shift as the one observed would have any significant impact in terms of clinical outcomes although numerically it is thought to have contributed to a more extreme location of the point estimate and upper bound of the confidence interval, shifting the latter beyond the pre-specified equivalence margin. Based on additional analysis and considering the evidence of similarity provided in terms of quality, non-clinical, PK, clinical efficacy and safety, biosimilarity has been sufficiently shown for Kanjinti compared to the reference product Herceptin.

3.3. Uncertainties and limitations about favourable effects

The exact magnitude of the effect of the observed ADCC shift for Herceptin on bpCR and clinical important endpoints is not known but the effect is likely to be small and not of clinical relevance. In view of the totality of the data, this remaining uncertainty does not question the biosimilarity between Kanjinti and Herceptin.

3.4. Unfavourable effects

Clinical

Study 20130119

The safety findings were comparable between the ABP980 group and the trastuzumab (EU) group.

Study 20120283

In the neoadjuvant phase the overall number of adverse events was comparable between the ABP980 and the trastuzumab groups (62.1% vs. 60.9%, respectively)

Safety results from the adjuvant phase reveal small differences in the ABP980 only arm, the rate of treatment-emergent adverse events (61.6% [N=215] vs 56.1% [N=96] vs 63.2% [N=108], respectively) and serious adverse events (5.2% [N=18] vs 3.5% [N=6] vs 3.5% [N=6] respectively), IP-related adverse events (16.9 [N=59] vs 14.0% [N=24] vs 15.2% [N=26], in the ABP980 only group, the trastuzumab only group and the trastuzumab/ABP980 group, respectively).

However, overall, the safety profile of ABP 980 and trastuzumab is consistent with the historical safety profile of trastuzumab and data reported in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties regarding the comparability of the clinical safety of Kanjinti with Herceptin.

3.6. Benefit-risk assessment and discussion

From the quality point of view beside the variability of the originator in the ADCC activity and the correlated other quality attributes a-fucose and FcγRIIIa binding, no differences in further quality attributes were identified and hence Kanjinti is considered similar to the originator product. The quality data demonstrate that the acceptance criteria were met in a narrow range indicating a robust and tightly controlled manufacturing process. A robust and well-controlled manufacturing process for drug substance as well as for drug product is in place, which is expected to consistently deliver drug substance and drug product of high quality. The provided drug substance and drug product batch analyses data support this conclusion. The proposed control strategy is considered appropriate and ensures that material with consistent quality will be released to the market.

From a clinical perspective, the observed results demonstrate strong evidence of similarity on PK level, which is generally considered a sensitive clinical model to evaluate biosimilarity. Results close to unity were observed for exposure in a single dose healthy volunteer PK study and confirmed in EBC patients in the applicant's efficacy trial.

It is considered that the variability in ADCC activity may contribute to the observed differences in terms of clinical efficacy. Additional factors that might have contributed to the observed efficacy results cannot be

completely ruled out. Taking into account the sensitivity of the primary endpoint and the small difference in the efficacy results between ABP 980 and Herceptin, this deviation is not considered clinically relevant and is unlikely to have any impact on clinically relevant time-dependent endpoints.

Overall the observed safety profiles of ABP 980 and trastuzumab are consistent with the historical safety profile of trastuzumab.

Considering the totality of evidence where similarity is supported by quality, non-clinical, PK as well as safety and immunogenicity data, similarity in terms of efficacy can be concluded.

Regarding extrapolation of all indications approved for the reference product Herceptin, scientific evidence is indicating that the mechanism of action of trastuzumab is similar in different target conditions like both early and metastatic breast cancer (HER2-positive) as well as HER2-positive gastric cancer. Hence, extrapolation to the non-studied oncology indications is considered acceptable.

3.7. Conclusions

Kanjinti is considered biosimilar to Herceptin and therefore the overall B/R is positive.

Divergent position(s) is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority that the benefit-risk balance of Kanjinti is favourable in the following indication:

Breast cancer

Metastatic breast cancer

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 two 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.

Early breast cancer

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) (see section 5.1).

- 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 tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Kanjinti should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

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 tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

New Active Substance Status

The CHMP, based on the available data, considers that trastuzumab is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Trastuzumab is contained in the marketing authorisation of Herceptin which was authorised in the European Union on 28 August 2000.

Appendix

Divergent positions to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 22 March 2018

DIVERGENT POSITION DATED 22 March 2018

KANJINTI EMEA/H/C/004361/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of KANJINTI indicated for:

Metastatic breast cancer

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 two 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.

Early breast cancer

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) (see section 5.1).

- 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 tumours > 2 cm in diameter (see sections 4.4 and 5.1).

KANJINTI should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

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 tumours have HER2 overexpression as defined by IHC 2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

The reason for divergent opinion was the following:

In respect of clinical efficacy, study 20120283 failed to demonstrate equivalence in pCR rates according to the pre-specified equivalence margins. Explorations of the relationship between ADCC activity of clinical trial batches, which have been hypothesised to impact efficacy, and pCR rates are inconclusive. Post hoc analyses that, variously, exclude patients and alter the covariates included in the primary analysis model risk introduction of important bias and are not accepted. Consequently, biosimilarity has not been demonstrated between ABP980 and the reference product Herceptin.

Kristina Dunder _____

Robert James Hemmings _____

Alar Irs _____