14 September 2023
EMA/514898/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Herwenda

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/005769/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

%AUCextrap	AUC extrapolated from time to infinity as a percentage of total AUC
AC	Anthracycline
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
AR	Acceptable range
AS	Active substance
AUC	Area under the serum concentration curve
AUC(0-inf)	AUC from time zero to infinity
AUC(0-t)	AUC from time zero to the last quantifiable concentration
AUCall	AUC from time zero to the time of the last measurement regardless of whether it is quantifiable
BCS	Breast conserving surgery
BSA	Body surface area
C	Cycle
C1q	Complement component 1q
CAS	Chemical abstracts services
CDC	Complement-dependent cytotoxicity
CDR	Complementarity-determining regions
CFG	Centrifuge
CFR	Code of Federal Regulations
cGMP	Current good manufacturing practices
CHF	Congestive heart failure
CHO	Chinese hamster ovary
CI	Confidence interval
CIP	Clean-in-place
CL	Body clearance
CM	Cynomolgus monkey
Cmax	Maximum serum concentration
CMC	Chemistry, manufacturing, and controls
COVID-19	Coronavirus disease 2019
CR	Complete response
CRO	Clinical Research Organization
CS	Clinically significant
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
D	Day
DB	Double-blind study treatment
DCIS	Ductal carcinoma in situ
DF	Diafiltration
DFS	Disease-free survival
DNA	Deoxynucleic acid
DP	Drug product
DS	Drug substance
DSP	Downstream process
DTL	Drug tolerance level
EBC	Early breast cancer
EC	Extinction coefficient
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECLA	Electrochemiluminescence assay

ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
ELISA	Enzyme linked immunosorbent assay
EOI	End of infusion
EoS	End of study
EoT	End of treatment
ER	Estrogen receptor
FAS	Full Analysis Set
FAS-neo	Full Analysis Set for the neoadjuvant part
FD&C	Food, Drug and Cosmetic
FISH	Fluorescence in situ hybridization
FLR	Fluorescence
FP	Finished product
FT	Flow-through
GGT	Gamma-glutamyl transferase
GMR	Geometric mean ratio
HER2	Human epidermal growth factor receptor 2
ICF	Informed consent form
ID	Identification
iDBL	Interim database lock
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational New Drug Application
IPC	In-process control
IQR	Interquartile range
IRB	Institutional Review Board
IRS	Interim reference standard
IRT	Interactive Response Technology
IV	Intravenous
ka	Association rate constant, kon
kd	Disassociation rate constant, koff
KD	Equilibrium disassociation constant, a ratio of koff/kon
KPP	Key process parameter
LAL	Limulus amebocyte lysate
LIVCA	Limit of in vitro cell age
LRV	Log reduction value
LVED	Left ventricular end diastolic
LVEF	Left ventricular ejection fraction
LVES	Left ventricular end systolic
mAb	Monoclonal antibody
Max	Maximum
MBC	Metastatic breast cancer
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MGC	Metastatic gastric cancer
Min	Minimum (in table) OR Minute (in table)
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition (scan)
MW	Molecular weight
NAb	Neutralising antibodies
NCCN	National Comprehensive Cancer Network
NCS	Not clinically significant
NF	Nanofiltration
NGHC	Non-glycosylated heavy chain
Nmiss	Number missing
NYHA	New York Heart Association
OR	Overall response
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PDE	Permitted daily exposure

PFS	Progression-free survival
PHS	Public Health Service
PI	Prescribing Information
PKS-neo	Pharmacokinetic Set for the neoadjuvant part
PopPK	Population pharmacokinetics
PP	Process parameter
PPQ	Process performance qualification
PPS	Per-Protocol Set
PPS-neo	Per-Protocol Set for the neoadjuvant part
PR	Partial response
PREA	Paediatric Research Equity Act
PrR	Progesterone receptor
PT	Preferred Term
PV	Process validation
Q	Quartile or Intercompartmental clearance
QTcB	Corrected QT interval using Bazett's formula
QToF	Quadrupole time-of-flight
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Risk ratio
RS	Reference standard
SA	Scientific advice
SAE	Serious adverse event
SAF	Safety Set
SAF-neo	Safety Set for the neoadjuvant part
SAP	Statistical Analysis Plan
SAWP	Scientific advice working party
SD	Standard deviation
SF	Shake flask
SMQ	Standardized MedDRA queries
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
Tmax	Time to reach Cmax
TNFα	Tumour necrosis factor alpha
TNM	Tumor, nodes, metastases
TOC	Total organic carbon
UBH	Unprocessed bulk harvest
USP	Upstream process
UV	Ultraviolet
Vc	Volume of central compartment
VCD	Viable cell density
Vp	Volume of peripheral compartment
Vz	Apparent volume of distribution at terminal phase
WBC	White blood cell count
WCB	Working cell bank
λz	Elimination rate constant at terminal phase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 21 December 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Herwenda, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The applicant applied for the following therapeutic indication:

Breast cancer:

Metastatic breast cancer

Herwenda 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

Herwenda 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 Herwenda therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herwenda 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:

Herwenda 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 gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herwenda 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 IHC3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

1.2. Legal basis, dossier content

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 Union provisions in force for not less than 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:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Medicinal product authorised in the Union/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:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- 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:
  - Union
- (Union) Marketing authorisation number(s): EU/1/00/145/001

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication that is subject to the present application:

Date	Reference	SAWP co-ordinators
23 July 2015	EMEA/H/SA/3147/1/2015/SME/III	Dr David Brown, Prof. Dieter Deforce
18 May 2017	EMEA/H/SA/3147/1/FU/1/2017/SME/III	Dr Olli Tenhunen, Prof Andrea Laslop
6 July 2017	EMEA/H/SA/3147/1/FU/1/2017/SME/III	Dr Olli Tenhunen, Prof Andrea Laslop
14 November 2019	EMEA/H/SA/3147/1/FU/2/2019/SME/III	Prof. Dieter Deforce, Dr Jeanette McCallion
25 June 2020	EMEA/H/SA/3147/1/FU/3/2020/SME/II	Prof. Flora Musuamba Tshinanu, Dr Sheila Killalea
15 October 2020	EMEA/H/SA/3147/1/FU/4/2020/SME/I	Dr Jens Reinhardt, Dr Sheila Killalea

The applicant received Scientific Advice on the development of trastuzumab biosimilar (EG12014) for the treatment in the same indications as the reference product Herceptin from the CHMP on 23 July 2015 (EMEA/H/SA/3147/1/2015/SME/III). The Scientific Advice pertained to the following Quality, Non-Clinical, and Clinical aspects:

- Recombinant cell clone selection strategy; strategy for characterisation, testing, and qualification of the master cell bank and the working cell bank.
- Scale-up strategy of the drug substance manufacturing process; upstream and downstream process control strategy for the drug substance; strategy to demonstrate viral clearance of the purification process, test programme for routine release testing of drug substance; programme for stability testing of the drug substance.
- Validation programme of analytical methods.
- Routine release testing of the drug product; drug product stability testing and in-use stability testing.
- Physico-chemical, biochemical, and biological testing strategy to demonstrate biosimilarity.

- Statistical pooling of quality data of the EU and US reference medicinal product.
- In vitro pharmacodynamics comparability testing program; proposal not to perform non-human primate toxicity studies; abbreviated non-clinical safety programme.
- Design of Phase I double-blind, randomized, parallel-group, single-dose, 3-arm, two-stage, comparative pharmacokinetic study of EG12014 and Herceptin sourced from the US and the EU administered to healthy male volunteers.
- Design of Phase III randomised, double-blind study to compare EG12014 plus paclitaxel with Herceptin sourced from the US plus paclitaxel as first-line treatment of HER2 positive metastatic breast cancer including primary endpoint, non-inferiority statistical approach, non-inferiority margin.
- Comparative immunogenicity assessment of EG12014 and Herceptin in Phase I pharmacokinetics study and Phase III efficacy and safety study.
- Extrapolation of results of the Phase III efficacy and safety study to all authorized indications of the reference medicinal product.

Summary of questions raised/ issues discussed in the Scientific Advice - 2017

The applicant received Scientific Advice on the development of trastuzumab biosimilar (EG12014) for the treatment in the same indications as the reference product Herceptin from the CHMP on 18 May 2017 (EMEA/H/SA/3147/1/FU/1/2017/SME/III). The Scientific Advice pertained to the following Quality and Clinical aspects:

- Recombinant cell cloning strategy.
- Strategy for viral testing of unprocessed bulk harvest to support Phase III clinical development and commercialization.
- Strategy on the host cell protein assay development and implementation of the routine release assay of drug substance.
- Extinction coefficient for protein concentration measurement.
- In vitro pharmacodynamics comparability testing program.
- Physico-chemical, biochemical, and biological testing strategy to demonstrate biosimilarity.
- Adequacy of Phase I clinical development programme to support a Phase III clinical trial, provide pivotal data for biosimilarity, and support extrapolation to all indications of the reference medicinal product.
- Design of a Phase III randomized, multicentre, double-blind study to compare efficacy and safety of EG12014 with Herceptin as neoadjuvant treatment in combination with anthracycline/paclitaxel-based systemic therapy in patients with HER2 positive early breast cancer.

Summary of questions raised/ issues discussed in the Scientific Advice - 2019

The applicant received Scientific Advice on the development of trastuzumab biosimilar (EG12014) for the treatment in the same indications as the reference product Herceptin from the CHMP on 14 November 2019 (EMEA/H/SA/3147/1/FU/2/2019/SME/III). The Scientific Advice pertained to the following Quality and Clinical aspects:

- Adequacy of risk assessments and control strategies to support drug substance manufacturing site change and process scaling up; analytical comparability and similarity assessments to be performed to confirm the comparability between the drug substance batches before and after the site change and scale-up for filing the new site as the manufacturing site in the marketing authorization application.
- Adequacy of Phase I pharmacokinetics and safety results to support biosimilarity between EG12014 and Herceptin.
- Use of PopPK analysis to obtain supportive data on pharmacokinetic similarity of EG12014 and Herceptin in HER2-positive early breast cancer patients.
- Phase III comparative efficacy and safety study equivalence margin.
- Adequacy of assays to detect the presence of anti-trastuzumab antibodies and neutralizing anti-trastuzumab antibodies in serum samples in the Phase III efficacy and safety study.

Summary of questions raised/ issues discussed in the Scientific Advice – 2020a

The applicant received Scientific Advice on the development of trastuzumab biosimilar (EG12014) for the treatment in the same indications as the reference product Herceptin from the CHMP on 25 June 2020 (EMEA/H/SA/3147/1/FU/3/2020/SME/II). The Scientific Advice pertained to the following Clinical aspects:

- Adequacy of the revised PopPK modelling strategy to obtain supportive data on the pharmacokinetic similarity of EG12014 and Herceptin in HER2-positive early breast cancer patients.

Summary of questions raised/ issues discussed in the Scientific Advice – 2020b

The applicant received Scientific Advice on the development of trastuzumab biosimilar (EG12014) for the treatment in the same indications as the reference product Herceptin from the CHMP on 15 October 2020 (EMEA/H/SA/3147/1/FU/4/2020/SME/I). The Scientific Advice pertained to the following Quality aspects:

- The strategy and plan for the evaluation of comparability between materials manufactured at old and new site.
- Revised specifications and methods for release testing of drug substance and drug product.
- The possibility of inclusion on the data obtained from all the EU-approved Herceptin lots when establishing the quality ranges for similarity assessment despite the atypical quality profile of the originator during a specific period of time as indicated by expiry dates.
- The statistical approach for similarity assessment.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Eva Skovlund Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	21 December 2021

The procedure started on	20 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	08 April 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	25 April 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 April 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 May 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 November 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 December 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 August 2023
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 Herwenda on	14 September 2023

2. Scientific discussion

2.1. Problem statement

Not applicable

2.2. About the product

Trastuzumab is a humanized recombinant IgG1 monoclonal antibody specifically directed against the HER2 receptor. 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.

Trastuzumab as Herceptin is currently authorised for the treatment of breast cancer and gastric cancer. Herceptin is available as a 150 mg Powder for concentrate for solution for infusion for intravenous (IV) use and as a 600 mg Solution for injection (SC) for subcutaneous use.

Herwenda (trastuzumab) also referred EG12014 has been developed as a biosimilar to the reference product Herceptin (trastuzumab) authorised in the European Union (EU) via the Centralised Procedure in 2000, claiming the same therapeutic indications than those of the reference product for the treatment of HER2-positive early and metastatic breast cancer (EBC and MBC), and metastatic gastric cancer (MGC).

Efficacy and safety study in early breast cancer patients are provided, and the other indications are sought to be extrapolated.

2.3. Type of application and aspects on development

This application is submitted under Article 10(4) of Directive 2001/83/EC relating to applications for biosimilar medicinal products. The reference product is Herceptin (150 mg powder for concentrate for solution for infusion: Roche Registration Limited). Herceptin was authorised in the EU on 28 August 2000.

CHMP scientific advice were given on quality, nonclinical and clinical development.

The development program of EG12014 included exercises to demonstrate similarity of EG12014 to EU Herceptin based on data derived from analytical, animal, and clinical studies (reported below). The clinical programme was initiated with the aim to show biosimilarity between both products in the setting of early breast cancer, and extrapolating similarity to the other indications in case biosimilarity was confirmed in EBC in regard to quality, non-clinical, PK, pharmacodynamic and clinical aspects.

To establish a PK bridge to EU Herceptin efficacy and safety data and justify the relevance of data generated using EU Herceptin as the comparator in the clinical phase 3 study **EGC002**, a study (**EGC001**) of biosimilarity in PK between EG12014, US Herceptin and EU Herceptin after a single 90 minutes IV infusion of 6 mg/kg trastuzumab was conducted. Study **EGC001** was a double blind, randomised, parallel-group, single-dose, three-arm, two-stage study in healthy male subjects. This study was designed in support of a global clinical development concept in consideration of regulatory guidelines, in particular "*Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues*" (*EMA/CHMP/BMWP/403543/2010, 2012*), "*Guideline on the Investigation of Bioequivalence*" (*CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 2010*). The methodological approach was in accordance with the EMA SA (*EMA/CHMP/SAWP/466179/2015*).

2.4. Quality aspects

2.4.1. Introduction

EG12014 is developed as a trastuzumab similar biological medicinal product (biosimilar) to the Reference Medicinal Product (RMP) Herceptin.

The finished product is presented as sterile, single-use, white to pale yellow, preservative-free, lyophilised powder for intravenous administration. The finished product (FP) is to be reconstituted with 7.2 mL of sterile water for injections prior to administration. Each vial of FP contains 150 mg EG12014

(trastuzumab). The composition is identical to that of the RMP and composed of L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and trehalose trihydrate. The lyophilised powder containing 150 mg of trastuzumab is presented in 20 mL clear glass type I vial with a fluoropolymer-coated butyl rubber stopper and aluminium seal with flip-off cap.

2.4.2. Active substance

2.4.2.1. General Information

The active substance trastuzumab is a humanised monoclonal antibody (MAb) that binds to Human Epidermal growth factor Receptor 2 protein (HER2) that is overexpressed in breast cancer cells. The mechanism of action of trastuzumab is known to be its inhibition of proliferation of human tumour cells that overexpress HER2. The active substance is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. EG12014 contains an identical amino acid sequence to the originator trastuzumab except that no Lys exists in the C-termini of heavy chains. The schematic structure of trastuzumab is presented and described in the submission. EG12014 contains four pairs of inter-chain disulphide bonds (two between heavy and light, and two between two heavy chains) and 12 pairs of intra-chain disulfide bonds, which is identical to the originator trastuzumab. EG12014 is heterogeneously glycosylated, with one glycosylation site at Asn-300 of the heavy chain carrying complex biantennary oligosaccharides. The average molecular mass with glycosylation is approximately 148 kDa.

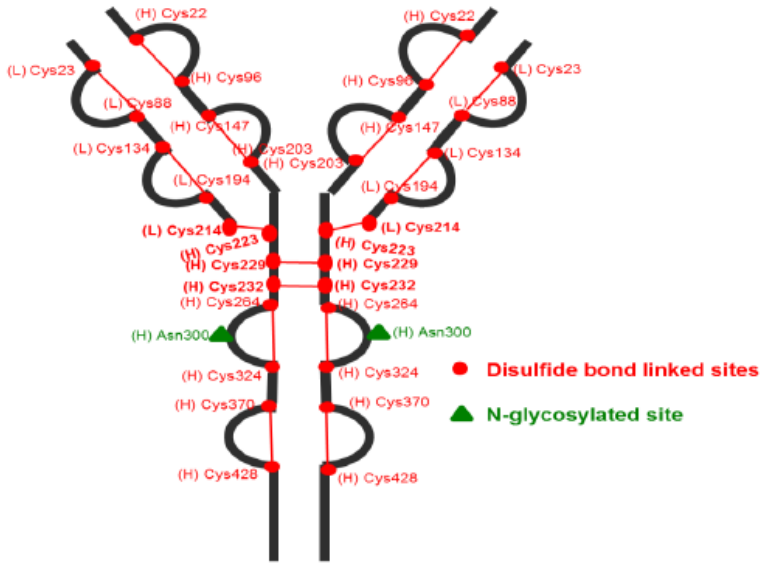


Figure 1. Illustration of disulphide bond linkages and N-glycosylation sites of EG12014

2.4.2.2. Manufacture, characterisation and process controls

Manufacture

EG12014 active substance (AS) is manufactured at the commercial manufacturing site. The manufacturing and analytical testing sites associated with the commercial manufacture of EG12014 AS are provided. A valid proof of GMP compliance has been provided for the sites responsible for the manufacture and storage of the Master Cell Bank (MCB) and Working Cell Bank (WCB), and for the active substance manufacturing and QC testing sites located in Taiwan. During the assessment, a Major

Objection relating to demonstration of GMP compliance for active substance manufacturing sites was resolved.

The manufacturing process for EG12014 AS uses a recombinant CHO cell line. The manufacturing process is a typical antibody manufacturing process, with preceding expansion steps followed by cell clarification and a series of purification steps. A detailed description of the manufacturing process is presented in the dossier. Several schematic overviews and flowcharts are included. The selected process parameters, their classification and acceptable ranges are provided in the detailed description of the manufacturing process. Reprocessing is proposed in nanofiltration and final AS bulk filtration. Reprocessing will only be performed in case of a failed filter integrity test. After manufacturing, EG12014 AS is filled and then frozen and stored at -30°C/-40°C.

Control of materials

The DNA coding sequences of trastuzumab used to construct the expression vector were initially synthesized based on the known amino acid sequence excluding the last C-terminal lysine in heavy chain.

The source, history and generation of the cell banking system is adequately described, and the cell banks have been properly qualified. The testing of cell banks (MCB and WCB) was performed with regards to cell and product identity as well as microbial and viral contaminations.

Characterisation of end-of-production-cells has been addressed and genetic stability has been demonstrated for WCB. The results provided for cell growth characteristics, production stability, target gene sequence, and gene copy number are acceptable. A release testing programme for future WCBs is presented.

Two master cell banks were prepared, characterised and used during EG12014 development. One MCB was used for manufacturing of the Phase 1 clinical batches. Another MCB was used to prepare the current WCB which was used for manufacturing of the Phase 3 clinical batches and future commercialization. To ensure similar product quality between the AS generated from the sub-clone and the parental clone, a series of comparative studies at different production scales were performed. The results are adequately presented.

The generation of the cell substrate is in accordance with ICH Q5D. The cell banking system of EG12014, as well as the characterization of established cell banks including identity, purity, and the cell substrate stability is in accordance with ICH Q5A and Q5D.

Details on raw materials as well as the compendial status of the raw materials used are included. Raw materials of animal origin which were used during cell line development and cell bank preparation are indicated. Method description of cell bank testing is included. A protocol for the preparation of future WCBs is described, and the detailed process parameters (PPs) and in process controls (IPC) for the preparation process are presented, with acceptance criteria.

Control of critical steps and intermediates

The applicant provided an overview of process parameters, as well as of all in-process controls. Overall, the control strategy is deemed sufficient. There are no AS intermediates isolated in the manufacturing process of EG12014.

Process validation

Process validation (PV) of the EG12014 AS manufacturing process was performed on several consecutive batches of AS manufactured according to the proposed commercial AS process

Results from process parameters and in-process monitoring were provided. All PPQ results presented for process parameters as well as in-process quality controls met the predefined acceptance criteria and are not significantly different between the PV batches.

The AS manufacturing process showed sufficient capacity for removal of process-related impurities,. The successful removal of product-related impurities was demonstrated for all validation batches.

Bioburden and endotoxins were monitored throughout the production process and after each critical step. The PPQ data demonstrate sufficient clearance and consistent low levels for both parameters.

Validation of the procedures for transport of the AS from the AS manufacturing site to the FP manufacturing site is presented.

Reprocessing is planned for nanofiltration and bulk filtration. An acceptable reprocessing protocol is presented.

Based on the process validation results presented for the AS batches, it can be concluded that the AS manufacturing process is capable of a consistent and reproducible production of AS that meets the relevant specifications.

Process development

The EG12014 AS manufacturing process development history is divided into four periods The key changes in materials, process parameters, equipment, utility and facility, and the purposes of changes in each period are summarized in the comparability report.

Based on the results provided, it is concluded that all quality attributes are analytically comparable for the batches.

Characterisation

Detailed characterisation has been performed on several batches of EG12014.

2.4.2.3. Specification

The applicant has presented a broad control panel of analytical procedures for release and stability testing of AS.

In general, the acceptance criteria are considered acceptable.

Analytical procedures

The analytical test methods for release testing of EG12014 AS and their validation/verification parameters are adequately presented. Further details on procedure validations are provided in the dossier as individual documents.

Batch analysis

An overview of all batches and full release testing data were provided, including the AS process validation batches manufactured according to the final commercial process. All results were compliant with the specifications.

Reference standards

The applicant has provided an overview of the establishment of the in-house reference standard system as well as acceptance criteria for the release of future working reference standards.

At the commercialisation stage, a two-tier reference standard system is applied. A qualified primary reference standard is used for qualifying future working reference standard, which is used in all assays where usage of a reference standard is required. The primary reference standard was manufactured via the commercial process and qualified by comprehensive characterisation.

The working reference standard (WRS) has been manufactured via the commercial process as well and has been qualified using primary reference standard. A protocol for qualification and the release specifications for future WRS is presented.

Container closure

The applicant has provided detailed information on the AS container which complies with Ph. Eur. quality standards. A release specification is defined. Identification test and endotoxin test are performed, and technical drawings are presented. Extractables and leachables studies have been performed, which did not indicate any safety risk.

2.4.2.4. Stability

Stability studies that included physicochemical and biological tests at different conditions (including temperature stress and repeated freezing and thawing stress) were performed according to stability protocols over the whole shelf-life of the AS.

When stored frozen, all parameters remained within specifications and no trends were observed.

The stability study is ongoing and the intention is to extend the shelf-life once the stability study results are available. The stability indicating parameters have been assigned based on results from accelerated and/or stress condition testing.

The protocol for shelf-life extension is provided. The dossier states that any shelf-life extensions will only be implemented following regulatory approval via the appropriate variation application.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

EG12014 FP is provided as a lyophilised powder in a dosage strength of 150 mg. The FP is to be reconstituted with 7.2 mL of sterile water for injection prior to administration. The same buffer system as the reference product Herceptin is used; L-histidine (buffering agent), L-histidine hydrochloride monohydrate (buffering agent) Polysorbate 20 (stabiliser and surfactant), trehalose dihydrate (bulking agent). The components of the finished product are commonly used in parenteral products and are described in sufficient detail with regards to function and standards. The product is delivered with an appropriate overfill to ensure a sufficient deliverable dose provided from each vial following reconstitution. The target fill volume was established to ensure that the deliverable amount EG12014 is comparable to that of Herceptin. The product is supplied without any overages.

A quality target product profile (QTPP) is defined and includes the targets for physico-chemical properties. Quality attributes were evaluated regarding their impact on biological activity/potency, pharmacokinetics/pharmacodynamics (PK/PD), immunogenicity and safety. The quality attributes with moderate to very high criticality were defined as Critical Quality Attributes (CQAs). Overall, the formulation development studies are adequately described. Data are presented to support the conclusion that the chosen formulation is sufficiently robust and are in accordance with the results of the stability studies.

Identification of the process parameters per unit operation and acceptable ranges for operation have been investigated through experiments in the laboratory and at small and production scale. Justification of process parameters with regards to criticality and impact on the quality of the product has been described in sufficient detail and the ranges are considered adequately justified.

The results on elemental impurities of EG12014 FP PPQ batches are provided, and also a summary of elemental impurity risk assessment on lyophilised FP, in accordance with pharmacopeia guidelines USP <232>, Ph. Eur. 5.20 and ICH Q3D.

The EG12014 FP manufacturing process development history is described. This includes manufacturing of clinical phase I supplies , clinical manufacture of Phase III supplies using commercial equipment and PPQ lots using the proposed commercial process. The differences during manufacturing development are mainly due to increase in batch scale and different manufacturing sites. The changes are summarised with regard to impact and risk and are appropriately justified. The applicant has presented a side-by-side comparison between the commercial and the clinical material. The FP manufacturing processes can be considered comparable.

Material compatibility studies revealed that polysorbate 20 (PS20) showed an increased adsorption to the sterile filters over time. Holding times and flush volumes are critical to recover PS20 content. A lyophilisation process robustness study has been performed. Together with the presented batch data, this supports the conclusion that the lyophilisation conditions are robust and do not impact the product quality.

The lyophilised powder containing 150 mg of trastuzumab is presented in 20 mL clear glass type I vial with a fluoropolymer-coated butyl rubber stopper and aluminium seal with flip-off cap.

Compatibility of the vial and stopper is demonstrated by the stability, extractable and leachable studies. The applicant committed to extend the ongoing leachables study in line with the stability protocol and should provide the remaining results of the leachables study post-approval.

The same quality of vials and stoppers was used during formulation development studies as well as in all clinical supplies and for the commercial product. Container closure integrity (CCI) through the claimed shelf-life is demonstrated. This approach is acceptable. Compatibility of the finished product has been shown for the container closure for lyophilised finished product, reconstituted finished product in vial, infusion diluent and materials for infusion. Based on the data presented, reconstituted EG12014 FP (in water for injection) is chemically and physically stable for 7 days when stored at 5 ± 3°C. Reconstituted FP further diluted in 0.9% sodium chloride at both low dose (80 mg dissolved in 250 ml) and high dose (1112 mg dissolved in 250 ml) was stable for 33 days, stored at 5 ± 3°C and for 48 hours stored at 30°C.

2.4.3.2. Manufacture of the product and process controls

Manufacture

The manufacturing sites involved in the manufacture and analytical testing of EG12014 FP are listed in the dossier. A valid proof of GMP compliance has been provided for the finished product manufacturing and QC testing sites. During the assessment a Major Objection relating to demonstration of GMP compliance for finished product manufacturing sites was resolved.

A standard manufacturing process is performed that comprises thawing of the active substance, preparation of excipient buffer solutions, compounding, sterile filtration, aseptic filling, lyophilization, stoppering and sealing.

Process controls and validation /verification

In process controls (IPCs) for each step of the manufacturing process are listed. Acceptable ranges for the process parameters (PP) have been defined, and criticality is specified. The PP ranges and criticality scores are based on existing process knowledge and existing data. IPCs are appropriately described, and acceptance ranges or limits are provided in addition to criticality score. The manufacturing process has been validated using consecutive commercial scale FP batches (PPQ). Results on process performance and batch release results of the PPQ batches confirms a consistent manufacturing process. Hold times are defined and validated through hold-time studies.

Filtration steps have been validated, and filter integrity testing is included as IPCs. Aseptic filling is validated by media fills. Consistency of the lyophilisation process has been adequately addressed.

Process performance and product quality are monitored as part of continuous process verification. A representative shipping qualification study has been performed and appropriate temperature conditions are ensured during shipment by qualified thermo-controlled shipping systems.

2.4.3.3. Product specification

Specifications

The analytical methods applied for release and shelf-life testing include: appearance, osmolality, pH, water content, reconstitution time, visible and sub-visible particles, uniformity of dosage unit, protein content, purity, activity, microbiological aspects and container integrity.

Analytical methods used for FP release testing have been described and validated or refers to Ph. Eur. In-house developed analytical methods are validated in line with ICH guideline Q2(R1). Method performance parameters are adequately addressed in the presented validation reports.

Batch analysis results of EG12014 FP have been presented. The data from all batches meet the acceptance criteria of the FP specifications, with reference to the specification valid at the time of release for each of the batches.

The relevant impurities are described for AS, and no impurities specific to the FP are known. A summary of nitrosamine risk evaluation is provided and considered satisfactory.

Reference standards

The applicant has provided an overview of the establishment of the reference standard – see active substance.

Specifications and drawings of all the container closure components are provided. The vial and rubber stopper complies with Ph. Eur. Stability studies support that the container closure system is suitable.

2.4.3.4. Stability of the product

The presented long-term (5°C ± 3°C) and accelerated data (25°C ± 2 °C / 60 ± 5% RH) for primary batches (commercial process) support a shelf-life of 36 months based on real time stability data as stated in SmPC.

Stability indicating parameters are defined. Data are within the defined specifications and showed no significant changes for 36 months at long-term. For the accelerated studies a decrease in purity is

observed with corresponding increase in impurities and product-related variants. A slight decrease in activity is observed for some batches but are within the method variability.

A temperature cycling study demonstrated the robustness of the product following repeated freeze thaw cycles.

In-use stability is supported by stability studies together with compatibility and robustness studies during pharmaceutical development. In-use stability studies demonstrate a chemical and physical stability for the reconstituted finished product for 7 days at 2°C – 8°C and for the diluted finished product up to 33 days at 2°C – 8°C and further 48 hours at temperatures not exceeding 30°C.

Photostability studies on both lyophilized and reconstituted product show that the finished product is sensitive to light and that the original carton provides adequate protection. The reconstituted product showed a more significant degradation than the lyophilized product. The testing of relative potency indicates that the light/UV exposure for the reconstituted FP can significantly impact the activity of EG12014. Photostability studies revealed that the relative potency to RS of all the testing samples was reduced, together with an increase in the level of aggregation and degradation and an increase in fragmentation .

A suitable post-approval stability protocol and commitment is presented. The dossier states that any shelf-life extensions will only be implemented following regulatory approval via the appropriate variation application.

2.4.3.5. Biosimilarity

Similarity between EG12014 and the reference product, EU-approved Herceptin, is addressed using a wide range of analytical exercises covering physiochemical and biological properties. A forced degradation study is also presented. The applicant has presented biosimilarity data also from US Herceptin. Overall, the US Herceptin quality profile is considered comparable to EU Herceptin and EG12014.

Critical quality attributes have been assigned to different categories and risk ranked according to their impact on safety, efficacy and immunogenicity.

The applicant has included data from batches of EG12014 and batches of EU approved Herceptin for biosimilarity analysis.

EG12014 has been designed without a C-terminal lysine, which makes the primary structure different form that of Herceptin. The modification has been justified and discussed with regards to possible differences in physiochemical and biological properties. Similarity between EG12014 and EU-Herceptin is shown for secondary and tertiary structure.

For the determination of intact mass, the MS spectra with different glycoforms between EG12014 and Herceptin have been compared.

Table 1. Summary of the biosimilarity exercise

Quality attribute	Tests/Methods	Analytical similarity summary
Primary structure	Peptide mapping	Similar to Herceptin except that EG12014 contains no Lys in the heavy chain C-terminus.
Identification of N- and C-terminal sequence	MS/MS	Similar
Protein concentration	UV280	Similar

Mass	Intact mass by LC/MS	Similar
Higher order structure	Melting temperature by differential scanning calorimetry	Similar
Secondary structure	Secondary structure elements by circular dichroism	Similar
Free thiol	Fluorometric Thiol Assay Kit	Slightly higher for EG12014 compared to Herceptin, difference justified
Disulfide bond linkage	LC/MS	Similar
Purity	SEC-HPLC	Slightly lower level of monomer and slightly higher level of aggregates in EG12014 compared to Herceptin. No effect is seen on target binding and effector functions.
	CE-SDS (non-reduced)	Similar
	CE-SDS (reduced)	Similar
Charge variants	cIEF	Similar
	Acidic variant by CEX-HPLC/	Similar
	Main variant by CEX- HPLC	Higher level of the main variant in EG12014 compared to Herceptin.
	Basic variant by CEX - HPLC	Lower level of basic variants in EG12014. Biological activities and potency assays are not affected by the lower level of basic variants in EG12014.
Modifications	Deamidation by LC/MS	Similar
	Oxidation by LC/MS	Higher level in EG 12014 compared to Herceptin, the overall oxidation level in EG12014 is low. The differences in oxidations does not affect biological activities and potency assays. The PK profile of EG12014 is similar to that of Herceptin.
Glycosylation	Glycosylation site by MS	Similar
	Galatosylated N-glycans by LC/MS	Slightly higher level in EG12014 compared to Herceptin. Similarity is shown for EG12014 and Herceptin in orthogonal assays.
	Galatosylated N-glycans by HILIC	
	Afucosylated N-glycans by LC/MS	Similar
	Afucosylated N-glycans by HILIC	Slightly lower level in EG12014 compared to Herceptin. Similarity is shown for EG12014 and Herceptin in orthogonal assays.
	High mannose N-glycans by LC/MS	Similar
	High mannose N-glycans by HILIC	Similar
	Sialysylated N-glycans by LC/MS	Similar
	Sialysylated Nglycans by HILIC	Similar

Biological activity/potency	HER2 ECD binding	Some EG12014 batches slightly exceed the limits of the quality range (QR) of Herceptin. These batches fall within the QR of Herceptin for the anti-proliferation potency assay.
	Fcγ receptor binding by SPR	Similar, minor differences justified
	C1q binding	Similar
	Inhibition of HER2 shedding	One batch is slightly exceeding the Herceptin QR upper limit. EG12014 are within the QR for the orthogonal assay.
	Anti-cell proliferation	Similar
	ADCC	Similar
	ADCP	One batch slightly exceeds the upper limit of the QR. Results from the orthogonal assay is within the QR.

The amount of free thiols in EG12014 compared to EU-Herceptin is slightly higher. The applicant claims that since low amounts of free-thiols have been routinely detected in IgG molecules including IgG from serum and recombinant mAbs, the minor difference between EU-Herceptin and EG12014 is considered non-critical. This can be accepted, since these small differences do not seem to impact structure/purity and biological activity/functionality, as shown by the available biosimilarity data.

Purity and impurities were addressed. The applicant claims that there is no clear correlation between purity, target binding and effector function of EG12014. The results show that the monomer level of EG12014 is outside the predefined quality range, with lower levels than that of the EU-approved Herceptin. The difference is due to increased levels of HMW, observed in EG12014. The applicant further justifies the observed difference in purity with EG12014 having similar efficacy and a similar safety/immunogenicity profile compared to EU-approved Herceptin. As a general comment, the EMA biosimilarity guideline states that clinical data cannot be used to justify substantial differences in quality attributes (CHMP/437/04 Rev 1). However, the applicant demonstrated with forced degradation data that there is no obvious change in binding and activity in case of increase in aggregates and concomitant decrease of monomer level upon high pH exposure.

Charged variants , deamidated and oxidation species , and glycosylation are determined by state of art methods. For the basic variants, some EG12014 lots are outside the lower limit of the quality range of EU Herceptin. It is acknowledged that the major variants of basic fractions in trastuzumab include aspartic acid converted to succinimide, and that the Asp102 in CDR3 of the trastuzumab heavy chain is susceptible to succinimide formation and isomerisation, leading to an increase of basic variants and potential loss of potency. The differences in charge variants do not seem to impact potency and biological activities, as shown by the available biosimilarity data.

Higher oxidation levels at Met in EG12014 compared to EU Herceptin is observed. The low overall oxidation level in EG12014 could support the low criticality score, also considering that there is no reported impact of oxidation on the complementarity-determining regions of trastuzumab. The stability of oxidation level during long-term storage, similarities in biological activity, and similar PK profile further indicate that the observed levels have no significant impact on clinical profile of EG12014 and does not preclude a biosimilarity claim.

For afucosylation, all batches fall within the predefined quality range while some EG12104 batches fall outside the quality range. The observed differences in the average level of afucosylation and the relevant batches displaying less afucosylation than the predefined QR are unlikely to have significant impact on

product quality. This is further justified by the similarities observed in biological activity , thus the observed differences do not preclude a biosimilarity claim.

In vitro comparative functional studies between EG12014 and EU Herceptin are addressed by functional assays for immunochemical properties , and biological activity .

In the statistical analysis of receptor binding, some EG12014 batches fall outside the quality range. These batches fall within the quality range in biological activity, and the data does not indicate a major deviation from the other batches in terms of magnitude. It can therefore be agreed that the difference in binding affinity does not preclude a determination of similarity for receptorbinding. Data presented for one of the batches show a binding affinity range well within the quality range during long-term storage which according to the applicant indicates that the values falling outside of the quality range is likely to be due to assay variability. Taken together, the observed differences in binding does not preclude a determination of similarity for EG12014.

Similarity was addressed for Fc binding affinity and similarity between EU Herceptin and EG12014 is supported by these analyses.

For C1q, although there is a weak trend for increased C1q binding in EG12014 batches, similarity with Herceptin can be agreed.

Comparison of potency was analysed using several analytical approaches. For the cell based assays, all EG12014 batches fall within the predefined QR, supporting similarity of EG12014 potency to Herceptin. For CDC activity, no activity was detected for EG12014 or the reference medicinal product, in line with the known mechanism of action for trastuzumab. For ADCP, one batch of EG12014 batches falls outside the upper limit of the QR. Taking into consideration the orthogonal assays falling within the QR of EU Herceptin, it can be agreed that the ADCP activity of EG12014 is not likely to impact clinical efficacy compared to the reference medicinal product and does not preclude a biosimilarity claim for EG12014.

Although batches from several attributes fail the biosimilarity acceptance criteria between EG12014 and the reference medicinal product, these do not preclude a conclusion of biosimilarity.

A forced degradation study has been included in the biosimilarity exercise. The samples were tested for formation of aggregation , fragmentation), changes of variants , and biological activities (.

The forced degradation study includes EG12014 FP batches as well as EU-approved Herceptin and US-licenced Herceptin batches. From the presented data, EG12014 seems to be somewhat more prone to aggregation upon low or high pH stress compared to EU-Herceptin.

The forced degradation study indicates that the EG12014 and EU Herceptin are sensitive for the same types of stress.

Based on the review of the submitted data, EG12014 is considered biosimilar to Herceptin and a benefit/risk balance comparable to the reference product can be concluded.

2.4.3.6. Adventitious agents

All raw materials used for manufacturing EG12014 AS and FP are of non-human/ non-animal origin except for goat anti-human IgG and HyClone medium. Goat anti-human IgG (Sigma, US origin) was extracted from goat blood and contains 1% bovine serum albumin (BSA) of US origin that serves as stabiliser. The antibody was used during cell pool selection prior to the second limiting dilution. Risk assessment was conducted by the supplier. Residual goat anti-human IgG and BSA is likely to be largely reduced in the subsequent steps of cell line preparation and poses a low risk in TS/BSR transmission.

HyClone medium contains cholesterol (country of origin New Zealand, source ovine wool) and cod liver oil (country of origin Norway, source: cod liver). Neither of these are considered as risk material as defined in Commission Decision 97/534/EC.

The risk of microbial and mycoplasma contamination is adequately addressed, and the cell banks (MCB, WCB and EPC) are demonstrated to be free from adventitious microbial contaminants.

Unprocessed bulk harvest (UBH) is tested routinely for mycoplasma and bacteria/fungi. The release specification includes tests for bacterial endotoxin and microbial sterility. UBH testing supports the absence of mycoplasma and bacteria/fungi during the manufacturing process. During manufacturing of FP, the compounded solution is sterilized by filters, followed by aseptic filling.

A virus clearance study was conducted to assess the virus removal capability of the manufacturing process.

The model viruses chosen for virus clearance studies are considered appropriate, and the LRV of removal or inactivation of each virus by the EG12014 purification process is considered acceptable.

The relevant testing methods for examining adventitious agents in cell banks and UBH have been briefly described in the dossier, and the original study reports for the adventitious agents safety evaluation studies are provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

EG12014 is developed as a trastuzumab similar biological medicinal product (biosimilar) to the Reference Medicinal Product Herceptin. A recommendation was raised for future development.

The manufacturing processes for AS and FP reflects a standard process used for the manufacture of monoclonal antibodies. Several sites are responsible for the manufacturing, cell bank manufacture and storage, packaging, release, in-process and stability testing. The batch release sites for EEA are Novartis Pharma GmbH, Nürnberg, Germany and Novartis Farmacéutica, S.A., Barcelona, Spain. During the assessment a Major Objection relating to demonstration of GMP compliance for manufacturing sites was resolved.

EG12014 has been thoroughly characterised using a comprehensive set of analytical methods. FP release and shelf-life specifications includes a broad panel of tests.

EG12014 FP is provided as a lyophilised powder in a dosage strength of 150 mg. The FP is to be reconstituted with 7.2 mL of sterile water for injection prior to administration. The same buffer system as the reference product Herceptin is used.

In-use stability studies demonstrate a chemical and physical stability for the reconstituted FP for 7 days at 2°C – 8°C and for the diluted FP up to 33 days at 2°C – 8°C and further 48 hours at temperatures not exceeding 30°C. The presented long-term (5°C ± 3°C) and accelerated data for primary batches (commercial process) supports a shelf-life of 36 months based on real time stability data.

Similarity between EG12014 and the reference product, EU-approved Herceptin, is addressed using a wide range of analytical exercises covering physiochemical and biological properties, as well as a forced degradation study. Most of the quality attributes proved to be highly similar. The main differences between EG12014 and Herceptin include level of aggregates, oxidation, free thiols and basic variants, however, these differences do not seem to have a significant impact on biological activities and potency assays. EG12014 can thus be considered as a biosimilar to EU-Herceptin.

The information provided in the adventitious agents sections is acceptable.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Herwenda is approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant should submit (through a post-approval variation application) the remaining results of the DP container closure system leachables study when these data become available.

2.5. Non-clinical aspects

2.5.1. Introduction

The EG12014 non-clinical programme consists of one pharmacodynamic xenograft mouse model study and a PK study in mice. The studies were done in comparison with Herceptin. The submitted non-clinical comparative in vivo studies included one primary PD study and one PK study that were conducted under non-GLP conditions.

2.5.2. Pharmacology

Trastuzumab is an immunoglobulin G1 (IgG1) kappa isotype antibody specific for human epidermal growth factor receptor-2 (HER2). Binding of trastuzumab to HER2 inhibits ligand independent HER2 signalling and inhibit the proliferation of human tumour cells that overexpress HER2. In addition, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro assays were conducted to address biocomparability between EG12014, Herceptin-EU and Herceptin-US. See 2.4. Quality aspects for critical evaluation of the similarity assessment.

An in vivo study was conducted in a xenograft mouse model, comparing the pharmacology of EG12014 to Herceptin-EU and Herceptin-US. Further, a single dose PK study was conducted in mice at three dose levels of EG12014 (1, 10, 100mg/kg) and one dose level of Herceptin (10mg/kg). An in vivo study was performed to compare the tumour growth inhibitory potential in a xenograft mouse model with BT-474 breast carcinoma cells (EG12014 and EU Herceptin). EG12014 and EU Herceptin showed a similar tumour growth inhibition rate relative to control animals.

Studies on secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions were not conducted.

2.5.2.1. Primary pharmacodynamic studies

In vitro studies

In vitro PD studies (**Table 1**) showed according to applicant similarity between EG12014, EU Herceptin and US Herceptin with regard to the biological activities associated with Fab- and Fc-mediated functions of trastuzumab (for more details, please refer to 2.4. Quality aspects).

Table 2: The in vitro studies of EG12014 demonstrating claimed similarity to EU Herceptin and US Herceptin

Functionality		Parameter measured	Clinical impact	Similarity
Fab-Fc mediated activity	ADCC: (PBMC, Reporter assay)	Relative ADCC potency (%)	Very High	Yes
	ADCP	Relative ADCP potency (%)	Moderate	Yes
	CDC	Relative CDC potency(%)	Very Low	Yes
Fab binding	HER2 ECD binding affinity (ELISA)	Relative HER2 ECD binding (%)	Very High	Yes
	Anti-proliferation: BT-474	Relative anti-proliferation (%)	Very High	Yes
	Inhibition of HER2 shedding	Inhibition (%)	Low	Yes
Fc binding	Fcγ RIIIa binding affinity (SPR)	Relative Fcγ RIIIa binding (%)	High	Yes
	FcRn binding affinity (SPR)	Relative FcRn binding (KD)	Moderate	Yes
	Fcγ RIa binding kinetics (SPR)	Relative Fcγ RIa binding (%)	Moderate	Yes
	Fcγ RIIabinding affinity (SPR)	Relative Fcγ RIIa binding (%)	Moderate	Yes
	Fcγ RIIb binding affinity (SPR)	Relative Fcγ RIIb binding (%)	Moderate	Yes
	Fcγ RIIIb binding affinity (SPR)	Relative Fcγ RIIIb binding (%)	Moderate	Yes
	C1q binding affinity (ELISA)	Relative C1q binding (%)	Very Low	Yes

In vivo study

Study R103XX317-1 V2

A non-GLP efficacy study was performed to compare anti-tumour effects between with EG12014 (lot B14007) and EU Herceptin (lot H4277) in a xenograft model using BT-474 breast carcinoma cells characterized by the overexpression of HER2 and oestrogen receptors.

BT-474 cells were subcutaneously implanted in the flank of severe combined immunodeficient (SCID) mice. Tumour-bearing mice (the average tumour volume reached 135 mm^3) received twice weekly intraperitoneal trastuzumab doses of 0.01 mg/kg, 0.1 mg/kg or 1 mg/kg or vehicle, for a 4- week period, and were assessed for changes in tumour growth that denoted anti-proliferative activity (Table 2:).

The percentage of tumour growth inhibition (TGI), based on tumour volume assessed twice weekly, was comparable between EG12014 1 mg/kg and EU Herceptin 1 mg/kg treated mice on Day 24 (56.0% and 51.1% for EG12014 and EU Herceptin, respectively; p=0.998) and on Day 28 (61.3% and 47.7% for EG12014 and EU Herceptin, respectively; p=0.984).

At a trastuzumab dose of 1 mg/kg, a comparable inhibitory effect on tumour growth was shown for EG12014 and EU Herceptin treated animals, which was significantly higher on Day 24 and Day 28 ($p<0.05$) compared to control animals.

At the lowest dose of 0.01 mg/kg there was no significant effect on tumour growth for EG12014 or EU Herceptin treated mice as compared to control mice up to Day 28. At a dose of 0.1 mg/kg, on Day 28 the tumour growth inhibition rate was 32.2% ($p=0.0320$) for EG12014, however the antitumor effect was not statistically significant at 0.1 mg/kg for EU Herceptin treated animals.

Table 3: Tumour growth inhibition rate of EG12014 or EU Herceptin treated animals.

Test treatment	Treatment dose	Tumor growth inhibition rate (%)**							
		Day 3	Day 7	Day 10	Day 14	Day 17	Day 21	Day 24	Day 28
EG12014	0.01 mg/kg	15.2	26.0	19.1	18.8	18.0	16.6	7.9	8.6
EU Herceptin		11.4	10.0	16.1	15.4	18.8	10.8	9.5	8.3
EG12014	0.1 mg/kg	6.3	13.9	17.7	19.2	27.0	28.2	31.7*	32.2*
EU Herceptin		5.8	-0.4	0.9	5.5	-1.2	0.8	7.2	5.0
EG12014	1 mg/kg	22.1	35.7*	35.1*	45.8*	47.9*	50.7*	56.0*	61.3*
EU Herceptin		18.0	22.1	36.7	36.9	43.7*	43.2	51.1*	47.7*

*p<0.05 (test treatment group vs. control group).

** % (1-T/C) where T and C represent the mean tumor volumes of the treatment group and the control group, respectively.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed.

2.5.2.3. Safety pharmacology programme

No stand-alone studies have been conducted with EG12014.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed with EG12014.

2.5.3. Pharmacokinetics

The non-clinical program of EG12014 included a single-dose pharmacokinetic (PK) study in mice, conducted to demonstrate similarity of EG12014 to the reference product EU Herceptin. The study was carried out at an early development stage of EG12014 (R&D lot B14007) in 2015.

Methods of analysis

An enzyme linked immunosorbent assay (ELISA) based method was used for the quantitative determination of trastuzumab (EG12014 or EU Herceptin) in mouse serum (qualification report SC-14/147-001). To assess accuracy and precision, both EG12014 and Herceptin qualification samples were analysed in 5 independent assay runs analysed by 3 analysts at 5 concentration levels covering the anticipated assay range. One assay failed because the standard curve failed.

The data for the calibration standards and quality control (QC) samples indicated that the method was performed reliably during the study sample analysis. The calibration curve ranged from 0.25 to 100.0 µg/mL and the linearity (mean R2) of the calibration curves was 0.995. The lower limit of quantification (LLOQ) and the upper limit of quantification (ULOQ) for trastuzumab in mouse serum samples was 1.00 µg/mL and 80.0 µg/mL, respectively. All runs passed the acceptance criteria for accuracy (% relative error [RE]) and precision (% coefficient of variation [CV]). All QC replicate responses were ± 20 %RE and ≤20 %CV of the nominal value. In mouse serum, EG12014 was stable through 5 freeze-thaw cycles. The stability at room temperature and at 2-8℃ was 24 hours.

Absorption

A pharmacokinetic (non-GLP) study in male CD1 mice after single IV administration with EG12014 (Study No. 146393)

Eight to nine weeks old male CD-1 mice were divided into four groups comprising 75 animals in each group and received a single IV bolus injection of EG12014 at doses of 1 mg/kg (Group 1), 10 mg/kg (Group 2), 100 mg/kg (Group 3) or 10 mg/kg of EU Herceptin (Group 4). Blood samples for determination of PK parameters were collected at 15 time points: pre-dose, 0.25, 1, 6, 24 hours and 2, 3, 4, 6, 8, 10, 15, 20, 28, 56 days after dosing and separated into serum. Five animals were used for each time point in each study group. Serum trastuzumab concentrations for PK analysis were measured using an ELISA based method and PK parameters were calculated by non-compartmental analysis.

The test doses of 1, 10 and 100 mg/kg were selected based on previously conducted comparative non-clinical studies for trastuzumab in mice (Trazimera, 2017, Hurst et al., 2014). The dose of 10 mg/kg was chosen to be compared between EG12014 and EU Herceptin as it was the most representative equivalent dose to the recommended clinical dose (i.e. weekly maintenance doses of 2 mg/kg in patients with HER2-overexpressing early or metastatic breast cancer) (EU Herceptin SmPC, 2021) among the three test doses.

The PK parameters and PK parameter ratios of EG12014 and EU Herceptin calculated from mean trastuzumab serum concentrations are presented in Table 3. IV administration of EG12014 or EU Herceptin at 10 mg/kg resulted in comparable trastuzumab exposures (AUC0-t: 19,342 hr*µg/mL and 21,599 hr*µg/mL for EG12014 and EU Herceptin, respectively; AUC0-inf: 22,648 hr*µg/mL and 22,142 hr*µg/mL for EG12014 and EU Herceptin, respectively).

EG12014 or EU Herceptin showed comparable values for Vz (189 mL/kg and 168 mL/kg) and CL (0.442 mL/hr/kg and 0.452 mL/hr/kg), and comparable t1/2 (297 hours and 258 hours). At the last PK timepoint (1344 hrs post-dose) both EG12014 and EU Herceptin serum concentrations were below the level of quantification (BLQ) for almost all mice sampled. All PK parameters showed less than 20% difference between EG12014 and EU Herceptin except for Cmax which was 23% higher for EG12014 (190 µg/mL) compared to EU Herceptin (154 µg/mL) despite comparable tmax (0.25 hours for EG12014 and EU Herceptin).

Table 4: PK parameters and PK parameter ratios of EG12014 and EU Herceptin (10 mg/kg dose level) calculated from mean trastuzumab serum concentrations.

PK parameter	EG12014 10 mg/kg	EU Herceptin 10 mg/kg	Ratio EG12014/EU Herceptin (%)
AUC0-t [hr*µg/mL]	19,342	21,599	89.6
AUC0-inf [hr*µg/mL]	22,648	22,142	102.3
Cmax [µg/mL]	190	154	123.4

tmax [hours]	0.25	0.25	100.0
t1/2 [hours]	297	258	115.1
Vz [mL/kg]	189	168	112.5
CL [mL/hr/kg]	0.442	0.452	97.8

Abbreviations: AUC0-inf, serum concentration-time curve from time zero to infinity; AUC0-t, serum concentration-time curve from time zero to the last observed concentration at time; CL, clearance; Cmax, maximum serum concentration; Vz, volume of distribution; tmax, time to reach Cmax; t1/2, terminal elimination half-life.

A recalculation of PK parameters was conducted due to several apparent outliers, and the desire for a more robust method of addressing BLQ values. Hence, the same PK calculation as originally performed were reconducted with the following changes to obtain more robust PK results: (1) The originally performed PK calculation was based on mean serum trastuzumab concentrations; the recalculation was based on median serum trastuzumab concentrations; (2) For the originally performed PK calculation, means of serum trastuzumab concentrations at any individual time point were only calculated if at least 2/3 of the values were above the LLOQ per time point; furthermore, for the calculation of mean values, the data point which was <LLOQ were set to zero. These restrictions were not applied for the PK recalculation; (3) For the PK recalculation, the first value which was <LLOQ was set to ½BLQ (i.e. 0.5 x 1.00 µg/mL).

The PK parameters and PK parameter ratios of EG12014 and EU Herceptin calculated from median trastuzumab serum concentrations are presented in Table 4.

Table 5: PK parameters and PK parameter ratios of EG12014 and EU Herceptin (10 mg/kg dose level) calculated from median trastuzumab serum concentrations.

PK parameter	EG12014 10 mg/kg	EU Herceptin 10 mg/kg	Ratio EG12014/EU Herceptin (%)
AUC0-t [hr*µg/mL]	20,395	20,033	101.8
AUC0-inf [hr*µg/mL]	20,526	20,162	101.8
Cmax [µg/mL]	189.6	141.5	134.0
tmax [hours]	0.25	0.25	100.0
t1/2 [hours]	181.0	178.2	101.5
Vz [mL/kg]	127.2	127.5	99.7
CL [mL/hr/kg]	0.487	0.496	98.2

*Calculated from trastuzumab serum concentrations available for the time point 0.25 hour and 1 hour after IV administration. Abbreviations: AUC0-inf, serum concentration-time curve from time zero to infinity; AUC0-t, serum concentration-time curve from time zero to the last observed concentration at time; CL, clearance; Cmax, maximum serum concentration; Vz, volume of distribution; tmax, time to reach Cmax; t1/2, terminal elimination half-life. Source: [Module 4, Section4.2.2.2 Study No. 146393, Section 10.3.2, Table 7].

For both mean based and median based calculations, the PK parameters AUC0-t, AUC0-inf, Vz, CL, t1/2 and tmax of trastuzumab were comparable between EG12014 and EU Herceptin after a single dose of 10 mg/kg. A higher Cmax was observed for EG12014 compared to EU Herceptin, however, the coefficient of variation of the measured serum trastuzumab concentrations at 0.25 hour or 1 hour after

administration was approximately 30% in the EG12014 treatment group and EU Herceptin treatment group.

No in vitro or in vivo distribution studies, no metabolism studies and no excretion studies have been conducted with EG12014.

Pharmacokinetic drug interaction studies with EG12014 have not been conducted.

2.5.4. Toxicology

No toxicology studies were performed with EG12014.

2.5.4.1. Single dose toxicity

No single dose toxicity studies were performed.

2.5.4.2. Repeat dose toxicity

No repeat-dose toxicity studies were performed.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted.

2.5.4.5. Reproductive and developmental toxicity

No reproductive or developmental toxicity studies were conducted.

2.5.4.6. Toxicokinetic data

No toxicokinetic data were provided.

2.5.4.7. Local Tolerance

No local toxicity studies were conducted.

2.5.4.8. Other toxicity studies

No other toxicity studies were conducted.

2.5.5. Ecotoxicity/environmental risk assessment

Trastuzumab is already marketed and no significant increase in environmental exposure is anticipated with Herwenda. Furthermore, the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr. 2) makes specific reference for certain types of

products such as proteins, that due to their nature they are unlikely to result in a significant risk to the environment.

2.5.6. Discussion on non-clinical aspects

As indicated in Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), a stepwise approach should be applied when evaluating non-clinical biosimilarity. Step 1 comprises several comparative in vitro studies. As the in vitro assays may be more specific and sensitive than studies in animals, these assays are considered paramount in the nonclinical comparability exercise. Based on the in vitro assay findings, a decision should then be made as to the extent of what, if any, in vivo work will be required. For Herwenda, however, an in vivo pharmacology study was conducted at an early research/development stage.

A number of in vitro functional assays were conducted to substantiate similarity between EG12014 and the EU reference product Herceptin with regard to biological activities associated with Fab- and Fc-mediated functions of trastuzumab (see 2.4. Quality aspects).

An in vivo study was performed to compare the tumour growth inhibitory potential in a xenograft mouse model with BT-474 breast carcinoma cells (EG1204 and EU Herceptin). EG12014 and EU Herceptin showed a similar tumour growth inhibition rate relative to control animals.

The in vivo PD study in a xenograft model showed no statistically significant differences in tumour inhibitory efficacy between EG12014 and Herceptin. This study was conducted when EG12014 was at its research and development stage in 2014/2015 and was retrospectively revisited in 2020/2021 by the sponsor in preparation for this MAA. The 2015 final Report of findings (version 1, dated 12-Feb-2015) was expanded, with more details of the study, in 2021, providing a revised, more comprehensive report, 103XX317-1 version 2 (dated 01-September-2021). Although the original data are provided in the Report, the documentation sources of raw data at the Department of Pharmacology, the Institute for Drug Evaluation Platform, Development Center for Biotechnology (hereinafter termed "DCB"), where the study was conducted in 2014/2015, are no longer available. This was according to the applicant attributed to the fact that the DCB was contracted to keep study documents and specimens for up to 1 year after the reports were finalized, namely until 2016. The study could, however, be regarded as supportive.

Studies on secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions were not conducted, in line with EMA/CHMP/BMWP/403543/2010.

The analytical method showed acceptable results in terms of precision, accuracy, and stability. Serum trastuzumab concentrations were determined by an ELISA assay, shown to be precise and accurate for the quantitative determination of trastuzumab in mouse serum samples.

The comparison of the PK was conducted at only one dose level (10 mg/kg) that was the most representative equivalent dose to the recommended clinical dose (i.e. weekly maintenance doses of 2 mg/kg in patients with HER2-overexpressing early or metastatic breast cancer) (EU Herceptin SmPC, 2021) among the three test doses.

The PK parameters AUC0-t, AUC0-inf, Vz, CL, t1/2 and tmax of trastuzumab were comparable between EG12014 and EU Herceptin after a single dose of 10 mg/kg in mice. Cmax was, however, approximately 30% higher for EG12014 than EU Herceptin. A high inter-animal coefficient of variation of serum trastuzumab concentrations ≤1 hour after administration might have limited the evaluation on Cmax comparability and contributed to the observed variability.

In the CHMP SA from 2015 it was stated that a definitive conclusion regarding the PK similarity between EG12014 and Herceptin could not be reached, since the study only included one dose level of Herceptin. Human PK data have however confirmed PK similarity between EG12014, EU Herceptin and US Herceptin in terms of AUC0-inf, AUC0-t and Cmax (Phase 1 study EGC001 in healthy volunteers). Thus, the lack of additional Herceptin dose levels in the PK study in mice is considered acceptable (see 2.6).

The lack of distribution, metabolism, excretion and interaction studies is acceptable, and in line with EMA/CHMP/BMWP/403543/2010.

Pharmacokinetic properties of EG12014 and Herceptin were characterised in mice following single iv infusions. An ELISA assay was used for quantification of EG12014 and Herceptin concentrations in mouse serum (ELISA). The analytical method is of adequate quality and is considered fit for purpose.

In mice, the main serum concentration profile and pharmacokinetic parameters of EG12014 were similar to EU-Herceptin after iv administration of 10 mg/kg. Maximum serum concentrations (Cmax) were however 34% higher for EG12014 than for EU Herceptin despite similar time to reach Cmax. The inter-animal variability in serum trastuzumab concentrations ≤1 hour after administration was approximately 30% in the EG12014 and EU Herceptin treatment groups. The differences in Cmax values are considered related to study conduct.

To conclude, the PK study in mice indicated similarity in most of the serum PK parameters, except for Cmax values that differed by approximately 30% due to inter-individual variability. Human PK data, however, have confirmed PK similarity between EG12014, EU Herceptin and US Herceptin in terms of AUC0-inf, AUC0-t and Cmax (Phase 1 study EGC001 in healthy volunteers). For the PK comparability, human data are considered more informative and, hence, supersede the animal data, including the formation of ADAs (see 2.6).

No distribution, metabolism or excretion studies were performed. This is acceptable, and in accordance with guideline EMEA/CHMP/BMWP/42832/2005 Rev1.

The lack of single-dose and repeat-dose toxicity studies, genotoxicity studies, reproductive or developmental toxicity studies and of other toxicity studies is considered acceptable and in line with current guidelines.

EG12014 is a monoclonal antibody, unlikely to pose a significant risk to the environment. Environmental risk assessment studies are therefore not required, in accordance with EMEA/CHMP/SWP/4447/00.

2.5.7. Conclusion on the non-clinical aspects

EG12014 can be considered similar to the reference product Herceptin from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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.

The clinical program comprised a phase 1 pharmacokinetic (PK) similarity study (**EGC001**) in healthy

males, and a phase 3 efficacy and safety study (**EGC002**) in female HERB-2 positive EBC patients. Immunogenicity has been evaluated in both clinical studies. Population pharmacokinetic (popPK) modelling of EG12014 and Herceptin in patients with HER2+ EBC using data from the neoadjuvant part of study **EGC002** is submitted as supportive PK information. In accordance with *EMEA/CHMP/BMWP/42832/2005 Rev1* and *EMEA/CHMP/BMWP/31329/2005*, further PK studies are not considered relevant for the development of a biosimilar product. Due to absence of validated PD biomarkers for trastuzumab, clinical PD and PK/PD studies were not performed.

Study **EGC002** is a randomised, multicentre, double-blind study in female HER2-positive early breast cancer (EBC) patients with the primary objective to demonstrate therapeutic equivalence between EG12014 and EU Herceptin in terms of efficacy and to compare the safety, immunogenicity and PK between the trastuzumab products. In accordance with the EMA SA (*EMA/CHMP/SAWP/306598/2017*) the use of EU Herceptin as comparator in this study was considered justified since comparative analytical and PK data of the pivotal **EGC001** study provided the scientific bridge between EG12014, EU Herceptin and US Herceptin.

Table 6. Tabular overview of clinical studies

Study number	Study population	Study design	Study objectives	Assessments for PK/Immunogenicity
EGC001*	Healthy male subjects (n=84; stage 1§)	• Phase 1, double blind, randomized, parallelgroup, single-dose, three-arm study • Two-stage study design§ • Single dose IV infusion of 6 mg/kg EG12014, US Herceptin or EU Herceptin • Subject study duration: up to 95 days from first screening to EOS visit	PK, safety & immunogenicity To investigate the PK similarity of EG12014 to US Herceptin, EG12014 to EU Herceptin and EU Herceptin to US Herceptin	*PK*: Primary PK parameter: AUC0-inf of trastuzumab; Secondary PK parameters: Cmax, AUC0-t, AUCres, t1/2, Tmax,VZ, λz, CL Sampling points: 0 (pre-dose), immediately before the end of infusion (EoI), 0.5, 1.5 , 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, 336, 504, 672, 1008, 1344 and 1680 h after the end of the infusion *Immunogenicity*: incidence of ADAs (predose and 1680 h post-infusion)
EGC002**	Female HER2-positive EBC patients (n=807; n=405 EG12014 group; n=402 EU	• Phase 3, double-blind, randomized, multicenter study • *Anthracycline-based neoadjuvant chemotherapy*: Epirubicin 90 mg/m2, IV every 3 w (4 cycles) + cyclophosphamide 600	Efficacy, safety, immunogenicity & PK To demonstrate therapeutic equivalence of EG12014 and EU Herceptin as part of	*PK*: Trastuzumab serum concentrations in neoadjuvant part, adjuvant part, and during complete study. Sampling points: prior to first infusion of study drug, at trough (pre-infusion) and peak (1 hour ± 10 min. post infusion) at neoadj C5 to C8, at 3 weeks post-dose

	Herceptin group)	mg/m2 IV every 3 weeks (4 cycles) • *Neoadjuvant therapy*: EG12014 or EU Herceptin 8 mg/kg IV loading dose & 6 mg/kg IV, thereafter, in combination with paclitaxel, 175mg/m2 IV, every 3weeks (4 cycles) *Adjuvant treatment* (post-surgery): EG12014 or EU Herceptin, 8 mg/kg IV loading dose and 6 mg/kg IV, thereafter, administered every 3 weeks up to 40 w (~9 months) • Subject study duration: approximately 88 weeks (~20 months) from screening to EOS visit	neoadjuvant therapy in HER2-positive EBC patients in terms of pCR at time of surgery	in neoadj C8. At all other time-points, a single blood sample will be taken during the visit (should be pre-infusion if on a dosing day; beginning of adjuvant treatment (C1D1) and every 4 cycles during adjuvant treatment (C5D1, C9D1, C13D1), and at 3 weeks after final dose (EoT). *Immunogenicity*: Incidence of ADAs and NAbs (baseline [pre-dose]; at Week 6, 12, and 18 of neoadjuvant therapy, presurgery, at beginning of adjuvant therapy, every 12 weeks during adjuvant therapy and at EoT follow-up (3 weeks after final administration of study treatment)

*Study EGC001 was conducted in Bulgaria. The study was completed in Aug 2016 (last subject out).

**Study EGC002 is conducted at 89 study sites in 10 countries. The study was completed in Jan 2022 (last patient out).

§ The study was planned to be either stopped after stage 1 if PK similarity was demonstrated or, if PK similarity was not achieved and evaluation of the study power was <80%, continued to stage 2 with a re-assessment of sample size (n=up to 162). Since PK similarity was achieved after stage 1, the study was stopped at this time point.

Abbreviations: IV, intravenous; n, number; w, weeks; m, months; h, hours; HER2, human epidermal growth factor 2; EBC, early breast cancer; pCR, pathological complete response; PK, pharmacokinetics; $AUC_{0\text{-}inf}$, area under the serum concentration-time curve from time zero to infinity; C_{max}, maximum serum concentration; $AUC_{0\text{-}t}$, AUC from time zero to the last observed concentration at time t; AUC_{res}, residual area under the curve; $t_{1/2}$; terminal elimination half-life; T_{max}, time to reach C_{max}; VZ, apparent volume of distribution at terminal phase; λz, elimination rate constant at terminal phase; CL, and total body clearance; C_{trough}, pre-dose serum concentration; ADA, anti-drug antibody; NAb, neutralizing antibody; EOS, end of study; EOT, end of treatment.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetic interaction studies

Pharmacokinetics using human biomaterials

Two clinical studies were submitted to support PK similarity between Herwenda and Herceptin: One pivotal phase I study, and a phase III study with secondary PK endpoint.

Study **EGC001** was a double blind, randomised, parallel-group, single-dose, three-arm, two-stage study in healthy male subjects.

Study **EGC002** is a randomised, multi-center, double-blind study in female HER2-positive early breast cancer (EBC) patients with the primary objective to demonstrate therapeutic equivalence between EG12014 and EU Herceptin in terms of efficacy and to compare the safety, immunogenicity and PK between the trastuzumab products.

In support, trastuzumab PK following administration of either EG12014 or Herceptin in the neoadjuvant part of study **EGC002** were characterised using two separate PopPK models. The effect of age, race, weight, clinical laboratory parameters, ECOG status and immunogenicity status were explored for both models.

Analytical methods

The concentration of free trastuzumab was determined in serum samples from healthy individuals (study EGC001) and in serum samples from HER-2 positive EBC patients (EGC002) using an ELISA method.

The ELISA method was shown to be accurate and precise within the detection range of 2,000-70,000 ng/mL EG12014 in human serum. A concentration of up to 2000 ng/ml recombinant human ErbB2/HER2 did not interfere with the assay. No effect was observed by 2.5% or 5% hemolysate or lipemic matrix. Long term stability of samples was addressed by QC samples (5,000 ng/ml or 60,000 ng/ml) stored at -70 or -20°C for 8 days, which is in line with the storage of study samples.

No samples for serum HER2 testing were collected and therefore no analysis has been carried out for the determination of HER2 levels in human breast cancer patient serum. High HER2 levels can interfere with the detection of trastuzumab and patients with higher baseline shed antigen levels are likely to have lower serum trough concentrations of trastuzumab. However, based on popPK, it is concluded that the serum HER2 concentrations among the population enrolled into the EGC002 study are much lower than the model predicted serum HER2 concentrations necessary to alter trastuzumab PK. In addition, it has been demonstrated in study EGC002 that levels up to 2,000 ng/mL serum HER2 did not interfere with the detection of EG12014.

Screening, confirmatory and characterisation assays were used to evaluate the immunogenicity of trastuzumab (see section 2.6.8.7.). Samples with signals above the screening cut point were considered positive and further analysed with the confirmatory assay. Confirmed positive ADA samples were further characterised by performing serial dilutions to determine the titer and neutralising capacity was analysed by a validated NAb screening assay. In study EGC001 (healthy individuals) the contract laboratory IPM GmbH conducted and validated the ECLA assay for ADA analysis, whereas in study EGC002 (HER-2 positive EBC patients) the ECLA assay was conducted and validated by ICON Laboratory Services.

An electrochemiluminescence (ECL) technology using a bridging assay format has been applied for the detection of ADAs directed against trastuzumab in human serum samples collected in studies EGC001 (healthy subjects; contract laboratory IPM GmbH) and EGC002 (HER2-positive EBC patients; ICON Laboratories services). In the applied assays, SULFO-tag labelled EG12014 is used for capturing and detection of ADAs against trastuzumab. Biotinylated EG12014 is used for capturing and bind the SULFO-tag-ADA complex to the microtiter plate. To increase drug tolerance, an acid dissociation pre-analytical step is included. The ECL signal detected is proportional to the amount of ADAs present in the sample.

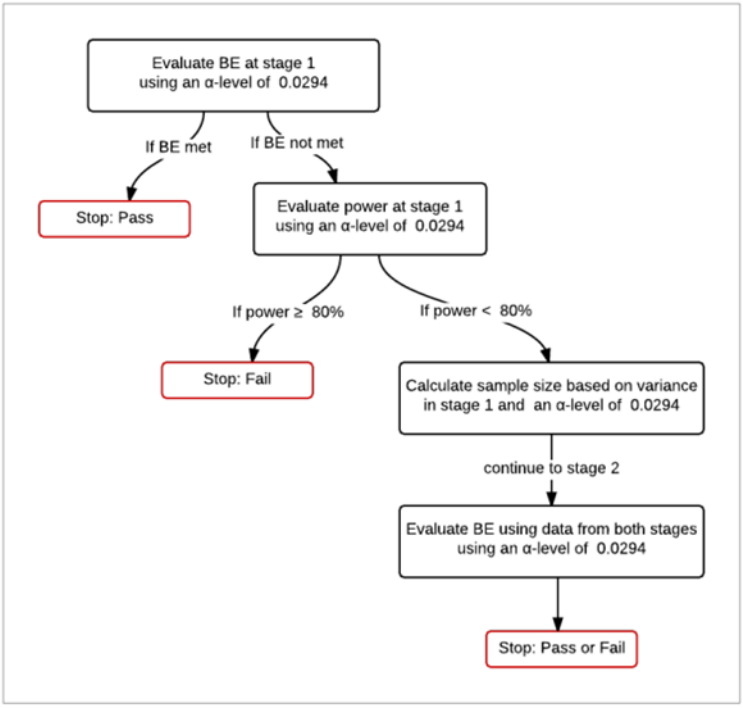
The NAb assay used a (non-cell-based) competitive ligand binding (CLB) format reflecting the mechanism of action (MOA) of trastuzumab, which involves the binding of trastuzumab to HER2. The CLB assay measures the binding of trastuzumab to HER2 and inhibition of the binding if NAbs are present. Biotinylated EG12014 was used to capture NAbs present in serum samples and to bind the NAbs to a streptavidin coated binding plate. The captured NAbs were eluted by acid dissociation, transferred to an EG12014-coated plate, and incubated with a SULFO-tag labelled target molecule.

Clinical studies

In the pivotal PK study, the primary PK endpoint was $AUC_{0\text{-}inf}$ of trastuzumab. Additional endpoints were the maximum serum concentration (C_{max}), AUC from time zero to the last observed concentration at time t ($AUC_{0\text{-}t}$), residual area under the curve (AUC_{res}), terminal elimination half-life ($t_{1/2}$), time to reach C_{max} (T_{max}), apparent volume of distribution at terminal phase (Vz), elimination rate constant at terminal phase (λz), and total body clearance (CL).

The trial was performed according to a two-stage design with interim power monitoring and sample size adaption as described by Potvin et al (Figure 2). The nominal alpha values to be used at stage 1 and at stage 2 evaluations were chosen as alpha1=0.0294 and alpha2=0.0294. These values are shown by Potvin et al. to maintain an overall alpha=0.05 of the two-stage test procedure.

Figure 2. Two-stage design for the pivotal PK study



The study was regarded as final at stage 1 since PK similarity between EG12014, EU Herceptin and US Herceptin for the primary endpoint (AUC0-inf of trastuzumab) was demonstrated.

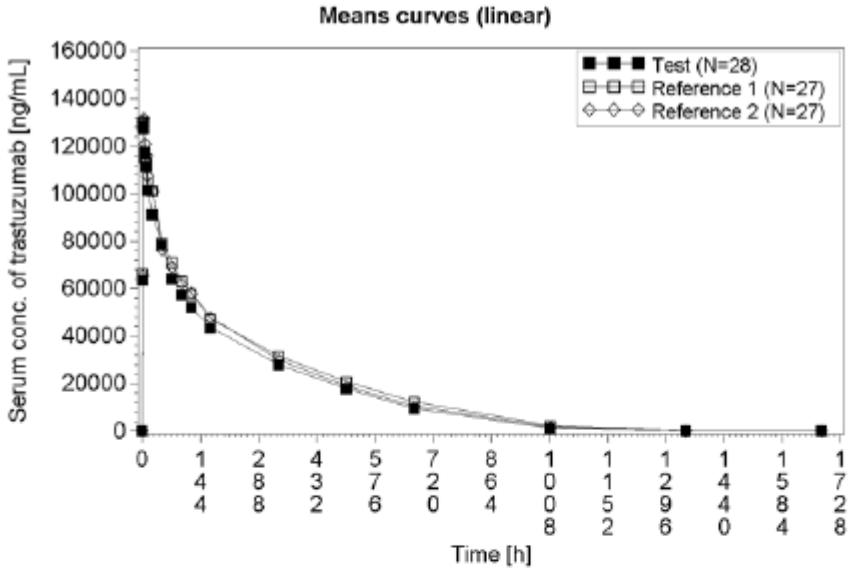
In the phase III study, blood samples for PK analysis were sampled as described in Table 4. Peak and trough concentrations were summarised by descriptive statistics according to treatment, cycle (C) and collection time.

Pivotal PK study EGC001

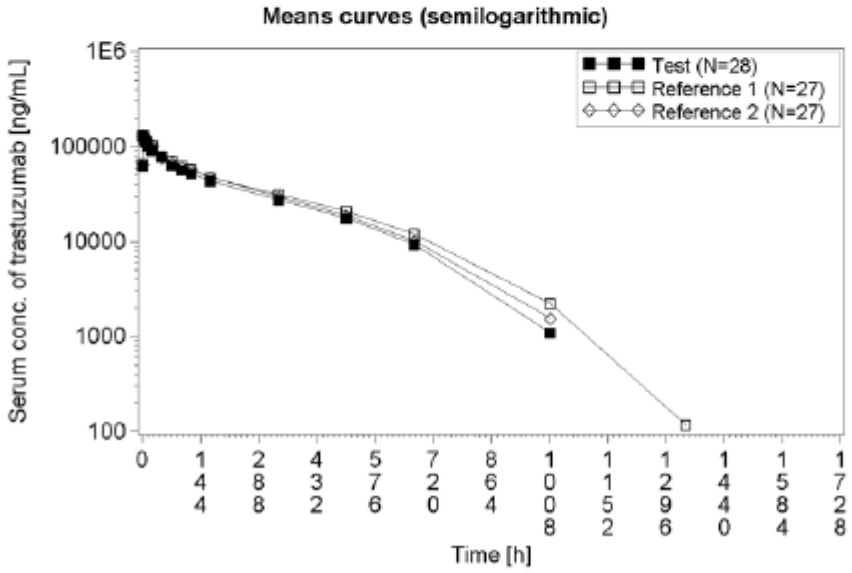
For the phase I clinical study EGC001, no GCP inspections have been conducted or requested, nor have been announced by any regulatory authority according to the applicant's knowledge. The sponsor has performed audits at the study site and the bioanalytical laboratory, and confirms that the study has been conducted and analysed in accordance with international GCP requirements.

Following a single dose IV infusion of 6 mg/kg trastuzumab, mean (±SD) trastuzumab serum concentration-time profiles by treatment group are presented in the figure below:

Figure 3. Mean (arithmetic) trastuzumab serum concentration-time profile (top panel linear; lower panel semilogarithmic)



TF 8 Mean (arithmetic) trastuzumab serum concentration-time profile (linear)



TF 9 Mean (arithmetic) trastuzumab serum concentration-time profile (semilogarithmic)

Test=EG12014, Reference 1= Herceptin EU, Reference 2 Herceptin FDA

Summary of trastuzumab serum PK parameters by treatment group are presented in Table 6 (primary parameters) and Table 7 (secondary parameters) below.

Table 7. Pharmacokinetic endpoints of trastuzumab after an IV infusion over 90 min single dose of 6 mg/kg (geometric mean, CV, arithmetic mean, SD, lower and upper ranges, median)

PK parameter	Statistics	TEST (N=28)	REFERENCE 1 (N=27)	REFERENCE 2 (N=27)
$AUC_{(0-\infty)}$ [ng*h/mL]	**Geom. Mean**	26275647	29257292	27855495
	Geom. Mean **CV (%)**	15.2	19.3	22.6
	Arithm. Mean (SD)	26565419 (4001560)	29769574 (5612088)	28553454 (6784994)
	Range	18436692 - 36273490	19623237 - 42352831	17918254 - 49764012
	Median	26347340	29894674	28754547
$AUC_{(0-t)}$ [ng*h/mL]	**Geom. Mean**	24125849	27398644	25850110
	Geom. Mean **CV (%)**	15.7	21.1	23.1
	Arithm. Mean (SD)	24411191 (3817872)	27976022 (5808181)	26528309 (6444977)
	Range	17915450 - 32530324	18615773 - 39899151	17175128 - 45665140
	Median	23968912	27126359	26044841
Cmax [ng/mL]	**Geom. Mean**	135388	135022	136046
	Geom. Mean **CV (%)**	16.5	17.3	17.8
	Arithm. Mean (SD)	137133 (22125)	137009 (24661)	138162 (25494)
	Range	88556 - 182374	102737 - 192153	101753 - 211437
	Median	137874	129414	134445
AUC_{res} [%]	**Geom. Mean**	7.05	4.98	6.33
	Geom. Mean **CV (%)**	62.1	77.0	58.4
	Arithm. Mean (SD)	8.10 (3.90)	6.25 (4.39)	7.15 (3.19)
	Range	2.31 - 13.48	1.88 - 14.98	1.89 - 12.40
	Median	8.07	4.40	6.85
$t_{½}$ [h]	**Geom. Mean**	211.803	216.734	205.074
	Geom. Mean **CV (%)**	15.0	14.2	17.5
	Arithm. Mean (SD)	213.981 (29.823)	218.855 (31.600)	208.077 (36.195)
	Range	135.980 - 270.083	164.660 - 294.531	151.276 - 276.993
	Median	221.792	210.840	202.481

Test=EG12014, Reference 1= Herceptin EU, Reference 2 Herceptin FDA

For all subjects, after administration of both EG12014 and Herceptin, the percentage of the AUC_{0-inf} due to extrapolation was less than 15%.

Table 8. Additional PK parameters of trastuzumab after an IV infusion over 90 minutes of a single dose of 6 mg/kg (n, geometric mean, CV, arithmetic mean, SD, lower and upper ranges, median) (EGC001 CSR amendment 2)

PK parameter	Statistics	EG12014 (N=28)	EU Herceptin (N=27)	US Herceptin (N=27)
T_{max} [h]	Geom. Mean	3.123	2.958	2.830
	Geom. Mean CV (%)	91.6	94.9	58.0
	Arithm. Mean (SD)	4.958 (8.943)	5.538 (13.660)	3.317 (2.375)
	Range	1.467 - 49.533	1.450 - 73.567	1.467 - 13.500
	Median	2.500	2.500	2.500
V_z [mL]	Geom. Mean	5545.64	4952.96	4871.26
	Geom. Mean CV (%)	19.0	19.9	17.0
	Arithm. Mean (SD)	5647.67 (1182.92)	5049.79 (1057.08)	4939.25 (846.09)
	Range	4218.60 - 9727.31	3335.14 - 8335.92	3660.66 - 6872.92
	Median	5355.66	4782.69	4808.88
λz [1/h]	Geom. Mean	0.00327	0.00320	0.00338
	Geom. Mean CV (%)	15.0	14.2	17.5
	Arithm. Mean (SD)	0.00331 (0.000536)	0.00323 (0.000449)	0.00343 (0.000596)
	Range	0.00257 - 0.00510	0.00235 - 0.00421	0.00250 - 0.00458
	Median	0.00313	0.00329	0.00342
CL [mL/h]	Geom. Mean	18.15	15.84	16.46
	Geom. Mean CV (%)	17.2	20.0	20.2
	Arithm. Mean (SD)	18.41 (3.29)	16.14 (3.21)	16.77 (3.19)
	Range	13.91 - 27.85	10.29 - 22.62	10.44 - 23.60
	Median	18.01	15.55	17.09

The results from the comparative statistical evaluation concerning pharmacokinetic (PK) similarity of the Test IMP compared to each one of both Reference IMPs with respect to the primary endpoint $AUC_{0-\infty}$ and additional endpoint AUC_{0-t} of trastuzumab are presented in Table 8 below:

Table 9. Comparison of 94.12% confidence intervals of EU vs US trastuzumab and EG12014

PK parameter	Statistics	EG12014 *vs.* EU Herceptin (N=28)	EG12014 *vs.* US Herceptin (N=27)	EU Herceptin *vs.* US Herceptin (N=27)
AUC_{0-inf} [µg*h/mL]	GMR*	89.81	94.33	105.03
	94.12% CI*	82.11 - 98.23	85.45 - 104.13	94.17 - 117.15
	CV*	17.33	19.16	20.99
AUC_{0-t} [µg*h/mL]	GMR*	88.05	93.33	105.99
	94.12% CI*	80.01 - 96.91	84.33 - 103.29	94.48 - 118.90
	CV*	18.56	19.65	22.12
C_{max} [µg/mL]	GMR*	100.27	99.52	99.25
	94.12% CI*	91.87-109.44	91.05-108.77	90.56-108.77
	CV*	16.91	17.19	17.56

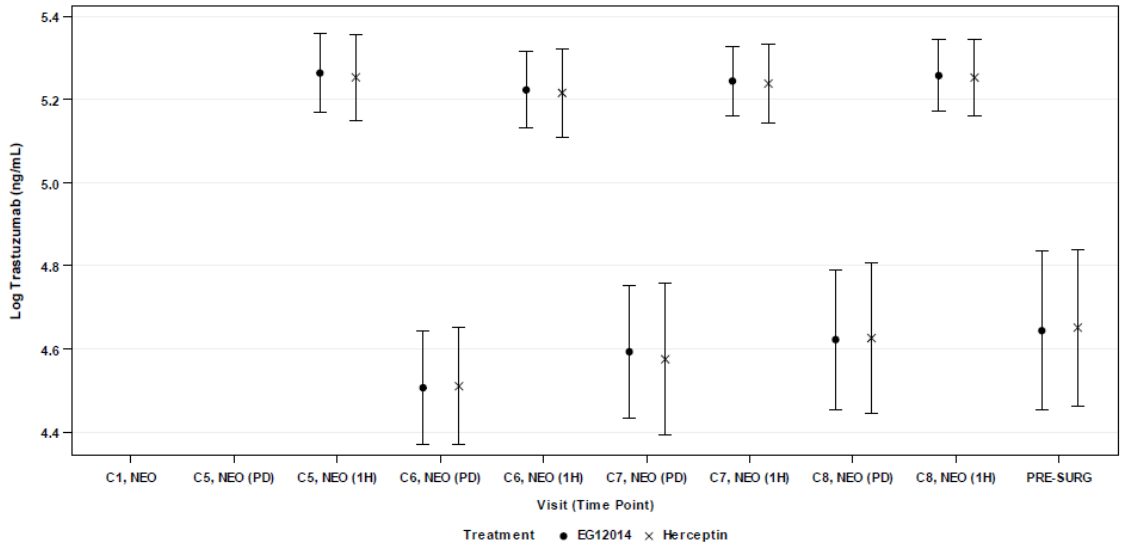
Pharmacokinetic data collected in the phase 3 Study EGC002

Table 10. Post-hoc analysis of trastuzumab concentrations (ng/mL) excluding outliers, by timepoint and treatment arm (PKS-neo) – Neoadjuvant Part

Scheduled Time (hour)	Statistic	EG12014 (N=399)	Herceptin (N=398)	Overall (N=797)
Baseline[a]	n	388	385	773
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Min/ Max	0/ 0	0/ 0	0/ 0
Cycle 5, Neoadjuvant Part, Pre-Dose	n	371	365	736
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Min/ Max	0/ 0	0/ 0	0/ 0
Cycle 5, Neoadjuvant Part, Post-Infusion	n	365	349	714
	Mean (SD)	187626.6 (39529.99)	184555.6 (42225.64)	186125.5 (40869.95)
	Min/ Max	68905/ 294829	82637/ 293167	68905/ 294829
Cycle 6, Neoadjuvant Part, Pre-Dose	n	363	346	709
	Mean (SD)	33635.5 (9313.76)	34081.5 (10102.85)	33853.2 (9702.54)
	Min/ Max	8612/ 61170	8854/ 60946	8612/ 61170
Cycle 6, Neoadjuvant Part, Post-Infusion	n	359	349	708
	Mean (SD)	170674.6 (34819.34)	168999.8 (38335.52)	169849.0 (36578.48)
	Min/ Max	58786/ 272569	69071/ 260216	58786/ 272569
Cycle 7, Neoadjuvant Part, Pre-Dose	n	375	348	723
	Mean (SD)	41559.5 (13101.75)	40463.7 (13939.66)	41032.1 (13513.25)
	Min/ Max	5018/ 79795	3114/ 78186	3114/ 79795
Cycle 7, Neoadjuvant Part, Post-Infusion	n	365	350	715
	Mean (SD)	178680.7 (33403.77)	176928.4 (36744.43)	177822.9 (35065.12)
	Min/ Max	94663/ 271278	82975/ 269998	82975/ 271278
Cycle 8, Neoadjuvant Part, Pre-Dose	n	357	353	710
	Mean (SD)	44797.8 (15023.85)	45586.9 (15767.82)	45190.1 (15392.43)
	Min/ Max	7234/ 90177	3956/ 89183	3956/ 90177
Cycle 8, Neoadjuvant Part, Post-Infusion	n	349	345	694
	Mean (SD)	184148.2 (35871.29)	182751.7 (36893.22)	183454.0 (36363.34)
	Min/ Max	90250/ 286828	92991/ 284155	90250/ 286828
Pre-Surgery	n	367	344	711
	Mean (SD)	47480.4 (16124.23)	48244.3 (16540.55)	47850.0 (16319.93)
	Min/ Max	2333/ 93701	2635/ 90920	2333/ 93701

Abbreviations: N, number of patients; PKS, pharmacokinetics set. a. Baseline is the last value prior to randomisation.

Figure 4. Trastuzumab mean (SD) serum concentration excluding outliers versus time (PKS-neo) – Neoadjuvant Part



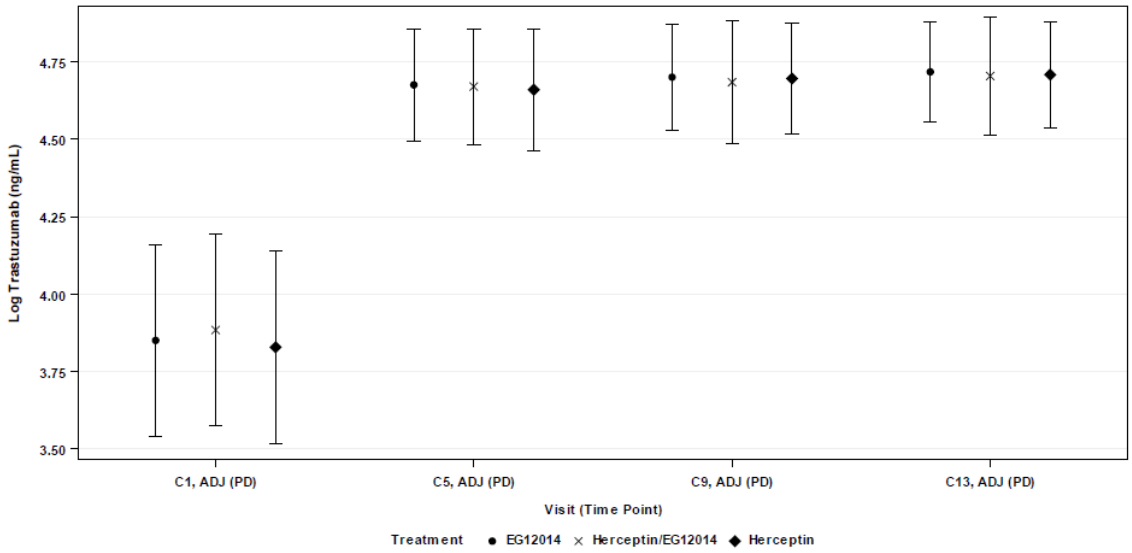
Abbreviations: PRE-SURG = Pre-Surgery, CX = Cycle X, NEO = Neoadjuvant Part, PD = Pre-Dose, 1H = 1 Hour Post Infusion.

Table 11. Post-hoc analysis of trastuzumab concentrations (ng/mL) excluding outliers, by timepoint and treatment arm – Adjuvant Part

Scheduled Time (hour)	Statistic	EG12014 (N=386)	Herceptin/ EG12014 (N=188)	Herceptin (N=188)	Overall (N=762)
Cycle 1, Adjuvant Part, Pre-Dose	n	342	167	173	682
	Mean (SD)	5391.8 (6640.34)	6124.5 (6880.73)	5563.7 (6573.21)	5614.8 (6679.99)
	Min/ Max	0/ 28084	0/ 26617	0/ 27012	0/ 28084
Cycle 5, Adjuvant Part, Pre-Dose	n	355	177	174	706
	Mean (SD)	50886.3 (16906.82)	50527.4 (17273.50)	49776.6 (18357.49)	50522.8 (17346.93)
	Min/ Max	2503/ 98361	4206/ 97731	5850/ 97980	2503/ 98361
Cycle 9, Adjuvant Part, Pre-Dose	n	348	176	170	694
	Mean (SD)	53543.0 (17987.50)	52460.1 (19054.24)	53324.0 (18828.84)	53214.7 (18448.58)
	Min/ Max	2529/ 107308	3757/ 105066	10804/ 100135	2529/ 107308
Cycle 13, Adjuvant Part, Pre-Dose	n	335	169	164	668
	Mean (SD)	55501.2 (18542.88)	54830.4 (19332.58)	54676.2 (18469.73)	55128.9 (18703.53)
	Min/ Max	8992/ 108276	3807/ 107476	8132/ 98698	3807/ 108276

Abbreviations: N, number of patients; PKS, pharmacokinetics set.

Figure 5. Trastuzumab mean (SD) serum concentration excluding outliers versus time – Adjuvant part



Abbreviations: PRE-SURG = Pre-Surgery, CX = Cycle X, NEO = Neoadjuvant Part, PD = Pre-Dose, 1H = 1 Hour Post Infusion.

However, it is noted that all subjects had C_{max} above the calibration curve (C_{max} range in the pivotal PK study 88.000-211.000 ng/ml; mean C_{max} in the phase 3 study around 180.000 ng/ml; calibration curve 2.000 to 70.000 ng/ml).

Sparse PK data have been collected during the phase 3 EGC002 study. Geometric mean peak and trough values for EG12014 and Herceptin in patients HER2 positive EBC receiving the 8 mg/kg + 6 mg/kg Q3W dosing regimen were comparable in neoadjuvant cycles C5-C8.

Population pharmacokinetic modelling

Separate population pharmacokinetic (popPK) models were developed for EG12014 and Herceptin in patients with HER2+ EBC using data from the neoadjuvant part of Study **EGC002** (*i.e.* 383 patients and 2927 observations for EG12014, and 380 patients and 2805 observations for Herceptin). Both EG12014 and Herceptin PK were described by two-compartment disposition models with zero-order input and first-order elimination, and with IIV on all parameters. Both CL and Vc increased with baseline body weight (Table 11).

Table 12. Parameter estimates of final popPK model for EG12014 (Run EGR004) and Herceptin (Run HER004)

	EG12014 (Run EGR004)				Herceptin (Run HER004)			
	CL = 0.00877 x (WT/70)$^{0.699}$; L/hr; Vc = 3.07 x (WT/70)$^{0.510}$ L				CL = 0.00977 x (WT/70)$^{0.609}$; L/hr; Vc = 3.08 x (WT/70)$^{0.533}$ L			
Parameter	**NONMEM Estimates**				**NONMEM Estimates**			
[Units]	**Point Estimate[a]**	**%RSE[b]**	**95% CI[a]**		**Point Estimate[a]**	**%RSE[b]**	**95% CI[a]**	
CL [L/hr]	0.00877	5.22	0.00792-0.00971		0.00977	2.44	0.00932-0.0103	
Vc [L]	3.07	0.948	3.02-3.13		3.08	0.993	3.02-3.14	
Q [L/hr]	0.00707	48.8	0.00272-0.0184		0.0157	24.0	0.00983-0.0252	
Vp [L]	2.91	9.37	2.42-3.49		2.78	8.64	2.34-3.29	
CL~weight [unitless]	0.699	9.70	0.566-0.831		0.609	10.7	0.481-0.736	
Vc~weight [unitless]	0.510	8.52	0.425-0.595		0.533	8.06	0.448-0.617	
Inter-individual variability				**CV%[c] or R**				**CV%[c] or R**
ω^2_{CL}	0.0556	27.8	0.0253-0.0859	CV=23.6%	0.0736	16.7	0.0496-0.0976	CV=27.1%
Covar η_{CL}, η_{Vc}	0.0158	34.5	0.00511-0.0264	R=0.439	0.0268	14.0	0.0195-0.0342	R=0.666
ω^2_{Vc}	0.0232	12.8	0.0174-0.0291	CV=15.2%	0.0221	16.0	0.0151-0.0290	CV=14.9%
Covar η_{CL}, η_{Q}	0.0153	617	-0.170-0.200	R=0.0638	0.151	46.4	0.0136-0.289	R=0.371
Covar η_{Vc}, η_{Q}	-0.0025	1621	-0.0819-0.0769	R=-0.0162	0.0761	44.1	0.0103-0.142	R=0.341
ω^2_{Q}	1.03	16.7	0.694-1.37	CV=134%	2.26	19.2	1.41-3.11	CV=293%
Covar η_{CL}, η_{Vp}	-0.037	144	-0.141-0.0673	R=-0.440	0.0565	39.3	0.0130-0.0999	R=-0.390
Covar η_{Vc}, η_{Vp}	0.0294	71.6	-0.0119-0.0707	R=0.540	0.0322	46.7	0.00271-0.0618	R=0.406
Covar η_{Q}, η_{Vp}	-0.0843	133	-0.305-0.136	R=-0.232	0.782	20.4	0.470-1.09	R=0.973
ω^2_{Vp}	0.128	77.5	-0.0664-0.322	CV=35.7%	0.286	48.2	0.0160-0.555	CV=57.5%
Residual variability				**CV% or SD**				**CV% or SD**
σ^2_{prop}	0.0198	12.1	0.0151-0.0245	CV%=14.1%	0.0209	11.3	0.0162-0.0255	CV%=14.4%
σ^2_{add} [µg/L]	5307080	44.3	701374-9912786	SD=2304	10580513	37.5	2802958-18358067	SD=3253

[a] Back-transformed from natural log scale (except for σ^2)

[b] RSE=SE.100 (except for σ^2). RSE for σ^2 =SE(θ)/θ.100

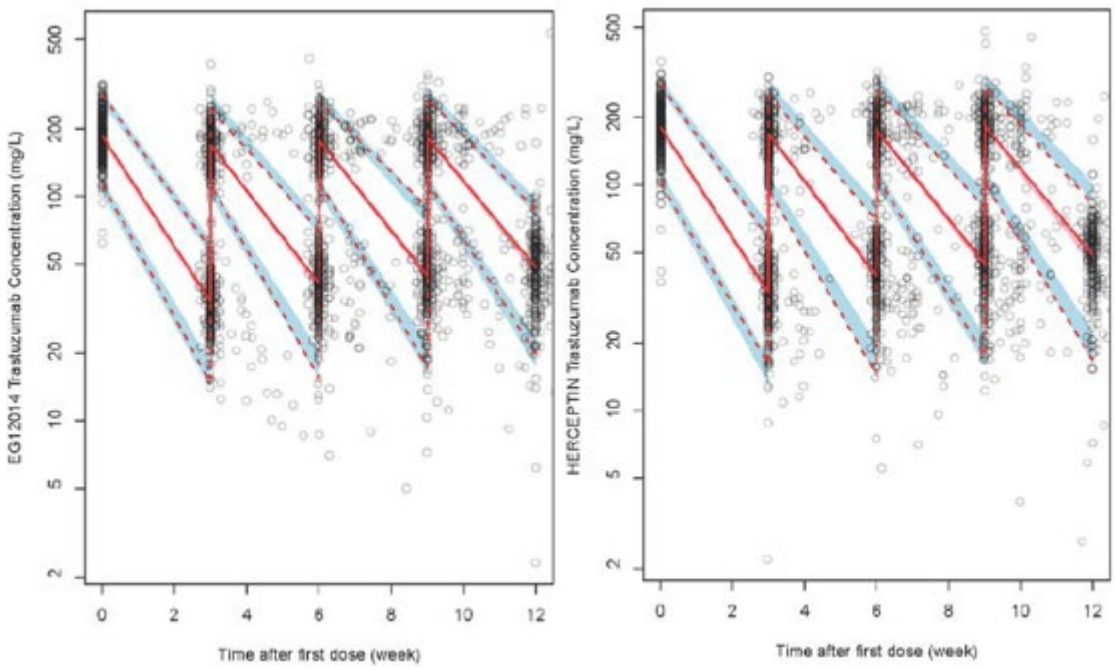
[c] CV for IIV calculated as $CV_{TVP}=\sqrt{e^{\omega^2_P}}$ .100 if $\omega^2_P \leq 0.15$, else $CV_{TV_p} = \sqrt{e^{\omega^2_P} - 1}$ .100

Abbreviations: CL = total clearance, Vc = volume of central compartment, Vp = volume of peripheral compartment, Q = inter compartment clearance between central and peripheral compartments, ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{VP} =variance of random effect of CL, V_c, Q and V_p, respectively; Covar η_X, η_Y = covariance of random effect of x and y, CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ^2_{prop} = proportional residual error, σ^2_{add} = additive residual error

The reference population is a 70-kg subject.

The shrinkages of individual random effects for CL, Vc, Q and Vp were estimated as 12, 12, 51, and 31% for Run EGR004 and as 8, 13, 40 and 37% for Run HER004. Body weight explained some of the observed variability, *e.g.* IIV for CL were 24.7 %CV and 31.0 %CV in base models and 23.6 %CV and 27.1 %CV in final models for EG12014 and Herceptin, respectively.

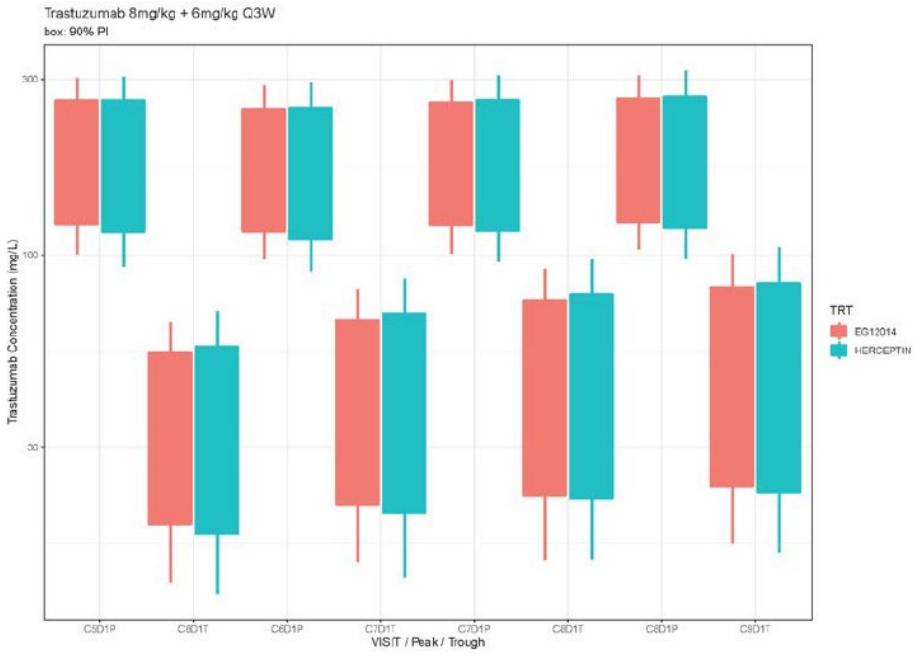
Figure 6. Visual predictive check for the final PK model for a) EG12014 (Run EGR004) and Herceptin (Run HER 004)



Left: Linear Y Scale; Right: Logarithmic Y Scale;
Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations.
Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of predicted concentrations

Simulated concentration peaks and troughs for EG12014 and Herceptin are shown below:

Figure 7. Comparison of model-simulated PK for EG12014 and Herceptin



Top: Linear Y Scale; Bottom: Logarithmic Y Scale;
Top and base of the box represent 5th and 95th percentile of the model predictions and whiskers represent the 1st and 99th percentile.
Source: EGR004vpc1000.tab & HER004vpc1000.tab; VPCcompare_EGC002_v1.R; EGC002_compare_box_v1.pdf

For a typical patient of 70 kg, the linear CL (0.166 and 0.160 L/day) and Vc (3.06 and 3.12 L) for EG12014 and Herceptin, respectively, were similar between treatment groups (Table below). Also, the non-linear elimination component was comparable between drug products.

The PK parameter estimates for the updated database containing both neoadjuvant and adjuvant data from study EGC002 (i.e. 9 139 post-dose trastuzumab concentrations from 795 patients) are shown below. To improve model fit of the observed data, the popPK models' structures were updated to describe elimination as a combination of non-linear and non-linear target-mediated elimination (which was observed between the neoadjuvant and adjuvant treatment with trastuzumab).

Table 13. Parameter estimates of final updated PopPK model for EG12014 and Herceptin (M3 method, neoadjuvant and adjuvant data) (popPK report, Table 5-4)

	EG12014 (Run EGR0083)				Herceptin (Run HER0083)			
	CL = 0.00690 x (WT/70)$^{0.954}$; L/hr; Vc = 3.06 x (WT/70)$^{0.530}$ L				CL = 0.00665 x (WT/70)$^{0.972}$; L/hr; Vc = 3.12 x (WT/70)$^{0.532}$ L			
Parameter	**NONMEM Estimates**				**NONMEM Estimates**			
[Units]	**Point Estimate[a]**	**%RSE[b]**	**95% CI[a]**		**Point Estimate[a]**	**%RSE[b]**	**95% CI[a]**	
CL [L/hr]	0.00690	4.31	0.00634 - 0.00751		0.00665	4.26	0.00611-0.00723	
Vc [L]	3.06	1.4	2.98 - 3.15		3.12	1.04	3.05-3.18	
Q [L/hr]	0.00680	97.5	0.00101- 0.0460		0.00602	55.0	0.00205-0.0177	
Vp [L]	2.19	28.1	1.26 - 3.79		1.93	8.35	1.64-2.27	
Vm[µg/hr]	136	22.2	88.0 - 210		154	13.6	118.- 202	
Km [µg/L]	1370	41.8	603 - 3108		1374	80.5	284.-6661	
WT~CL[unitless]	0.954	7.49	0.814 - 1.09		0.972	8.31	0.814-1.13	
WT~Vc [unitless]	0.530	8.55	0.441 - 0.619		0.532	10.0	0.427-0.637	
Inter-individual variability				**CV%[c] or R**				**CV%[c] or R**
ω^2_{CL}	0.0476	37.7	0.0124-0.0827	CV=21.8%	0.0479	56.8	-0.00539-0.101	CV=21.9%
Covar η_{CL}, η_{Vc}	0.0149	25.2	0.00757-0.0223	R=0.438	0.0212	28.1	0.00951-0.0328	R=0.588
ω^2_{Vc}	0.0245	12.3	0.0186-0.0303	CV=15.6%	0.0271	11.1	0.0212-0.0330	CV=16.5%
Covar η_{CL}, η_{Q}	0.0629	271	-0.272-0.397	R=0.448	-0.0245	791	-0.405-0.356	R=0.180
Covar η_{Vc}, η_{Q}	-0.0168	186	-0.0781-0.0444	R=-0.167	0.00801	581	-0.0833-0.0993	R=-0.0783
ω^2_{Q}	0.414	179	-1.04-1.87	CV=71.7%	0.387	58.1	-0.0537-0.827	CV=68.7%
Covar η_{CL}, η_{Vp}	-0.0125	353	-0.0986-0.0737	R=-0.118	-0.0349	141	-0.131-0.0616	R=-0.285
Covar η_{Vc}, η_{Vp}	0.0214	61.4	-0.00434-0.0470	R=0.282	0.0283	50.6	0.000231-0.0565	R=0.308
Covar η_{Q}, η_{Vp}	-0.0321	184	-0.148-0.0838	R=-0.103	0.157	140	-0.273-0.586	R=0.451
ω^2_{Vp}	0.234	66.2	-0.0697-0.539	CV=51.4%	0.312	29.7	0.131-0.494	CV=60.5%
ω^2_{Vm}	0.128	28.3	0.0571-0.199	CV=35.8%	0.122	43.7	0.0175-0.226	CV=34.9%
ω^2_{Km}	0.00787	1741	-0.260-0.276	CV=8.87%	0.00834	1605	-0.254-0.271	CV=9.13%
Residual variability				**CV% or SD**				**CV% or SD**
σ_{prop}	0.123	9.67	0.100-0.147	CV%=12.3%	0.138	7.07	0.119-0.157	CV%=13.8%
σ_{add} [µg/L]	8017	11.6	6191.-9842.	SD=8017	6560	10.5	5207.-7912.	SD=6560

[a] Back-transformed from natural log scale (except for σ, WT~CL, WT~Vc)

[b] RSE=SE.100 except for σ, WT~CL, WT~Vc, RSE =SE(θ)/θ.100

[c] CV for IIV calculated as $CV_{IIV}=\sqrt{e^{\omega^2}}.100$ if $\omega^2_p \leq 0.15$, else $CV_{IIV} = \sqrt{e^{\omega^2}-1}.100$

Abbreviations: CL = total clearance, Vc = volume of central compartment, Vp = volume of peripheral compartment, Q = inter compartment clearance between central and peripheral compartments, Vm = maximum elimination rate , Km = concentration at ½ maximum elimination rate, WT=baseline body weight, ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp}, ω^2_{Vm}, ω^2_{Km} =variance of random effect of CL, Vc, Q, Vp, Vm and Km respectively; Covar ηx, ηy = covariance of random effect of x and y, CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ_{prop} = proportional residual error estimated as theta, σ_{add} = additive residual error estimated as theta

The reference population is a 70-kg subject.

Source: EGR0083.cnv/ext; BackTransformMU_RunEGR0083na.R; MUBT_RunEGR0083.csv

Source: HER0083.cnv/ext; BackTransformMU_RunHER0083na.R; MUBT_RunHER0083.csv

The shrinkages of individual random effects for CL, Vc, Q, Vp, Vm and Km were estimated at 14, 11, 47, 36, 48 and 97% for Run EGR0083 and as 15, 11, 45, 30, 46 and 97% for Run HER0083.

2.6.2.2. Pharmacodynamics

See discussion on clinical pharmacology.

2.6.3. Discussion on clinical pharmacology

The clinical development program for the applied drug product was conducted in accordance with current EMA guidelines relevant for biosimilars, and in accordance with Scientific Advice received from the CHMP. The proposed indications, body-weight-based dosage, and IV route of administration for EG12014 are identical to those for EU Herceptin.

The concentration of free trastuzumab was determined in serum samples from healthy individuals (study EGC001) and in serum samples from HER-2 positive EBC patients (EGC002) using an ELISA method. The ELISA method was shown to be accurate and precise within the detection range of 2,000-70,000 ng/mL EG12014 in human serum.

Screening, confirmatory and characterisation assays were used to evaluate the immunogenicity of trastuzumab. See section 2.6.9. Discussion on clinical safety.

EMA Scientific advice was received on the two-stage design approach of the pivotal PK study EGC001 and this approach was supported (EMA/CHMP/SAWP/466179/2015, EMA/CHMP/SAWP/306598/2017). In the case of a monoclonal antibody with per definition a long half-life and a potential of immunogenicity, a parallel design is accepted by EMA and commonly used. Efforts were made to reduce the risk for potential imbalance between the groups. Crossover study is not practical, due to the long half-lives leading to long treatment periods and long washout interval. PK sampling up to 70 days was considered adequate. The study design was considered acceptable.

The test and reference products and the mode of administration were considered adequate for a bioequivalence study. The certificates of analysis of the bio-batches and the protein concentrations for each product were presented in annex 16.1.1 to the clinical study report. The test- and reference products were comparable in terms of assay (well within the ± 5% requirement).

The pivotal phase I PK study EGC001 in healthy volunteers, apparently demonstrates similarity of the pharmacokinetics of EG12014 and Herceptin. Following a single dose IV infusion of 6 mg/kg trastuzumab, highly similar pharmacokinetic profiles were observed among all three groups of subjects. No significant differences in serum exposures or half-life of trastuzumab was observed between Test (EG12014), Reference 1 (EU Herceptin) or Reference 2 (US Herceptin) trastuzumab products.

For all subjects, after administration of both EG12014 and Herceptin, the percentage of the $AUC_{0\text{-}inf}$ due to extrapolation was less than 15% demonstrating that the sampling schedule ensured the majority of AUC was captured.

The applicant referred to EPARs for other trastuzumab biosimilars Trazimera, Ogivri and Ontruzant, where similar observations to the results of comparative statistical evaluation concerning pharmacokinetic (PK) similarity of the test IMP compared to each one of both Reference IMPs with respect to the primary endpoint $AUC_{0\text{-}\infty}$ and additional endpoint $AUC_{0\text{-}t}$ of trastuzumab were made: Trazimera vs. EU Herceptin (86.03% - 98.69%), Ogivri vs. EU Herceptin (89% - 99%) and Ontruzant vs. US Herceptin (87% - 99%). These results support the conclusion of biosimilarity of EG12014 to the reference product Herceptin in terms of PK, irrespective of the observation that the 90.0% CI fell below 100% for the GMR of $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$.

In the phase 3 study EGC002, trastuzumab median concentrations pre-dose and 1-hour post-dose were comparable for the EG12014 and Herceptin treatment arms and consistent for the two arms at neoadjuvant Cycles 5, 6, 7, and 8 visits, and at the pre-surgery visit. Comparable exposures were also observed in the adjuvant phase.

The results from the two clinical studies indicate that the test product EG12014 and Herceptin are bioequivalent.

Similar PK (CL and Vc) of EG12014 and Herceptin in EBC patients is also indicated based on popPK modelling using sparse PK data from the neoadjuvant part of study ECG002. Similar steady state PK were indicated in the updated and refined model analysis using PK observations from both the neoadjuvant and adjuvant parts of study **EGC002** (D121 response). Based on examination of GoF plots, the models were able to describe the central tendency and the variability of the available data reasonably well for the current use of the models.

Analyses in special populations are not relevant in the context of a biosimilar application. No formal drug-drug interaction studies are considered needed.

2.6.4. Conclusions on clinical pharmacology

The PK data support biosimilarity of EG12014 versus the reference product Herceptin.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

Not applicable.

2.6.5.2. Main study(ies)

The EGC002 study

The pivotal phase III study **EGC002** was performed in patients with HER2-positive early breast cancer. The objective was to demonstrate therapeutic equivalence of EG12014 and EU Herceptin (clinical efficacy and safety) as neoadjuvant treatment in combination with anthracycline/paclitaxel-based systemic therapy. It is a randomised, multicentre, double-blinded study. Study completion was 20 Jan 2022.

Primary endpoint for the pivotal phase III study is the risk difference of pathological complete response. The study is divided into 2 parts: The neoadjuvant part (Part 1) consists of data until the interim analysis with database lock in February 2021, including the first randomisation. This part is the basis of this MAA. The adjuvant part (Part 2) was finished by the time of responses to the Day 120 LoQ. The applicant finalised their report by September 2022, based on database lock date 18 February 2022.

Table 14. Overview of the EGC002 study

Study number	Study population	Study design	Study objectives	Primary endpoints
EGC002	Female HER2* positive early breast cancer patients In total n=807 n=405 EG12014 treatment group n=402 Herceptin treatment group	▪ Phase 3, double-blind, randomised, multicenter study ▪ *Anthracycline-based neoadjuvant chemotherapy*: Epirubicin 90 mg/m^2, IV every 3 weeks (4 cycles) + cyclophosphamide 600 mg/m^2 IV every 3 weeks (4 cycles) ▪ *Neoadjuvant therapy*: EG12014 or Herceptin 8 mg/kg IV loading dose & 6 mg/kg IV, thereafter, in combination with paclitaxel, 175 mg/m^2 IV, every 3 weeks (4 cycles) ▪ *Adjuvant treatment (post-surgery)12 months of trastuzumab+≤20-week safety follow up:* EG12014 or Herceptin, 8 mg/kg IV loading dose and 6 mg/kg IV, thereafter, administered every 3 weeks up to 40 weeks (~9 months) ▪ Patient study duration: approximately 88 weeks (~20 months) from screening to end-of-study visit	Efficacy, safety, immunogenicity & PK To demonstrate therapeutic equivalence of EG12014 and Herceptin as part of neoadjuvant and adjuvant therapy in HER2-positive early breast cancer patients	pCR** at time of surgery

* HER2: Human epidermal growth factor receptor 2. ** pCR: pathological complete response. Defined as absence of residual invasive cancer of the resected breast specimen and all sampled lymph nodes, assessed by central laboratory.

Methods

- **Study Participants**

Inclusion criteria:

1. Female, ≥18 and ≤65 years of age.
2. Histologically confirmed invasive carcinoma of the breast (American Joint Committee on Cancer [AJCC] Stage II, IIIa).
3. Operable breast cancer with planned surgical resection of breast tumour (mastectomy or lumpectomy) and sentinel or axillary lymph nodes.
4. Ipsilateral, measurable tumour of the breast ≥2 cm in diameter, assessed by ultrasound and/or mammography.
5. HER2-positive tumour, defined as 3+ score by immunohistochemistry or fluorescence positive by FISH, confirmed at a central lab.
6. Known estrogen receptor (ER) and progesterone receptor (PrR) status at study entry.

Adequate bone marrow function, hepatic- and renal function, normal haemoglobin concentration, ECOG PS 0 or 1 are additional inclusion criteria. A normal heart function defined as LVEF ≥55% is also an inclusion criterion.

Key exclusion criteria for the **EGC002** study:

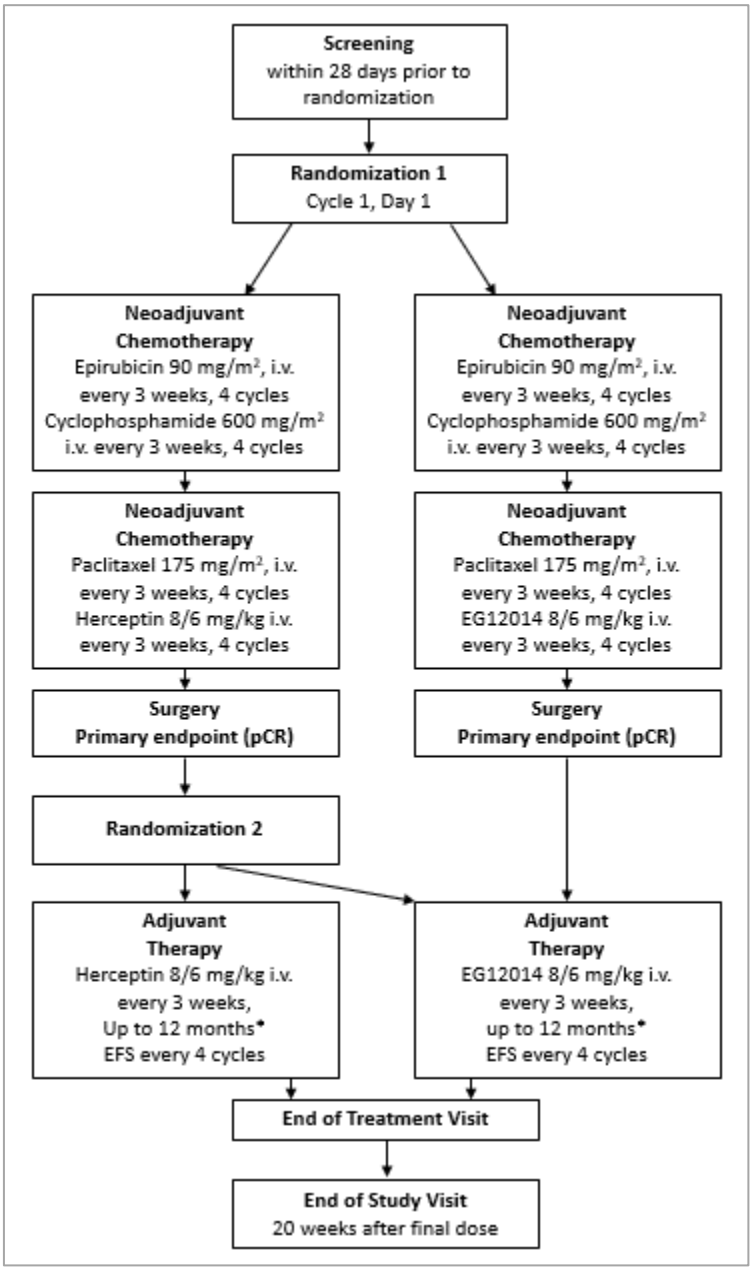
1. Bilateral breast cancer. Locally advanced breast cancer above stage T3N2M0.
2. Pregnancy or lactation or considering becoming pregnant.
3. Metastases, other than sentinel/axillary lymph nodes.

4. Previous treatment (chemotherapy, biologic therapy, radiation, or surgery) for invasive malignant disease or other concomitant active malignancy.

Additional exclusion criteria are other serious illnesses or disorders, previous treatment with Herceptin, arrhythmia, coronary heart disease or heart failure.

The EGC002 study was conducted at 89 sites in 10 countries: The Republic of Korea, Taiwan, India, Russia, Belarus, Georgia, Ukraine, South Africa, Chile, and Colombia.

Figure 8. Flow chart in the EGC002 study, with two randomisation points (Randomisation 1 and 2).



- **Treatments**

Neoadjuvant study treatment

Patients fulfilling the eligibility criteria were randomly assigned in a 1:1 ratio to one of two active, parallel trastuzumab treatment groups (EG12014 or Herceptin), as seen in

Figure 8.

1. Study subjects received four 3-week cycles Anthracycline-based chemotherapy (90 mg/m^2 epirubicin; 600 mg/m^2 cyclophosphamide; given as separate intravenously, IV, infusions). The applicant based their choice of epirubicin rather than doxorubicin on the fact that epirubicin is known to have a slightly more favourable cardiovascular toxicity profile and is more commonly applied in Canada, Europe and parts of Asia.
2. Four 3-weekly cycles paclitaxel (175 mg/m^2; IV infusion) and trastuzumab (EG12014 or EU Herceptin; loading dose: 8 mg/kg; maintenance dose: 6 mg/kg body, IV infusion).
3. Surgery consisted of breast and axillary lymph nodes resection at 3 to 6 weeks after completion of neoadjuvant chemotherapy (approximately Week 24 to 27). During surgery, either segmental or total mastectomy, samples were collected for assessment of pCR as the primary endpoint. Hole-breast radiation was offered to all patients with breast-conserving surgery.

Adjuvant study treatment following surgery

Eligibility criterion for adjuvant therapy were no sequelae, e.g., impairment in cardiac function, have occurred after neoadjuvant therapy.

Treatment with trastuzumab started 2 to 6 weeks after surgery. Patients previously administered EG12014 continued with EG12014 treatment. Those previously treated with i.v. Herceptin were randomly assigned (Randomisation 2 [1:1]) to either switch to treatment with EG12014 or to continue Herceptin. In the protocol, a 3:1 randomisation was planned in the Herceptin study arm, while the EG12014 arm was planned for a mock randomisation. The randomisation was planned to occur at visit 12, after eligibility for the adjuvant part. Interactive response technology was applied in the randomisation process, which is no further described. Treatment was continued up to 12 months of monotherapy with trastuzumab, with safety follow-up until 20 weeks after final dose of study drug. Trastuzumab (EG12014 or EU Herceptin; loading dose: 8 mg/kg; maintenance dose: 6 mg/kg, IV infusion every 3 weeks) was continued to complete 12 months of overall trastuzumab treatment.

All data from the neoadjuvant part of the EGC002 study are based on the interim analysis. Data from the adjuvant part of the EGC002 study are based on final analysis.

- **Objectives**

The primary objective for this study was to demonstrate therapeutic equivalence of EG12014 and Herceptin of EU origin in subjects with HER2+ early breast cancer.

- **Outcomes/endpoints**

The efficacy of EG12014 was determined by pathological complete response (pCR), regardless of in-situ changes, assessed by a central laboratory.

A stratified 2-sided 95% CI for the pCR probability difference was calculated for the different data sets. The null hypothesis H0 was rejected if the stratified 2-sided 95% CI for the pCR probability difference was covered by the equivalence region (-0.13; 0.13).

The secondary objectives were: Further evaluation of pCR at surgery (1. absence of residual invasive cancer and of in-situ changes. 2. Absence of invasive cancer in breast tissue only), event-free survival, EFS, overall response, ORR, and overall survival, OS, in addition to immunogenicity.

- **Sample size**

Sample size determination was based on the following considerations of the primary endpoint:

1. Neoadjuvant pCR risk difference
2. The equivalence region for pCR risk difference: [-0.13, 0.13]
3. Two-sided 95% CI for pCR risk difference
4. True pCR probability of 0.35 EG12014 and EU Herceptin based on historical data

Drop-outs during the neoadjuvant study part included in the primary statistical efficacy analysis as pCR non-responders (same for patients with missing pCR data due to other reasons).

These assumptions resulted in a planned sample size of 400 patients in the EG12014 treatment group and 400 patients in the EU Herceptin treatment group (in total 800 patients) and a power of approximately 95% for the FAS-neo, and 93% for the PPS-neo, assuming 5% of FAS-neo patients were excluded from the PPS-neo. The sample size was discussed with EMA prior to study conduct (EMA/CHMP/SAWP/306598/2017).

- **Randomisation and Blinding (masking)**

The randomization scheme and codes were not provided in the interim Clinical Study Report (CSR Part 1). This information was included in the final Clinical Study Report (CSR Parts 1 + 2).

The EGC002 study includes two points of randomisation: In the allocation to neoadjuvant treatment (study part 1) and to adjuvant treatment (study part 2). The randomisation was done during a visit, at a point where all screening procedures were completed. Randomisation was stratified by tumour stage (stage II or IIIa), ER status and geographic region.

At the end of study part 1, a second randomisation was planned. This randomisation happened at visit no. 12, either a randomisation or a sham/mock-randomisation in a 1:1 ratio. Study participants who had complications of treatment in the neoadjuvant part were excluded. In the second randomisation, interactive response technology was applied. The two study arms were further divided into three arms in part two (as seen in the study flow chart, Figure 8). The second randomisation affected only study subjects in the Herceptin arm, while the study subjects in the EG12014 arm were involved in a sham-randomisation. According to the protocol, a randomisation ratio of 3:1 was originally planned. However, the second randomisation was later changed to a 1:1 ratio. This randomisation in the Herceptin arm is termed the switch strategy.

- **Statistical methods**

Analysis sets, neoadjuvant part (Part 1)

Full Analysis Set (FAS-neo): All patients randomized at the start of the neoadjuvant study part, analysed according to the randomized treatment group (Herceptin or EG12014). Per-Protocol Set (PPS-neo): All patients in the FAS-neo who did not experience any major protocol deviations having a potential impact on the primary efficacy endpoint pCR up to the end of the neoadjuvant study part, who received at least one dose of study drug in the neoadjuvant part and underwent surgery.

Safety Set (SAF-neo): All patients in the FAS-neo who received at least one dose of study treatment in the neoadjuvant study part. Patients will be analysed according to the actual study drug received (EG12014, Herceptin, or none). If a patient receives both EG12014 and Herceptin in error in the neoadjuvant study part, then the treatment group assigned for the statistical analysis will be that of the first dose of study drug they received in the neoadjuvant study part.

PK Set (PK-neo): All patients in the SAF-neo who had at least one study drug concentration recorded after administration of study drug (Herceptin or EG12014) in the neoadjuvant study part.

Analysis sets for neoadjuvant + adjuvant part (Part 1 + 2)

Full Analysis Set (FAS): All patients randomized at the start of the neo-adjuvant study part. Patients will be analyzed according to the randomized treatment group (Herceptin or Herceptin/EG12014, or EG12014).

Per-Protocol Set (PPS): All patients in the FAS who did not experience any major protocol deviations having a potential impact on the primary efficacy endpoint pCR and received at least one dose of study drug in both the neoadjuvant and adjuvant study parts and underwent surgery.

Primary efficacy analysis

To analyse therapeutic equivalence, the difference in pCR proportion between the two study arms was estimated. Therapeutic equivalence was claimed when the stratified 2-sided Newcombe 95% confidence interval (CI) for the pCR probability difference was covered by the equivalence region (-0.13; 0.13). Therapeutic equivalence regions for pCR probability difference were justified by fixed effects meta-analyses of existing studies comparing Herceptin plus chemotherapy against chemotherapy alone, according to protocol. The analysis was stratified by tumor stage (stage II or stage IIIa), ER status (positive or negative) and geographic region. The result was compared to the corresponding 95% confidence interval to equivalence margins. The analysis was done in both the intention-to-treat and the per-protocol population.

The null hypothesis for the primary statistical analysis

H0: $|\pi EG - \pi Her| \geq 0.13$ ("pCR probabilities differ by at least 0.13") was tested against the respective alternative hypothesis:

HA: $-0.13 < \pi EG - \pi Her < 0.13$ ("pCR probabilities differ by less than 0.13").

An equivalence region of (-0.13; 0.13) for pCR probability differences was justified in two randomized studies of Herceptin plus chemotherapy versus chemotherapy alone, as seen in Table 14. Treatment effects expressed as pCR probability differences were estimated as 0.389 in the Buzdar et al. study and 0.190 in the NOAH/Gianni et al. study.

Table 15. Meta-analysis for the equivalence margins of pCR

Study	Herceptin + Chemotherapy			Chemotherapy alone		
	Number of responders	Number of patients	Estimated pCR probability	Number of responders	Number of patients	Estimated pCR probability
Buzdar et al (7)	15	23	0.652	5	19	0.263
NOAH/Gianni (6)	45	117	0.385	23	118	0.195

Interim Analyses

Interim analysis for efficacy and safety after completion of the neoadjuvant part was conducted on the 12th of February 2021. Time of interim analysis was planned to be when all data from the neoadjuvant part were at the clinical research organization. Further, interim analysis was planned when all related data queries had been resolved, and the assignment of participants to the analysis sets had been completed, the study was unblinded to a dedicated team of statisticians, otherwise not involved in study operations. The entire study team, site personnel, participants, and third-party providers remained blinded. The Sponsor was partially unblinded for the interim clinical study report (Part 1) and regulatory submission document preparation. All data from the neoadjuvant part and the available safety data from

the adjuvant part were analysed and reported in CSR part 1. Final analyses were reported in CSR part 1+2.

Multiplicity

There is no need for any multiplicity adjustment as only one pre-specified hypothesis linked to the primary objective was tested for the EMA analysis. Moreover, no hypothesis testing was planned for the secondary endpoints and the statistics were purely descriptive.

Results

- **Participant flow**

Enrolment: A total of 1048 participants were screened for enrolment in the study. Of these, 202 participants were considered screening failures, all of which were due to ineligibility (reasons for ineligibility are not described).

Table 16 Summary of Participants Screened (All Screened Participants)

Participant Disposition	**Overall**
Screened	1048
Screening Failure	241
Reason for screening failure:	
Consent withdrawn	36 (14.9%)
Patient is not eligible	202 (83.8%)
Adverse Event	0 (0.0%)
Death	0 (0.0%)
Other[a]	3 (1.2%)
Enrolled patients	807 (77.0%)

a "Other" reasons for screen failure: One Participant was not eligible due to multifocal tumor; another participant was not eligible due to long lapse since biopsy and informed consent form signature; another participant was not eligible due to being lost to follow-up (participant did not visit the hospital).

Database lock: February 2022

In total, 39 participants who met eligibility criteria were not enrolled.

Table 17 Disposition of Participants, by Treatment Arm (FAS-neo) – Entire Study (at the First Randomization)

Participant Disposition	**EG12014 (N=405)**	**Herceptin (N=402)**	**Overall (N=807)**
Enrolled	405 (100%)	402 (100%)	807 (100%)
Completed the Neoadjuvant Part[a]	389 (96.0%)	380 (94.5%)	769 (95.3%)
Completed the Study[b]	345 (85.2%)	336 (83.6%)	681 (84.4%)
Study Treatment Discontinuation[c]	19 (4.7%)	26 (6.5%)	45 (5.6%)
Withdrawn from the Study[c]	19 (4.7%)	26 (6.5%)	45 (5.6%)
Randomized into Neoadjuvant Part	405 (100%)	402 (100%)	807 (100%)
Received Chemotherapy in the Neoadjuvant Part	404 (99.8%)	401 (99.8%)	805 (99.8%)

Participant Disposition	EG12014 (N=405)	Herceptin (N=402)	Overall (N=807)
Received Study Drug in the Neoadjuvant Part	399 (98.5%)	398 (99.0%)	797 (98.8%)
Underwent surgery	392 (96.8%)	387 (96.3%)	779 (96.5%)
Randomized into Adjuvant Part	386 (95.3%)	376 (93.5%)	762 (94.4%)
Received Study Treatment in the Adjuvant Part	386 (95.3%)	376 (93.5%)	762 (94.4%)
Completed the follow-up period (20 weeks after final dose of study drug)	358 (88.4%)	353 (87.8%)	711 (88.1%)

Note: The table is stratified by planned treatment arm at first randomization.

a The Neoadjuvant Part (Part I) began at Visit 2 (Neoadjuvant Cycle 1 Day 1 visit) and ended at Visit 11 (post-surgery visit).

b Includes participants who completed the EOS visit.

c Includes participants who completed the Neoadjuvant Part, but who also discontinued study treatment and/or withdrew from the study prior to randomization into the Adjuvant Part.

Database lock: 18 February 2022

In sum, 807 subjects were enrolled in the study, of which 405 in the EG12014 arm and 402 in the Herceptin arm. In **Table 18** baseline characteristics and demographics of the study participants are shown.

Allocation: Randomisation of participants to the neoadjuvant part of the study, occurred at visit 2 after all screening procedures had been performed and eligibility for the study had been confirmed. After surgery, patients were eligible for adjuvant therapy with blinded EG12014 or Herceptin monotherapy if no sequelae have occurred after neoadjuvant therapy, in particular cardiac function.

For the adjuvant study part, (mock) randomisation of patients to adjuvant study treatments occurred at visit 12 after eligibility for the adjuvant study part has been confirmed. For any (mock) randomisation of patients, the investigator applied an interactive response technology.

Table 18 Disposition of Participants, by Treatment Arm (FAS) – Entire Study (at the Second Randomization)

Participant Disposition	EG12014 (N=405)	Herceptin/ EG12014 (N=188)	Herceptin (N=214)	Overall (N=807)
Enrolled	405 (100%)	188 (100%)	214 (100%)	807 (100%)
Completed the Adjuvant Part[a]	358 (88.4%)	179 (95.2%)	173 (80.8%)	710 (88.0%)
Completed the Study[b]	345 (85.2%)	168 (89.4%)	168 (78.5%)	681 (84.4%)
Study Treatment Discontinuation	47 (11.6%)	9 (4.8%)	41 (19.2%)	97 (12.0%)
Withdrawn from the Study	60 (14.8%)	20 (10.6%)	46 (21.5%)	126 (15.6%)
Randomized into Neoadjuvant Part	405 (100%)	188 (100%)	214 (100%)	807 (100%)

Participant Disposition	EG12014 (N=405)	Herceptin/ EG12014 (N=188)	Herceptin (N=214)	Overall (N=807)
Received Chemotherapy in the Neoadjuvant Part	404 (99.8%)	188 (100%)	213 (99.5%)	805 (99.8%)
Received Study Drug in the Neoadjuvant Part	399 (98.5%)	188 (100%)	210 (98.1%)	797 (98.8%)
Underwent surgery	392 (96.8%)	188 (100%)	199 (93.0%)	779 (96.5%)
Randomized into Adjuvant Part	386 (95.3%)	188 (100%)	188 (87.9%)	762 (94.4%)
Received Study Treatment in the Adjuvant Part	386 (95.3%)	188 (100%)	188 (87.9%)	762 (94.4%)
Completed the follow-up period (20 weeks after final dose of study drug)	358 (88.4%)	171 (91.0%)	182 (85.0%)	711 (88.1%)

Source: Table 14.1.2.2

Note: The table is stratified by planned treatment arm at second randomization.

[a] The Adjuvant Part (Part II) began at Visit 12 (Adjuvant Cycle 1 Day 1 visit) and ended at Visit 24 (Adjuvant Cycle 13 Day 1 visit).

[b] Participant completed the EOS visit.

Database lock: 18 February 2022

Protocol deviations: Protocol deviations involved 666 subjects (83%) in the neoadjuvant part of the study (FAS-neo). The total number of protocol deviations of the neoadjuvant part of the study were 2426. Major protocol deviations included 129 (16%) study participants, with 164 (7%) events in total. Major protocol deviation included (in descending order) study procedure or assessment, randomisation procedure, study medication, visit completion or timing, serious adverse events, adverse events, inclusion/exclusion criteria or informed consent.

In the adjuvant part, overall protocol deviations involved 338 subjects (44%), with a total number of 634 deviations (FAS). Major protocol deviations were 103 in 80 study participants.

- **Recruitment**

The EGC002 study was initiated on 16 October 2018. The neoadjuvant part was defined to start at visit no. 2 and end at the post-surgery visit, no. 11. The study was completed on 20 January 2022.

- **Conduct of the study**

There were several changes in the study conduct, which were implemented by different protocol amendments. The main changes are as follows:

- Adjuvant study part: Change in randomisation scheme for randomisation 2 (1:1 ratio of participants previously treated with Herceptin during the neoadjuvant part to receive EG12014 or Herceptin. The ratio was 3:1 prior to the change, with 75% receiving EG12014 and 25% Herceptin).
- Planned recruitment was changed from approximately 84 centres

- Clarification of instruction in participants who were clinically node-negative from requirement to a recommendation to be further assessed by sentinel lymph node biopsy.
- Clarification of the duration of treatment with the study drug.
- Changes to the biostatistics section with a widening of the equivalence region from (-0.11, 0.11) to (-0.13, 0.13) and submission of the neoadjuvant part before the adjuvant part was completed. The widening of the equivalence margins was done by the sponsor, for the reason that other trastuzumab biosimilars had similar or wider equivalence margins.
- Central Pathology Charter removed as appendix.

- **Baseline data**

The demographic and baseline characteristics of the treatment groups (EG12014 and Herceptin) are presented in Table 18.

Table 19. Patient demographics and baseline characteristics by treatment arm - Entire study (FAS).

Parameter	Statistic	EG12014 (N=405)	Herceptin/ EG12014 (N=188)	Herceptin (N=214)	Overall (N=807)
Age (yrs.)	n	405	188	214	807
	nmiss	0	0	0	0
	Mean (SD)	50.5 (9.72)	49.3 (9.06)	49.7 (9.87)	50.0 (9.61)
	Median	51.0	51.0	50.0	51.0
	Q1/ Q3	44.0/ 59.0	43.5/ 57.0	43.0/ 58.0	44.0/ 58.0
	Minimum/ Maximum	23/ 65	24/ 65	26/ 65	23/ 65
Age Category (years) [n (%)]	<65	387 (95.6%)	184 (97.9%)	207 (96.7%)	778 (96.4%)
	=65	18 (4.4%)	4 (2.1%)	7 (3.3%)	29 (3.6%)
Race [n (%)]	N of Patients	404	188	214	806
	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)
	Asian	26 (6.4%)	14 (7.4%)	17 (7.9%)	57 (7.1%)
	Black or African American	6 (1.5%)	2 (1.1%)	4 (1.9%)	12 (1.5%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White	372 (92.1%)	171 (91.0%)	192 (89.7%)	735 (91.2%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Reported	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.1%)
Ethnicity [n (%)]	N of Patients	405	188	214	807
	Hispanic or Latino	13 (3.2%)	4 (2.1%)	4 (1.9%)	21 (2.6%)
	Not Hispanic or Latino	390 (96.3%)	184 (97.9%)	209 (97.7%)	783 (97.0%)
	Unknown	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Not Reported	1 (0.2%)	0 (0.0%)	1 (0.5%)	2 (0.2%)
Sex [n (%)]	N of Patients	405	188	214	807
	Male	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Female	405 (100%)	188 (100%)	214 (100%)	807 (100%)
Childbearing Potential [n (%)]	N of Patients	405	188	214	807
	Yes	183 (45.2%)	93 (49.5%)	99 (46.3%)	375 (46.5%)
	No, Surgical Sterilization or Hysterectomy	30 (7.4%)	19 (10.1%)	19 (8.9%)	68 (8.4%)
	No, Post-menopausal more than 1 year	192 (47.4%)	76 (40.4%)	96 (44.9%)	364 (45.1%)
Pregnancy Test Results [n (%)]	N of Patients	184	93	101	378

Note: The table is stratified by planned treatment arm at second randomization.

- **Numbers analysed**

Numbers of participants in the different data sets [Full analysis set (FAS) and per-protocol set (PPS) in the neoadjuvant part (part 1)] are shown in the table below.

Table 20. Data Sets analysed by treatment arm – entire study. Source: CSR Part 1+Part 2.

Participant Populations	EG12014 (N=405)	Herceptin/ EG12014 (N=188)	Herceptin (N=214)	Overall (N=807)
FAS[a]	405 (100%)	188 (100%)	214 (100%)	807 (100%)
PPS[b]	372 (91.9%)	179 (95.2%)	177 (82.7%)	728 (90.2%)
SAF[c]	404 (99.8%)	188 (100%)	213 (99.5%)	805 (99.8%)
PKS-neo[d]	399 (98.5%)	188 (100%)	210 (98.1%)	797 (98.8%)

a. FAS: All participants randomised at the start of the neoadjuvant part. b. PPS: All participants in the FAS who did not experience any major protocol deviations having a potential impact on the primary efficacy endpoint pCR. c. SAF: All participants in the FAS who received at least one dose of study treatment. d. PKS-neo: All participants in the SAF-neo, who had at least 1 study drug concentration recorded after administration of study drug.

Exposure

Table 21. Exposure to EG12014 or Herceptin, by treatment arm (SAF-neo) - Neoadjuvant Part. Source: CSR Part 1+Part 2.

Statistic	EG12014 (N=399)	Herceptin (N=398)	Overall (N=805)
Overall Cycle			
Planned Total Dose (mg)			
n	399	398	797[a]
n missing	0	0	0
Mean (SD)	1911.67 (379.228)	1905.00 (436.220)	1908.34 (408.440)
Median	1890.00	1853.00	1878.00
Q1/Q3	1647.0/2151.0	1578.4/2182.0	1618.0/2161.0
Minimum/Maximum	1100/3682	624/3470	624/3682
Actual Dose Administered (mg)			
n	399	398	797[a]
n missing	0	0	0
Mean (SD)	1911.67 (379.229)	1905.00 (436.220)	1908.34 (408.441)
Median	1890.00	1853.00	1878.00
Q1/Q3	1647.0/2151.0	1578.4/2182.0	1618.0/2161.0
Minimum/Maximum	1100/3682	624/3470	624/3682
Dose Delayed	104 (26.1%)	107 (26.9%)	211 (26.5%)
Reason for the delay:			
COVID-19	14 (3.5%)	13 (3.3%)	27 (3.4%)
Left Ventricular Ejection Fraction Decreased	3 (0.8%)	1 (0.3%)	4 (0.5%)
Non-Hematological Toxicity Grade III-IV	7 (1.8%)	8 (2.0%)	15 (1.9%)
Other[b]	89 (22.3%)	87 (21.9%)	176 (22.1%)
Deviation	4 (1.0%)	3 (0.8%)	7 (0.9%)

Table 22. Exposure to EG12014 or Herceptin, by treatment arm (SAF-neo) - Adjuvant Part. Source: CSR Part 1+Part 2.

Statistic	EG12014 (N=386)	Herceptin/ EG12014 (N=188)	Herceptin (N=188)	Overall (N=762)
Overall Cycle				
Planned Total Dose (mg)				
n	386	188	188	762
n missing	0	0	0	0
Mean (SD)	5792.58 (1330.459)	5785.38 (1240.890)	5840.99 (1561.199)	5802.75 (1368.692)
Median	5836.00	5686.90	5887.00	5813.00
Q1/Q3	4943.0/6629.0	4884.5/6494.5	4914.0/6813.0	4915.0/6624.0
Minimum/Maximum	840/11630	2640/9880	488/10642	488/11630
Actual Dose Administered (mg)				
n	386	188	188	762
n missing	0	0	0	0
Mean (SD)	5792.58 (1330.459)	5784.57 (1240.669)	5840.99 (1561.199)	5802.55 (1368.646)
Median	5836.00	5686.90	5887.00	5813.00
Q1/Q3	4943.0/6629.0	4884.5/6494.5	4914.0/6813.0	4915.0/6624.0
Minimum/Maximum	840/11630	2640/9880	488/10642	488/11630
Dose Delayed	132 (34.2%)	58 (30.9%)	75 (39.9%)	265 (34.8%)
Reason for the delay:				
COVID-19	55 (14.2%)	19 (10.1%)	31 (16.5%)	105 (13.8%)
Left Ventricular Ejection Fraction Decreased	3 (0.8%)	4 (2.1%)	10 (5.3%)	17 (2.2%)
Non-Hematological Toxicity Grade III-IV	1 (0.3%)	4 (2.1%)	0 (0.0%)	5 (0.7%)
Other[a]	88 (22.8%)	43 (22.9%)	44 (23.4%)	175 (23.0%)
Deviation	4 (1.0%)	4 (2.1%)	5 (2.7%)	13 (1.7%)

- **Outcomes and estimation**

The primary efficacy endpoint was pathological complete response (pCR) between EG12014 and Herceptin at the time of surgery. Pathological complete response was defined as absence of residual cancer, regardless of ductal carcinoma in situ. The primary analysis for equivalence was a risk difference test (Newcombe approach) including a 95% CI with equality margins of (-0.13; 0.13). The risk difference calculation was stratified by:

- Tumour stage
- ER status
- Geographic region

The risk difference (95% CI) for EG12014 vs Herceptin was -0.026 (95% CI: -0.089 to 0.037) for the FAS-neo and -0.024 (95% CI: -0.091 to 0.043) for the PPS-neo, as seen in Table 22. The 95% CIs contained 0 and fell within the pre-defined equivalence margins (-0.13, 0.13).

Table 23. Primary efficacy endpoint; pathological complete response of neoadjuvant treatment at the time of surgery by treatment arm in the two data sets. Source: Module 5, Section 5.3.5.1. CSR, section 11.1. Table 11-1.

Data Set		EG12014	Herceptin	Overall
FAS-neo		**(N=405)**	**(N=402)**	**(N=807)**
	Number of responders	191 (47.2%)	192 (47.8%)	383 (47.5%)
	Number of non-responders	200 (49.4%)	194 (48.3%)	394 (48.8%)
	Number of missing assessment	14 (3.5%)	16 (4.0%)	30 (3.7%)
	Responder Proportion [95% CI]	0.472 [0.423, 0.520]	0.478 [0.429, 0.526]	0.475 [0.440, 0.509]
	Risk Difference (EG12014 versus Herceptin) (95% CI)[a]			-0.004 (-0.072, 0.065)
PPS-neo		**(N=377)**	**(N=365)**	**(N=742)**
	Number of responders	186 (49.3%)	186 (51.0%)	372 (50.1%)
	Number of non-responders	191 (50.7%)	179 (49.0%)	370 (49.9%)
	Number of missing assessment	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Responder Proportion [95% CI]	0.493 [0.443, 0.544]	0.510 [0.458, 0.561]	0.501 [0.465, 0.537]
	Risk Difference (EG12014 versus Herceptin) (95% CI)[a]			-0.007 (-0.079, 0.064)

Abbreviations: FAS-neo, full analysis set in the neoadjuvant part. PAS-neo, per protocol set, neoadjuvant part.

Secondary efficacy endpoints of resected specimen

Secondary efficacy endpoints related to resected specimen were pathological complete response without ductal carcinoma in situ and pathological complete response as absence of invasive cancer in breast tissue only. For the Neoadjuvant Part (FAS-neo and PPS-neo), results from secondary efficacy analysis of pCR without DCIS were a risk difference of -0.026 [95% CI: -0.089 to 0.037] for the FAS-neo and -0.024 [95% CI: -0.091 to 0.043] for the PPS-neo). Similarly, results from analysis of pCR as absence of invasive cancer in breast tissue only were a risk difference of -0.001 [95% CI: -0.070 to 0.067] for the FAS-neo and -0.007 [95% CI: -0.079 to 0.065] for the PPS-neo). See Table 23.

Event-free survival (EFS) and overall survival (OS)

As of the interim analysis, 13 participants in the EG12014 arm and 22 participants in the Herceptin arm met the definition for EFS. For OS, three participants in the EG12014 arm and four participants in the Herceptin arm met the definition. Because of the small percentage (≤5.5%) of participants with EFS events in each treatment arm, no Kaplan-Meier estimates could be calculated. Similarly for OS, (≤ 1.0%) of participants with events in each treatment arm, no Kaplan-Meier estimates could be calculated.

At the final analysis, 25 (6.2%) participants in the EG12014 arm and 30 (7.5%) participants in the Herceptin arm met the definition of an event in the EFS analysis. For OS, 4 (1.0%) participants in the EG12014 arm and 5 (1.2%) participants in the Herceptin arm met the definition of an event. The HR estimate for EFS was 0.775 (95% CI 0.45, 1.33) and for OS 0.74 (95% CI: 0.20, 2.77), respectively.

Objective response rate

ORR is defined as PR or CR according to RECIST v1.1 in FAS-neo analysis set in neoadjuvant treatment. The overall ORR (PR and CR categories combined) (95% CI) were for the EG12014: 83.8% [95% CI: 79.8% to 87.4%] and for Herceptin 83.6% [95% CI: 79.5% to 87.1%] treatment arms. The overall

RECIST response in PPS-neo analysis set was 83.8% (95% CI: 79.7% to 87.4%]) for the EG12014 arm and 84.9% (95% CI: 80.7% to 88.4%) for the Herceptin arm.

- **Ancillary analyses**

In two ancillary analyses the result differed from the primary endpoint:

- In the subgroup analysis of age, the result differed: For participants equal to 65 years of age (n =18 for the EG12014 arm and n = 11 for the Herceptin arm), the proportion of responders to EG12014 was 4/18 (22 %) and for Herceptin 5/11 (45 %). The subgroup's risk difference (95% CI) was -0.449 (95% CI: -0.732 to -0.067); the 95% CI did not contain 0.
- The number of progesterone receptor positive responders in the two study arms were for EG12014 n=56 and Herceptin n=78. The risk difference (95% CI) in the PrR positive category of EG12014 vs Herceptin was -0.071 (95% CI: -0.170 to 0.031). The 95% CI contained 0 but was outside the lower bound of the pre-defined equivalence margins (-0.13, 0.13).

In the other subgroup analysis, the results were supporting the primary endpoint.

- **Summary of main efficacy results**

The following Table 23 summarises the efficacy results from the main study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 24. Summary of efficacy for trial EGC002

Title: A Phase III, Randomized, Multicentre, Double-blind Study to Compare Therapeutic Equivalence (Efficacy and Safety) of EG12014 and EU Herceptin as Neoadjuvant Treatment in Combination with Anthracycline/Paclitaxel-based Systemic Therapy in Patients with HER2-positive Early Breast Cancer		
Study identifier	**EG12014 – EGC002** EudraCT Number: 2017-003973-33	
Design	This is a multicentre, randomised, double-blind equivalence study to compare the efficacy and safety of EG12014 with Herceptin as neoadjuvant treatment for 12 weeks, followed by surgery and subsequent EG12014 or Herceptin adjuvant treatment for up to 12 months.	
	Duration of main (Neoadjuvant) Phase: Duration of Run-in Phase: Duration of Adjuvant Phase:	~30 weeks not applicable ~40 weeks
Hypothesis	Equivalence	
Treatments groups	EG12014	EG12014 Neoadjuvant Part, EG12014 Adjuvant Part N 1st randomisation (Neoadjuvant Part): 405 N 2nd randomisation (pseudorandomisation): 386

	Herceptin		Herceptin Neoadjuvant Part, Herceptin Adjuvant Part N 1st randomisation (Neoadjuvant Part): 402 N 2nd randomisation (Adjuvant Part): 188
	Herceptin/EG12014		Herceptin Neoadjuvant Part, EG12014 Adjuvant Part N 2nd randomisation (Adjuvant Part): 188 (*1st randomisation not applicable*)
Endpoints and definitions	Primary endpoint	pCR (ypT0/is ypN0)	pCR at time of surgery, where pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen (regardless of ductal carcinoma in situ [DCIS]) and all sampled sentinel and/or axillary lymph nodes (ypT0/is ypN0), as assessed by central laboratory.
	Secondary endpoint	pCR (ypT0 ypN0)	pCR at the time of surgery, where pCR is defined as the absence of residual invasive cancer and of DCIS (ypT0 ypN0) from breast tissue and sentinel/axillary lymph nodes, as assessed by central laboratory.
	Secondary endpoint	pCR (ypT0/is)	pCR at the time of surgery, defined as the absence of invasive cancer in breast tissue only (ypT0/is), as assessed by central laboratory.
	Secondary endpoint	Objective response	Objective response prior to surgery, defined as partial response or complete response according to RECIST v1.1.
Study initiation date	16 Oct 2018		
Study completion date	20 Jan 2022		
Interim Database lock	12 Feb 2021		
Final Database lock	18 Feb 2022		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	pCR (ypT0/is ypN0) at time of surgery for the Full Analysis Set Neoadjuvant Part (FAS-neo) and the Per Protocol Set Neoadjuvant Part (PPS-neo)		
Descriptive statistics and estimate variability	Analysis set	FAS-neo	PPS-neo
	Number of subjects	807	742
	Risk difference (EG12014 versus Herceptin) (95% CI)	-0.004 (-0.072, 0.065)	-0.007 (-0.079, 0.064)

	Responder proportion (95% CI)	0.475 (0.440, 0.509)	0.501 (0.465, 0.537)
Notes	For the Neoadjuvant Part of the study, the most common reasons (reported in > 10% of participants in either arm) for discontinuation of study treatment were withdrawal by subject, disease progression, AE, and protocol non-compliance; and for withdrawal from the study were withdrawal by subject, disease progression, AE, and death.		
Analysis description	**Secondary Analysis**		
Analysis population and time point description	pCR (ypT0 ypN0) at time of surgery for the Full Analysis Set Neoadjuvant Part (FAS-neo) and the Per Protocol Set Neoadjuvant Part (PPS-neo)		
Descriptive statistics and estimate variability	Analysis set	FAS-neo	PPS-neo
	Number of subjects	807	742
	Risk difference (EG12014 versus Herceptin) (95% CI)	-0.026 (-0.089, 0.037)	-0.024 (-0.091, 0.043)
	Responder proportion (95% CI)	0.297 (0.266, 0.329)	0.315 (0.282, 0.349)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	pCR (ypT0/is) at time of surgery for the Full Analysis Set Neoadjuvant Part (FAS-neo) and the Per Protocol Set Neoadjuvant Part (PPS-neo)		
Descriptive statistics and estimate variability	Analysis set	FAS-neo	PPS-neo
	Number of subjects	807	742
	Risk difference (EG12014 versus Herceptin) (95% CI)	-0.001 (-0.070, 0.067)	-0.007 (-0.079, 0.065)
	Responder proportion (95% CI)	0.509 (0.475, 0.544)	0.536 (0.501, 0.572)
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Objective response prior to surgery for the Full Analysis Set Neoadjuvant Part (FAS-neo) and the Per Protocol Set Neoadjuvant Part (PPS-neo)		
Descriptive statistics and estimate variability	Analysis set	FAS-neo	PPS-neo

	Number of subjects	807	742
	Overall RECIST response (95% CI) EG12014	83.8% (79.8%, 87.4%)	83.8% (79.7%, 87.4%)
	Overall RECIST response (95% CI) Herceptin	83.6% (79.5%, 87.1%)	84.9% (80.7%, 88.4%)

2.6.5.3. Clinical studies in special populations

Not applicable

2.6.5.4. In vitro biomarker test for patient selection for efficacy

HER2-positivity of the tumour was defined as 3+ score by immunohistochemistry (IHC) or fluorescence positive by FISH. The result was confirmed centrally, according to the applicant. In the HER2 IHC test, a Herceptest from Dako was applied. In the case of the FISH-test, a test from Pathvision, Vysis, was utilised. Both tests are commercially available.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program to show potential biosimilarity between EG12014 and Herceptin is, beside a pivotal PK-study (**EGC001**), also based on a phase III study (**ECG002**) comparing the efficacy and safety of EG12014 and Herceptin in neoadjuvant and adjuvant treatment in HER2-positive early breast cancer.

A single pivotal phase III equivalence study comparing the test- and reference product was considered adequate by CHMP to support the biosimilar application. Overall, the in- and exclusion criteria as defined are considered adequate in face of the investigational setting and questions. As noted later, the study design includes a second randomisation step at the start of the adjuvant phase. The demographic and baseline characteristics including mean age, race/ethnicity (with approximately 90% Caucasian in each treatment arm), childbearing potential, tumour stage (with the majority [>83%] in tumour stage II), geographic region, hormone receptor status and time from date of diagnosis were comparable between the two treatment groups (EG12014 and Herceptin) in the different data sets. Mostly, the study is in line with the CHMP guidance: the applicant has chosen a patient population with early breast cancer (rather than metastatic breast cancer), which is considered a more sensitive population for evaluating biosimilarity. Furthermore, the CHMP accepted widening of the equivalence margins, that should be clinically and statistically justified, however. The second randomisation, prior to the adjuvant phase, also

termed 'the switch strategy', was not endorsed by the CHMP. Consequently, the randomisation ratio was changed by the applicant from 3:1 to 1:1 (i.e., from 75% of the participants switching from Herceptin to EG12014, to 50% switching from Herceptin to EG12014).

The risk for loss of long-term data was considered present at the time of application. The applicant claimed that the switch strategy may demonstrate interchangeability between the reference product and EG12014. In addition, the switch strategy could increase the exposure of EG12014 in the studied population. The risk of compromising safety and survival data in subjects who received Herceptin and EG12014, is considered reduced by a sufficient number of study subjects in each treatment group. The safety and survival profile between study and reference product seem comparable and there is no need to further analyse study subjects in this perspective. The study was conducted in different regions of the world, although predominantly subjects of Caucasian origin were included.

Efficacy data and additional analyses

Pathologic complete response (pCR) was chosen as primary efficacy endpoint for biosimilarity assessment and was considered acceptable and sensitive for this purpose.

The equivalence margins of pCR have been discussed in several scientific advice procedures, and clinical and statistical justification has been warranted. The margins applied in EGC002 are comparable to, or even narrower than, equivalence margins in previous approved biosimilars, [i.e., up to (-0.15, 0.15)]. The equivalence margins are considered acceptable. Further discussion of the efficacy results is not decisive in a study of biosimilarity, and no further data are requested.

The EGC002 trial has demonstrated that the risk difference of pCR at the time of surgery was within its predefined margins of ±13%. However, in the progesterone receptor positive responders, the result did not support similarity since the estimated risk difference was outside the lower bound of the pre-defined equivalence margins (data not shown).

Secondary efficacy endpoints related to resected specimen (pathological complete response without ductal carcinoma in situ and pathological complete response as absence of invasive cancer in breast tissue only) had comparable findings in FAS-neo and PPS-neo analysis sets. The 95% CIs contained 0 and fell within the pre-defined equivalence margins (-0.13, 0.13). Overall, results of secondary surgery-related endpoints of the study, sensitivity analyses and most of the sub-group analyses reflect the primary endpoint and are also supporting therapeutic similarity (see Table 23). As anticipated after surgical and medical treatment, the overall survival is expected to be high and hence not ideal to distinguish absence of therapeutical similarity relatively early after treatment. Maturity of EFS and OS are <8% and <2%, respectively. No indications of any detrimental effects are seen in the study arms.

2.6.7. Conclusions on the clinical efficacy

The efficacy study met its primary endpoint with the 95% CI of the treatment difference contained within the equivalence margins. Overall, secondary endpoints also supported the outcome of therapeutic equivalence of EG12014 to Herceptin in both a neoadjuvant and an adjuvant setting. In the subgroup analysis there are some opposing results, with uncertain meaning. Equivalence is not unambiguously supported in some subgroups, but for these, sample sizes are relatively small and hence it is difficult to conclude on its statistical or clinical relevance (Table 23). This is the case for subjects with positive progesterone receptor, oestrogen receptor negative subjects and subjects with breast cancer stage IIIa. Event-free and overall survival are, as expected, highly immature. Apart from these inconsistencies, that may be anticipated and unremarkable, the submitted efficacy data support therapeutic similarity.

The robustness of the results is determined by the primary endpoint of the study, pCR, which is frequently applied in studies of early breast cancer, even if pCR has obvious limitations. Pragmatically

speaking, pCR is believed to be a sensitive endpoint and considered appropriate for demonstration of biosimilarity of trastuzumab in HER2 positive early breast cancer. Overall, biosimilarity between EG12014 and reference product is supported by clinical efficacy data.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Phase 1 Study EGC001

In the completed PK-study **EGC001**, the safety set included 84 enrolled healthy male subjects which received a single dose of trastuzumab (6 mg/kg as IV infusion). Twenty-eight (28) of the 84 subjects received EG12014, 28/84 of subjects received EU Herceptin and 28/84 subjects received US Herceptin.

Two (2) subjects discontinued prematurely from the study due to severe adverse events (SAEs)/adverse events (AEs), one subject who received EU Herceptin and one subject who received US Herceptin.

Phase 3 Study EGC002

EGC002 is a study where HER2-positive EBC patients (n=807) were randomized in a 1:1 ratio to receive trastuzumab (EG12014 or EU Herceptin with a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg) for four cycles every three weeks (12 weeks in total) in the neoadjuvant study part, prior to surgery. Following surgery, the patients received trastuzumab (with a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg) every 3 weeks to complete 12 months of overall trastuzumab treatment. Patients treated neoadjuvantly with EG12014, continued treatment with EG12014 in the adjuvant setting; patients treated neoadjuvantly with EU Herceptin, were randomized in a 1:1 ratio to either continue treatment with EU Herceptin or to switch to EG12014 treatment in the adjuvant setting. The overall trastuzumab treatment duration did not exceed 12 months.

Patients received four 3-weekly cycles anthracycline (AC)-based chemotherapy (90 mg/m2 epirubicin; 600 mg/m2 cyclophosphamide; given as separate IV infusions) before start of the trastuzumab therapy.

Trastuzumab (EG12014 or EU Herceptin) was administered in combination with paclitaxel (175 mg/m^2 IV infusion) in the neoadjuvant study part, and as single treatment in the adjuvant study part.

The safety sets for the neoadjuvant part (SAF-neo) comprised all patients who received at least one dose of study treatment in the neoadjuvant part. The safety set for the entire study (SAF) comprised all patients who received at least one dose of study treatment. Safety analyses were performed for the neoadjuvant part (SAF-neo) according to the actual study drug received (EG12014, Herceptin, or 'None') and were performed for the adjuvant part and entire study (SAF) according to the actual study drug received (EG12014, Herceptin/EG12014, Herceptin, or "None").

For the neoadjuvant part, a total of 807 female patients were enrolled; 805 (99.8%) patients received chemotherapy at neoadjuvant cycle 1 visit, 797 (98.8%) patients received study drug (EG12014 or EU Herceptin) at neoadjuvant cycle 5 visit, and 779 (96.5%) patients, evenly distributed in both groups, underwent surgery. For the adjuvant part, safety data have been analysed for 762 (94.4%) patients (386 in the EG12014 arm, 188 in the EU Herceptin/EG12014 arm, and 188 in the EU Herceptin arm) who were randomized and received study treatment at adjuvant cycle 1 visit, 754 (93.4%) patients have received study treatment at adjuvant cycle 5 visit, 736 (91.2%) patients at adjuvant cycle 9 visit, and 713 (88.4%) patients at adjuvant cycle 13 visit.

A total of 711 (88.1%) patients have completed the follow-up period (20 weeks after final dose of study drug) of whom 681 (84.4%) completed the study (completed the EoS visit).

When all data from the Neoadjuvant Part and the Adjuvant Part were transferred to the CRO and all related data queries had been resolved, the study was unblinded. All data as of the final DBL on 18 February 2022 were analysed and reported in the final CSR (Part 1+ Part 2).

Exposure to trastuzumab

The exposure to study drug (EG12014 or EU Herceptin) during the neoadjuvant part is presented in Table 24.

Table 25. Exposure to EG12014 or Herceptin, by Treatment Arm (SAF-neo) – Neoadjuvant Part

	EG12014 (N=399)	Herceptin (N=398)	Overall (N=805)
Number of Cycles			
Median [Q1;Q3]	4 [4.0;4.0]	4 [4.0;4.0]	4 [4.0;4.0]
Number of Patients per Cycle			
Cycle 5	399	398	797[a]
Cycle 6	399	395	794
Cycle 7	399	393	792
Cycle 8	397	393	790
Duration of Treatment [weeks]			
Mean (SD)	9.4 (0.94)	9.3 (1.23)	9.4 (1.10)
Median [Q1;Q3]	9.1 [9.14;9.29]	9.1 [9.14;9.29]	9.1 [9.14;9.29]
Actual Cumulative Dose Administered [mg]			
N	399	398	797[a]
Mean (SD)	1911.67 (379.228)	1905.00 (436.220)	1908.34 (408.440)
Actual Dose Intensity [mg/weeks]			
N	399	398	797[a]
Mean (SD)	204.8 (42.36)	241.27 (420.41)	223.0 (298.97)
Relative Dose Intensity [%][b]			
N	399	398	397
Mean (SD)	100.0 (0.002)	100.0 (0.000)	100.0 (0.001)
Dose delayed n(%)	105 (26.3)	106 (26.6)	211 (26.5)

a. Eight (8) patients received only AC-based chemotherapy (epirubicin and cyclophosphamide) but did not receive EG12014 or Herceptin during the neoadjuvant part as patients withdrew prior first study drug administration.
b. Relative dose intensity was defined as ratio between the planned total volume and the actual volume administered (displayed as compliance in the CSR EGC002).

The exposure to EG12014 or EU Herceptin during the adjuvant part is presented in Table 25 for the SAF.

Table 26. Exposure to EG12014, Herceptin/EG12014, or Herceptin, by Treatment Arm (SAF) – Adjuvant Part

	EG12014 (N=386)	Herceptin (N=188)	Herceptin/EG12014 (N=188)	Overall (N=762)
Number of Cycles				
Median [IQR]	13 [13.0;13.0]	13 [13.0;13.0]	13 [13.0;13.0]	13 [13.0;13.0]
Number of Patients per Cycle				
Cycle 1	386	188	188	762
Cycle 2	385	188	185	758
Cycle 3	385	188	185	758
Cycle 4	383	188	184	755
Cycle 5	382	188	184	754
Cycle 6	380	188	184	752
Cycle 7	378	187	183	748
Cycle 8	374	187	181	742
Cycle 9	370	186	180	736
Cycle 10	369	185	176	730
Cycle 11	367	184	176	727
Cycle 12	365	184	174	723
Cycle 13	360	180	173	713
Duration of Treatment [weeks]				
Mean (SD)	35.8 (4.91)	35.7 (6.35)	36.5 (2.70)	35.9 (4.90)
Median [Q1;Q3]	36.3[36.14;37.00]	36.3 [36.14;37.14]	36.3 [36.14;36.71]	36.3 [36.14;37.00]

Exposure to Epirubicin, Cyclophosphamide and Paclitaxel

According to the applicant, the total mean (SD) dose of epirubicin and cyclophosphamide, administered at cycles 1 to 4 (neo adjuvant part) was consistent for all 4 cycles and was comparable for the EG12014 and EU Herceptin treatment arms. The applicant also states that delay in administration and dose adjustment of epirubicin and cyclophosphamide was comparable for the EG12014 and EU Herceptin arms.

The applicant also states that the total mean (SD) dose of paclitaxel administered at cycles 5 to 8 (neoadjuvant part) was consistent for all 4 cycles and was comparable for the EG12014 and EU Herceptin treatment arms. According to the applicant, delay in administration and dose adjustment of paclitaxel were comparable for the EG12014 and EU Herceptin arms.

Disposition of Subjects

A total of 807 patients were enrolled in the study and randomized into the neoadjuvant part, 405 in the EG12014 arm and 402 in the EU Herceptin arm (FAS-neo). For the entire study, 405 patients were included in the EG12014 arm, 188 patients in Herceptin/EG12014 arm (switch arm), and 214 patients in the Herceptin arm (FAS).

Study treatment was discontinued for 19 (4.7%) EG12014 patients and 26 (6.5%) EU Herceptin patients during the neoadjuvant part. During the entire study, withdrawal from the study was reported for 60 (14.8%) EG12014 patients, 20 (10.6%) EU Herceptin/EG12014 patients, and 46 (21.5%) EU Herceptin patients.

2.6.8.2. Adverse events

The AEs recorded were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 in study **EGC001**, and the MedDRA version 23.0 in study **EGC002**.

The AEs in both studies are assessed by severity grade (mild, moderate, severe in study **EGC001** and severity grade 1-5 in **EGC002**). The probability of AEs being caused by study treatment was assessed by the investigator, using a five-level causality scale.

Adverse events of special interest (AESI) were defined in study **EGC002,** and include cardiac dysfunction, embryo-foetal toxicity, infusion reactions, allergic-like reactions, hypersensitivity, haematotoxicity, and pulmonary events. The AESIs were identified considering the warnings and precautions and undesirable effects of Herceptin (EU Herceptin SmPC, 2021, US Herceptin Prescribing Information, 2021).

3.3.7.2.1. Treatment Emergent Adverse Events (TEAEs)

Phase 1 Study EGC001

A summary of treatment emergent adverse events in study **EGC001** is presented in Table **26**. A total of 86 TEAEs were reported across the treatment groups and no severe TEAEs were reported in the study.

Table 27. Summary of Treatment-Emergent Adverse Events Reported in Study EGC001.

Adverse Event	**EG12014 (N=28)**		**US Herceptin (N=28)**		**EU Herceptin (N=28)**	
	Subjects n (%)	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Any TEAE	19 (67.9)	25	17 (60.7)	42	13 (46.4)	19
*by severity**						
mild	15 (53.6)	20	16 (57.1)	35	11 (39.3)	13
moderate	4 (14.3)	5	5 (17.9)	7	4 (14.3)	6
severe	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
*by causality**						
certain	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
probable	7 (25.0)	10	12 (42.9)	24	5 (17.9)	6
possible	7 (25.0)	7	7 (25.0)	9	3 (10.7)	5
unlikely	3 (10.7)	4	5 (17.9)	8	5 (17.9)	7
not related	3 (10.7)	4	1 (3.6)	1	1 (3.6)	1
not assessable	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Source: [Module 5, Section 5.3.3.1 CSR EGC001, Section 14.3.1].

Abbreviations: TEAE, treatment-emergent adverse event; PT, preferred term; N, number of subjects in the safety set; n, number of subjects in the treatment group who experienced AE(s).

* Multiple count of subjects with multiple TEAEs.

Phase 3 Study EGC002

A summary of treatment emergent adverse events for the neoadjuvant part is presented in Table 27. The "none" column represents patients who received only AC based chemotherapy during the neoadjuvant part and who did not receive EG12014 or EU Herceptin during the study.

Table 28. Summary of Treatment-Emergent Adverse Events Reported in Study EGC002 (SAF-neo) – Neoadjuvant Part.

Adverse Event	**EG12014 (N=399)** X (%) Y	**Herceptin (N=398)** X (%) Y	**None (N=8)** X (%) Y	**Overall (N=805)** X (%) Y
Any TEAE	396 (99.2%) 2777	392 (98.5%) 2778	6 (75.0%) 14	794 (98.6%) 5569
*By severity**				
Grade 1	301 (75.4%) 1351	299 (75.1%) 1366	4 (50.0%) 6	607 (75.4%) 2714
Grade 2	336 (84.2%) 1249	335 (84.2%) 1241	3 (37.5%) 6	674 (83.7%) 2496
Grade 3	103 (25.8%) 157	89 (22.4%) 134	2 (25.0%) 2	194 (24.1%) 293
Grade 4	19 (4.8%) 19	14 (3.5%) 17	0 (0.0%) 0	33 (4.1%) 36
Grade 5	1 (0.3%) 1	3 (0.8%) 3	0 (0.0%) 0	4 (0.5%) 4
Missing	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
*By causality**				
Related to Trastuzumab	89 (22.3%) 229	94 (23.6%) 240	0 (0.0%) 0	183 (22.7%) 469
Related to Chemotherapy	394 (98.7%) 2275	384 (96.5%) 2317	6 (75.0%) 11	784 (97.4%) 4603
Not related to Trastuzumab	396 (99.2%) 2548	391 (98.2%) 2538	6 (75.0%) 14	793 (98.5%) 5100

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.2.1, Table 12-5].

Abbreviations: N, number of patients; TEAE, treatment-emergent adverse events.

* Multiple count of subjects with multiple TEAEs.

Note: 'None' category includes patients who only received AC-based chemotherapy.

For the adjuvant part, a summary of TEAEs is presented in Table 28.

Table 29. Summary of Treatment-Emergent Adverse Events Reported in Study EGC002 (SAF) – Adjuvant Part.

Adverse Event	**EG12014 (N=386)** X (%) Y	**Herceptin/EG12014 (N=188)** X (%) Y	**Herceptin (N=188)** X (%) Y	**Overall (N=762)** X (%) Y
Any TEAE	225 (58.3%) 619	106 (56.4%) 351	124 (66.0%) 365	455 (59.7%) 1335
*By severity**				
Grade 1	172 (44.6%) 387	81 (43.1%) 208	85 (45.2%) 214	338 (44.4%) 809
Grade 2	120 (31.1%) 186	55 (29.3%) 123	75 (39.9%) 130	250 (32.8%) 439
Grade 3	28 (7.3%) 39	16 (8.5%) 19	15 (8.0%) 17	59 (7.7%) 75
Grade 4	4 (1.0%) 4	1 (0.5%) 1	1 (0.5%) 2	6 (0.8%) 7
Grade 5	3 (0.8%) 3	0 (0.0%) 0	2 (1.1%) 2	5 (0.7%) 5
Missing	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
*By causality**				
Related to Trastuzumab	73 (18.9%) 164	46 (24.5%) 109	41 (21.8%) 101	160 (21.0%) 374
Related to Chemotherapy	19 (4.9%) 25	15 (8.0%) 28	13 (6.9%) 16	47 (6.2%) 69
Not related to Trastuzumab	195 (50.5%) 455	91 (48.4%) 242	106 (56.4%) 264	392 (51.4%) 961

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.2.1,Table 12-6]

Abbreviations: N, number of patients; TEAE, treatment-emergent adverse events.

* Multiple count of subjects with multiple TEAEs.

Note: X is number of patients with event, Y is total number of events.

Common Treatment Emergent Adverse Events

Phase 1 Study EGC001

The most common TEAEs in study **EGC001** are presented in Table 29. The most common reported TEAEs in this study (headache, pyrexia and nausea) are known for the pharmacological class of HER2-inhibiting mAbs and are consistent with the safety profile of Herceptin.

Table 30. Summary of the Treatment-Emergent Adverse Events with Frequency of ≥5% by Preferred Term, Reported in Study EGC001.

Adverse Event	EG12014 (N=28)		US Herceptin (N=28)		EU Herceptin (N=28)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	19 (67.9)	25	17 (60.7)	42	13 (46.4)	19
*by PT (for the most common AEs)**						
Nausea	3 (10.7)	3	0 (0.0)	0	0 (0.0)	0
Toothache	2 (7.1)	2	1 (3.6)	1	1 (3.6)	1
Pyrexia	4 (14.3)	4	10 (35.7)	11	4 (14.3)	4
Headache	5 (17.9)	5	12 (42.9)	18	5 (17.9)	5

Source: [Module 5, Section 5.3.3.1 CSR EGC001, Section 14.3.1].

Abbreviations: TEAE, treatment-emergent adverse event; PT, preferred term; N, number of subjects in the safety set; n, number of subjects in the treatment group who experienced AE(s).

* Multiple count of subjects with multiple TEAEs.

Phase 3 Study EGC002

The incidence of TEAEs occurring in ≥5% of patients in any study treatment arm is summarised by system organ class (SOC) and Preferred Term (PT) in Table 30 for the neoadjuvant part.

Table 31. Treatment-Emergent Adverse Events with Frequency of ≥5%, by Treatment Arm and MedDRA SOC and PT (SAF-neo) – Neoadjuvant Part

System Organ Class Term Preferred Term	EG12014 (N=399) X (%) Y	Herceptin (N=398) X (%) Y	None (N=8) X (%) Y	Overall (N=805) X (%) Y
Any TEAE	396 (99.2%) 2777	392 (98.5%) 2778	6 (75.0%) 14	794 (98.6%) 5569
Blood and lymphatic system disorders	154 (38.6%) 349	140 (35.2%) 311	1 (12.5%) 1	295 (36.6%) 661
Anaemia	69 (17.3%) 90	64 (16.1%) 87	0 (0.0%) 0	133 (16.5%) 177
Leukopenia	57 (14.3%) 97	46 (11.6%) 74	0 (0.0%) 0	103 (12.8%) 171
Neutropenia	89 (22.3%) 162	82 (20.6%) 150	1 (12.5%) 1	172 (21.4%) 313
Gastrointestinal disorders	161 (40.4%) 425	153 (38.4%) 396	2 (25.0%) 2	316 (39.3%) 823
Diarrhoea	28 (7.0%) 38	22 (5.5%) 26	0 (0.0%) 0	50 (6.2%) 64
Nausea	139 (34.8%) 331	133 (33.4%) 307	1 (12.5%) 1	273 (33.9%) 639

System Organ Class Term **Preferred Term**	**EG12014 (N=399)** X (%) Y	**Herceptin (N=398)** X (%) Y	**None (N=8)** X (%) Y	**Overall (N=805)** X (%) Y
Stomatitis	10 (2.5%) 11	10 (2.5%) 10	1 (12.5%) 1	21 (2.6%) 22
Vomiting	30 (7.5%) 45	28 (7.0%) 53	0 (0.0%) 0	58 (7.2%) 98
General disorders and administration site conditions	117 (29.3%) 260	143 (35.9%) 326	2 (25.0%) 2	262 (32.5%) 588
Asthenia	90 (22.6%) 216	104 (26.1%) 255	0 (0.0%) 0	194 (24.1%) 471
Fatigue	25 (6.3%) 38	38 (9.5%) 66	1 (12.5%) 1	64 (8.0%) 105
Pyrexia	6 (1.5%) 6	5 (1.3%) 5	1 (12.5%) 1	12 (1.5%) 12
Infections and infestations	6 (1.5%) 6	8 (2.0%) 8	2 (25.0%) 2	16 (2.0%) 16
Respiratory tract infection	6 (1.5%) 6	8 (2.0%) 8	1 (12.5%) 1	15 (1.9%) 15
Varicella	0 (0.0%) 0	0 (0.0%) 0	1 (12.5%) 1	1 (0.1%) 1
Injury, poisoning and procedural complications	40 (10.0%) 40	41 (10.3%) 41	0 (0.0%) 0	81 (10.1%) 81
Procedural pain	40 (10.0%) 40	41 (10.3%) 41	0 (0.0%) 0	81 (10.1%) 81
Investigations	118 (29.6%) 243	125 (31.4%) 255	0 (0.0%) 0	243 (30.2%) 498
Alanine aminotransferase increased	65 (16.3%) 79	56 (14.1%) 78	0 (0.0%) 0	121 (15.0%) 157
Aspartate aminotransferase increased	37 (9.3%) 48	37 (9.3%) 52	0 (0.0%) 0	74 (9.2%) 100
Blood cholesterol increased	21 (5.3%) 26	20 (5.0%) 24	0 (0.0%) 0	41 (5.1%) 50
Gamma-glutamyltransferase increased	28 (7.0%) 35	38 (9.5%) 42	0 (0.0%) 0	66 (8.2%) 77
Neutrophil count decreased	23 (5.8%) 34	23 (5.8%) 34	0 (0.0%) 0	46 (5.7%) 68
Weight increased	20 (5.0%) 21	24 (6.0%) 25	0 (0.0%) 0	44 (5.5%) 46
Metabolism and nutrition disorders	16 (4.0%) 20	10 (2.5%) 18	1 (12.5%) 1	27 (3.4%) 39
Decreased appetite	16 (4.0%) 20	10 (2.5%) 18	1 (12.5%) 1	27 (3.4%) 39
Musculoskeletal and connective tissue disorders	123 (30.8%) 305	124 (31.2%) 302	0 (0.0%) 0	247 (30.7%) 607
Arthralgia	53 (13.3%) 116	63 (15.8%) 135	0 (0.0%) 0	116 (14.4%) 251
Bone pain	34 (8.5%) 73	25 (6.3%) 44	0 (0.0%) 0	59 (7.3%) 117
Myalgia	30 (7.5%) 56	33 (8.3%) 75	0 (0.0%) 0	63 (7.8%) 131
Pain in extremity	29 (7.3%) 60	23 (5.8%) 48	0 (0.0%) 0	52 (6.5%) 108

System Organ Class Term Preferred Term	EG12014 (N=399) X (%) Y	Herceptin (N=398) X (%) Y	None (N=8) X (%) Y	Overall (N=805) X (%) Y
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.0%) 4	3 (0.8%) 3	1 (12.5%) 1	8 (1.0%) 8
Breast cancer	4 (1.0%) 4	3 (0.8%) 3	1 (12.5%) 1	8 (1.0%) 8
Nervous system disorders	51 (12.8%) 70	48 (12.1%) 71	0 (0.0%) 0	99 (12.3%) 141
Headache	27 (6.8%) 39	28 (7.0%) 48	0 (0.0%) 0	55 (6.8%) 87
Peripheral sensory neuropathy	25 (6.3%) 31	22 (5.5%) 23	0 (0.0%) 0	47 (5.8%) 54
Respiratory, thoracic and mediastinal disorders	4 (1.0%) 7	2 (0.5%) 2	1 (12.5%) 1	7 (0.9%) 10
Cough	4 (1.0%) 7	2 (0.5%) 2	1 (12.5%) 1	7 (0.9%) 10
Skin and subcutaneous tissue disorders	352 (88.2%) 355	337 (84.7%) 341	4 (50.0%) 4	693 (86.1%) 700
Alopecia	352 (88.2%) 355	337 (84.7%) 341	4 (50.0%) 4	693 (86.1%) 700

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.2, Table 12-10]

Abbreviations: N, number of patients; SOC, system organ lass; PT, preferred term.

Note: X is number of patients with event, Y is total number of events.

Note: A patient reporting the same treatment-emergent adverse event more than once is counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination.

Note: 'None' category includes patients who only received AC-based chemotherapy.

Table 32. Incidence of the most common TEAEs by all severity grades (Grade 1 to Grade 5, according to investigator assessment) for the Neoadjuvant Part (SAF-neo).

	EG12014	Herceptin
Alopecia	88.2%	84.7%
Grade 1	18.5%	22.9%
Grade 2	67.4%	58.8%
Grade 3	2.3%	3.0%
Grade 4	0%	0%
Grade 5	0%	0%
Nausea	34.8%	33.4%
Grade 1	16.3%	15.3%

Grade 2	18.3%	17.8%
Grade 3	0.3%	0.3%
Grade 4	0%	0%
Grade 5	0%	0%
Asthenia	22.6%	26.1%
Grade 1	17.5%	20.4%
Grade 2	4.8%	5.5%
Grade 3	0.3%	0.3%
Grade 4	0%	0%
Grade 5	0%	0%
ALT increase	16.3%	14.1%
Grade 1	8.0%	5.0%
Grade 2	5.8%	6.3%
Grade 3	2.5%	2.5%
Grade 4	0%	0.3%
Grade 5	0%	0%

Source: extracted from table 14.3.2.17.1

For the adjuvant part, the TEAEs reported in ≥ 5% of patients in any study drug arm were weight increased, ejection fraction decreased, ALT increased, asthenia, leukopenia and neutropenia (**Table 32**).

Table 33. Treatment-Emergent Adverse Events Related to Trastuzumab (Reported in ≥ 5 Participants in Either Treatment Arm), by Treatment Arm and MedDRA SOC and PT (SAF-neo) – Neoadjuvant Part.

SOC Term **Preferred Term**	**EG12014 (N=386)** **X (%) Y**	**Herceptin/EG12014 (N=188)** **X (%) Y**	**Herceptin (N=188)** **X (%) Y**	**Overall (N=762)** **X (%) Y**
Any TEAE	225 (58.3%) 619	106 (56.4%) 351	124 (66.0%) 365	455 (59.7%) 1335
Blood and lymphatic system disorders	18 (4.7%) 29	16 (8.5%) 28	9 (4.8%) 13	43 (5.6%) 70
Leukopenia	13 (3.4%) 17	11 (5.9%) 14	5 (2.7%) 5	29 (3.8%) 36
Neutropenia	9 (2.3%) 12	11 (5.9%) 14	5 (2.7%) 8	25 (3.3%) 34
General disorders and administration site conditions	19 (4.9%) 27	11 (5.9%) 14	10 (5.3%) 19	40 (5.2%) 60
Asthenia	19 (4.9%) 27	11 (5.9%) 14	10 (5.3%) 19	40 (5.2%) 60

SOC Term Preferred Term	EG12014 (N=386) X (%) Y	Herceptin/EG12014 (N=188) X (%) Y	Herceptin (N=188) X (%) Y	Overall (N=762) X (%) Y
Investigations	50 (13.0%) 56	27 (14.4%) 31	37 (19.7%) 39	114 (15.0%) 126
ALT increased	18 (4.7%) 20	11 (5.9%) 12	9 (4.8%) 9	38 (5.0%) 41
Ejection fraction decreased	7 (1.8%) 8	6 (3.2%) 6	12 (6.4%) 12	25 (3.3%) 26
Weight increased	25 (6.5%) 28	12 (6.4%) 13	17 (9.0%) 18	54 (7.1%) 59

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.2, Table 12-11]

Abbreviations: N, number of patients; SOC, system organ lass; PT, preferred term.

Note: X is number of patients with event, Y is total number of events.

Note: A patient reporting the same treatment-emergent adverse event more than once is counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination.

3.3.7.2.2. Adverse Events of Special Interest

Phase 3 Study EGC002

The incidence of AESIs in study **EGC002** is summarised in Table 33 for the neoadjuvant part.

Table 34. Adverse Events of Special Interest, by Treatment Arm and MedDRA SOC and PT (SAF-neo) – Neoadjuvant Part.

SOC Term Preferred Term	EG12014 (N=399) X (%) Y	Herceptin (N=398) X (%) Y	None (N=8) X (%) Y	Overall (N=805) X (%) Y
Any TEAE of Special Interest	27 (6.8%) 40	38 (9.5%) 53	0 (0.0%) 0	65 (8.1%) 93
Blood and lymphatic system disorders	20 (5.0%) 28	22 (5.5%) 32	0 (0.0%) 0	42 (5.2%) 60
Anaemia	10 (2.5%) 12	11 (2.8%) 12	0 (0.0%) 0	21 (2.6%) 24
Leukopenia	7 (1.8%) 9	5 (1.3%) 5	0 (0.0%) 0	12 (1.5%) 14
Neutropenia	6 (1.5%) 7	10 (2.5%) 14	0 (0.0%) 0	16 (2.0%) 21
Thrombocytopenia	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1
Cardiac disorders	1 (0.3%) 1	5 (1.3%) 5	0 (0.0%) 0	6 (0.7%) 6
Cardiac failure chronic	1 (0.3%) 1	3 (0.8%) 3	0 (0.0%) 0	4 (0.5%) 4
Myocardial infarction	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1
Ventricular arrhythmia	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1
General disorders and administration site conditions	1 (0.3%) 2	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 2

SOC Term Preferred Term	EG12014 (N=399) X (%) Y	Herceptin (N=398) X (%) Y	None (N=8) X (%) Y	Overall (N=805) X (%) Y
Chills	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Pyrexia	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Immune system disorders	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1
Anaphylactic reaction	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1
Injury, poisoning and procedural complications	1 (0.3%) 2	4 (1.0%) 4	0 (0.0%) 0	5 (0.6%) 6
Infusion-related reaction	1 (0.3%) 2	4 (1.0%) 4	0 (0.0%) 0	5 (0.6%) 6
Investigations	6 (1.5%) 7	9 (2.3%) 11	0 (0.0%) 0	15 (1.9%) 18
Ejection fraction decreased	3 (0.8%) 3	6 (1.5%) 6	0 (0.0%) 0	9 (1.1%) 9
Neutrophil count decreased	2 (0.5%) 3	1 (0.3%) 1	0 (0.0%) 0	3 (0.4%) 4
White blood cell count decreased	1 (0.3%) 1	2 (0.5%) 4	0 (0.0%) 0	3 (0.4%) 5

Source: [Module 5, Section 5.3.5.1 CSR (Part 1 + 2) EGC002, Section 12.3.4, Table 12-23]

Abbreviations: N, number of patients; SOC, system organ class; PT, preferred term.

Note: X is number of patients with event, Y is total number of events.

Note: A patient reporting the same treatment-emergent adverse event more than once is counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination.

Note: 'None' category includes patients who only received AC-based chemotherapy.

For the adjuvant part, the incidence of AESIs is summarised in Table 34. AESIs occurring during the adjuvant part were reported in 26 (6.7%) EG12014 patients (34 events), 20 (10.6%) EU Herceptin/EG12014 patients (31 events), and 20 (10.6%) EU Herceptin patients (27 events).

Table 35. Adverse Events of Special Interest, by Treatment Arm and MedDRA SOC and PT (SAF) – Adjuvant Part.

SOC Term Preferred Term	EG12014 (N=386) X (%) Y	Herceptin/EG12014 (N=188) X (%) Y	Herceptin (N=188) X (%) Y	Overall (N=762) X (%) Y
Any TEAE of Special Interest	26 (6.7%) 34	20 (10.6%) 31	20 (10.6%) 27	66 (8.7%) 92
Blood and lymphatic system disorders	12 (3.1%) 16	10 (5.3%) 19	6 (3.2%) 7	28 (3.7%) 42
Anaemia	5 (1.3%) 5	3 (1.6%) 4	2 (1.1%) 2	10 (1.3%) 11
Leukopenia	8 (2.1%) 8	6 (3.2%) 8	3 (1.6%) 3	17 (2.2%) 19

SOC Term **Preferred Term**	**EG12014 (N=386)** X (%) Y	**Herceptin/EG12014 (N=188)** X (%) Y	**Herceptin (N=188)** X (%) Y	**Overall (N=762)** X (%) Y
Neutropenia	2 (0.5%) 2	5 (2.7%) 5	2 (1.1%) 2	9 (1.2%) 9
Thrombocytopenia	1 (0.3%) 1	2 (1.1%) 2	0 (0.0%) 0	3 (0.4%) 3
Cardiac disorders	6 (1.6%) 7	3 (1.6%) 3	4 (2.1%) 5	13 (1.7%) 15
Angina pectoris	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Angina unstable	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1	1 (0.1%) 1
Cardiac dysfunction	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1	1 (0.1%) 1
Cardiac failure	0 (0.0%) 0	1 (0.5%) 1	2 (1.1%) 2	3 (0.4%) 3
Cardiac failure chronic	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0	1 (0.1%) 1
Cardiotoxicity	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Left atrial dilatation	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Left ventricular failure	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1	1 (0.1%) 1
Myocardial infarction	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Systolic dysfunction	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Toxic cardiomyopathy	1 (0.3%) 2	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 2
Ventricular arrhythmia	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0	1 (0.1%) 1
General disorders and administration site conditions	1 (0.3%) 1	0 (0.0%) 0	1 (0.5%) 1	2 (0.3%) 2
Chest pain	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1	1 (0.1%) 1
Chills	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 1
Injury, poisoning and procedural complications	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0	1 (0.1%) 1
Infusion-related reaction	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0	1 (0.1%) 1
Investigations	7 (1.8%) 8	8 (4.3%) 8	14 (7.4%) 14	29 (3.8%) 30
Ejection fraction decreased	7 (1.8%) 8	6 (3.2%) 6	12 (6.4%) 12	25 (3.3%) 26
Electrocardiogram QT shortened	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0	1 (0.1%) 1
Neutrophil count decreased	0 (0.0%) 0	1 (0.5%) 1	1 (0.5%) 1	2 (0.3%) 2
Platelet count decreased	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1	1 (0.1%) 1
Respiratory, thoracic and mediastinal disorders	1 (0.3%) 2	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 2
Dyspnoea	1 (0.3%) 2	0 (0.0%) 0	0 (0.0%) 0	1 (0.1%) 2

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.3.4, Table 12-24]

Abbreviations: N, number of patients; SOC, system organ class; PT, preferred term.

Note: X is number of patients with event, Y is total number of events.

Note: A patient reporting the same treatment-emergent adverse event more than once is counted only once when calculating incidence 1) within a given SOC, and 2) within a given SOC and PT combination.

Note: 'None' category includes patients who only received AC-based chemotherapy.

AESIs (> 5 patients in any treatment arm) during the entire study were, for EG12014, EU Herceptin/EG12014 and EU Herceptin arms; ejection fraction decreased (2.5%, 4.8%, and 6.7%, respectively), anaemia (3.8%, 4.8%, and 3.3%, respectively), neutropenia (2.0%, 4.8%, and 3.8%, respectively), and leukopenia (3.8%, 3.7%, and 3.8%, respectively).

2.6.8.3. Serious adverse event/deaths/other significant events

3.3.4.3.1. Deaths

Phase 1 Study EGC001

No deaths were reported in study **EGC001**.

Phase 3 Study EGC002

Treatment-emergent AEs leading to death, are presented in Table 35. There was a total of nine deaths during the study, out of which seven were considered "not related" to trastuzumab (EG12014 or EU Herceptin) by the investigator, while two of the deaths (myocardial infarction and cerebrovascular accident) were considered "unlikely related" to trastuzumab.

Table 36. Treatment-Emergent Adverse Events Leading to Death

	Treatment Arm	Cause of Death (MedDRA Preferred Term)	Relationship to Trastuzumab	Study Part*/ Study Day
Neoadjuvant Part				
	Herceptin	*Myocardial infarction*	Unlikely related	Part I/Day 113
	Herceptin	*Cerebrovascular accident*	Unlikely related	Part I/Day 96
	Herceptin	*Hepatic failure*	Not related	Part I/Day 247
	EG12014	*Metastases to meninges*	Not related	Part I/Day 162
Adjuvant Part				
	EG12014	*Metastases to central nervous system*	Not related	Part II/Day 337
	Herceptin	*Metastases to peritoneum*	Not related	Part II/Day 407
	Herceptin	*Breast cancer metastatic*	Not related	Part II/Day 325
	EG12014	*Pulmonary embolism*	Not related	Part II/Day 338
	EG12014	*Metastases to central nervous system*	Not related	Part II/Day 251

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.3.1, Table 12-16]

* Note: Part I, Neoadjuvant Part; Part II, Adjuvant Part

3.3.7.3.2 Serious Adverse Events

Phase 1 Study EGC001

No serious adverse event (SAE) was reported in the EG12014 or US Herceptin treatment group in study **EGC001**. One SAE was reported in a subject in the EU Herceptin treatment group, gastrointestinal bacterial infection (PT) requiring a 4-day hospitalization, which was assessed by the investigator to be of moderate intensity and to be unlikely related to EU Herceptin.

Phase 3 Study EGC002

In study **EGC002,** a total of 54 SAEs (listed in **Table 36**) occurred in 48 patients during the neoadjuvant part (28 SAEs occurred in 25 patients [6.3%] in the EG12014 arm and 26 SAEs occurred in 23 patients [5.8%] in the EU Herceptin group [SAF-neo]). Each PT was reported in ≤ 4 [1.0%] patients for all study treatment arms.

Table 37. Serious Adverse Events (SAEs) Occurring After the First Dose of Study Treatment by MedDRA SOC and Preferred Term and by Treatment Arm (SAF-neo) – Neoadjuvant Part.

SOC Term Preferred Term	EG12014 (N=399) X (%) Y	Herceptin (N=398) X (%) Y	None (N=8) X (%) Y
Any SAE	25 (6.3%) 28	23 (5.8%) 26	0 (0.0%) 0
Blood and lymphatic system disorders	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0
Febrile neutropenia	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0
Cardiac disorders	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Myocardial infarction	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Gastrointestinal disorders	2 (0.5%) 2	2 (0.5%) 3	0 (0.0%) 0
Abdominal pain	0 (0.0%) 0	1 (0.3%) 2	0 (0.0%) 0
Gastric ulcer perforation	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Haemorrhoids	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Vomiting	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
General disorders and administration site conditions	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Infusion site extravasation	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	0 (0.0%) 0
Bile duct stone	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Hepatic failure	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Infections and infestations	15 (3.8%) 15	11 (2.8%) 11	0 (0.0%) 0
Abscess limb	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Acute hepatitis B	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Asymptomatic COVID-19	2 (0.5%) 2	2 (0.5%) 2	0 (0.0%) 0
Bronchitis	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
COVID-19	3 (0.8%) 3	1 (0.3%) 1	0 (0.0%) 0
COVID-19 pneumonia	4 (1.0%) 4	1 (0.3%) 1	0 (0.0%) 0
Hepatitis B	1 (0.3%) 1	2 (0.5%) 2	0 (0.0%) 0
Influenza	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Liver abscess	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0

Pneumonia	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Postoperative wound infection	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Rectal abscess	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Urinary tract infection	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Wound infection	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Injury, poisoning and procedural complications	2 (0.5%) 2	1 (0.3%) 1	0 (0.0%) 0
Infusion related reaction	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Lower limb fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Post procedural haematoma	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Investigations	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Liver function test abnormal	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Metabolism and nutrition disorders	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Hyperglycaemia	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.0%) 4	4 (1.0%) 4	0 (0.0%) 0
Breast cancer	2 (0.5%) 2	3 (0.8%) 3	0 (0.0%) 0
Breast cancer recurrent	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Fibroadenoma of breast	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Metastases to meninges	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Nervous system disorders	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Cerebrovascular accident	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Reproductive system and breast disorders	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Uterine haemorrhage	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0
Respiratory, thoracic and mediastinal disorders	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Pulmonary embolism	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Vascular disorders	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Hypertension	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0

Source: Table 14.3.2.4.7

The most frequently reported (>2 patients in any treatment arm) serious TEAEs were related to COVID-19 infection, including COVID-19 (3 [0.8%] EG12014 patients and 1 [0.3%] EU Herceptin patients) and COVID-19 pneumonia (4 [1.0%] and 1 [0.3%], respectively). According to the applicant, none of the SAEs reported in the neoadjuvant part of the study were considered as related to trastuzumab.

During the adjuvant part, a total of 93 SAEs occurred in 90 patients (46 SAEs occurred in 44 patients [11.4%] in the EG12014 arm, 21 SAEs occurred in 20 patients [10.6%] in the EU Herceptin/EG12014 arm, and 26 SAEs in 26 patients [13.8%] in EU Herceptin arm (

Table 37).During the adjuvant part, the most frequently reported (>2 patients in any treatment arm) SAEs were related to COVID 19 including *asymptomatic COVID-19* (4 [1.0%] EG12014 patients, 6 [3.2%] EU Herceptin/EG12014 patients, and 4 [2.1%] EU Herceptin patients), *COVID-19* (16 [4.1%], 4 [2.1%], and 9 [4.8%], respectively), and *COVID-19 pneumonia* (15 [3.9%], 2 [1.1%], and 7 [3.7%], respectively).

Table 38. Serious Adverse Events (SAEs) Occurring After the First Dose of Study Treatment by MedDRA SOC and Preferred Term and by Treatment Arm (SAF-neo) – Adjuvant Part.

SOC Term Preferred Term	EG12014 (N=386) X (%) Y	Herceptin/EG12014 (N=188) X (%) Y	Herceptin (N=188) X (%) Y
Any SAE	44 (11.4%) 46	20 (10.6%) 21	26 (13.8%) 26
Blood and lymphatic system disorders	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Anaemia	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Cardiac disorders	1 (0.3%) 1	1 (0.5%) 1	2 (1.1%) 2
Angina unstable	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Atrial fibrillation	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Cardiac failure	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Myocardial infarction	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
General disorders and administration site conditions	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Implant site inflammation	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Hepatobiliary disorders	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Bile duct stone	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Infections and infestations	37 (9.6%) 37	14 (7.4%) 15	20 (10.6%) 20
Acute hepatitis B	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Asymptomatic COVID-19	4 (1.0%) 4	6 (3.2%) 7	4 (2.1%) 4
COVID-19	16 (4.1%) 16	4 (2.1%) 4	9 (4.8%) 9
COVID-19 pneumonia	15 (3.9%) 15	2 (1.1%) 2	7 (3.7%) 7
Phlebitis infective	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Pneumonia	1 (0.3%) 1	1 (0.5%) 1	0 (0.0%) 0
Injury, poisoning and procedural complications	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Suture related complication	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.3%) 5	1 (0.5%) 1	2 (1.1%) 2
Breast cancer	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Breast cancer metastatic	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Breast cancer recurrent	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Intraductal papilloma of breast	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Metastases to central nervous system	3 (0.8%) 3	0 (0.0%) 0	0 (0.0%) 0
Metastases to peritoneum	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Reproductive system and breast disorders	1 (0.3%) 1	1 (0.5%) 1	0 (0.0%) 0
Heavy menstrual bleeding	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Ovarian cyst	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Respiratory, thoracic and mediastinal disorders	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Pulmonary embolism	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Vascular disorders	1 (0.3%) 1	1 (0.5%) 1	0 (0.0%) 0
Hypertensive crisis	1 (0.3%) 1	1 (0.5%) 1	0 (0.0%) 0

Source: Table 14.3.2.4.8

The SAEs considered related (possibly or probably) to trastuzumab (EG12014 or EU Herceptin) treatment observed during the entire study are listed in Table 38. Myocardial infarction, angina unstable and hypertensive crisis were reported as suspected unexpected serious adverse reactions (SUSARs) in the study.

Table 39. Serious Adverse Events Considered Related to Trastuzumab

Treatment Arm	Cause of Death (MedDRA Preferred Term)/ CTCAE Grade	Relationship to Trastuzumab	Study Part/ Study Day	Outcome
EG12014	*Myocardial infarction*/ Grade 4	Probably related	Adjuvant/ Day 456	Unknown
Herceptin/ EG12014	*Cardiac failure*/ Grade 3	Probably related	Adjuvant/ Day 472	Not recovered/Not resolved
Herceptin/ EG12014	*Anaemia*/ Grade 2	Probably related	Adjuvant/ Day 389	Recovered /Resolved
Herceptin	*Angina unstable*/ Grade 3	Possibly related	Adjuvant/ Day 441	Recovered /Resolved with Sequelae
Herceptin/ EG12014	*Hypertensive crisis*/ Grade 4	Possibly related	Adjuvant/ Day 311	Recovered/Resolved

Source: [Module 5, Section 5.3.5.1 CSR EGC002, Section 12.3.2, Table 12-19]

Abbreviations: CTCAE, common terminology criteria for adverse events.

2.6.8.4. Laboratory findings

Phase 1 Study EGC001

Haematology/Urinanalysis

According to the applicant, there were no clinically meaningful changes from baseline (entry visit) in haematological or urinalysis parameters in the EG12014, US Herceptin or EU Herceptin treatment group.

Clinical Chemistry

According to the applicant, there were no clinically meaningful changes from baseline (entry visit) in clinical chemistry parameters in the EG12014, EU Herceptin or US Herceptin treatment group except for one subject in the EU Herceptin treatment group who experienced a clinically significant increase in hepatic enzymes which was reported as secondary AE to the SAE gastrointestinal bacterial infection in this subject. The investigator suspected that the intake of food supplements and other drugs caused the increase in liver enzymes and assessed the AE (PT hepatic enzyme increased) as unlikely related to EU Herceptin.

Phase 3 Study EGC002

Haematology

For both the neoadjuvant and adjuvant part, according to the applicant, the majority of patients had normal haematology values for all parameters at all timepoints and the percentage of patients with normal or abnormal (clinically significant or non-clinically significant (CS or NCS)) values was comparable for the EG12014 and EU Herceptin arms for all parameters at all timepoints. The parameters with the

highest percentage of patients who had abnormal-CS values were, according to the applicant, haemoglobin and neutrophils.

The majority of participants in the EG12014 and Herceptin arms had worst grade values that remained at a Grade 0 or shifted from Grade 0 to Grade 1 after Cycle 1. The parameter with the highest percentage of participants with shifts to a worst grade of ≥ Grade 2 was lymphocyte count decreased for both treatment arms. A shift from Grade 0 to a worst grade of Grade 4 was reported for lymphocyte count decreased (3 participants), neutrophil count decreased (1 participant), and platelet count decreased (1 participant) in the EG12014 arm.

Serum chemistry

For the neoadjuvant part, according to the applicant, the majority of patients had normal serum chemistry values for all parameters at all timepoints, and the percentage of patients with normal or abnormal (CS or NCS) values was comparable for the EG12014 and Herceptin arms for all parameters at all timepoints. For ALT, the percentage of patients in the EG12014 and EU Herceptin arms with abnormal-CS values increased from baseline (0.3% and 0.3%, respectively) to cycle 8 (8.8% and 8.4%, respectively); and then decreased by pre-surgery (7.6% and 7.2%, respectively) and post-surgery (4.8% and 4.1%, respectively). For AST, the percentage of patients in the EG12014 and EU Herceptin arms with abnormal-CS values increased from baseline (0% and 0.3%, respectively) to cycle 7 (4.5% and 4.8%, respectively); and then decreased by cycle 8 (3.5% and 4.6%, respectively), pre-surgery (2.8% and 2.8%, respectively) and post-surgery (2.4% and 1.6%, respectively).

Shift results were summarized in the CSR for serum chemistry parameters by timepoint for the neoadjuvant part. For all the parameters, the majority of participants in the EG12014 and Herceptin arms had worst grade values that remained at a Grade 0 or shifted from Grade 0 to Grade 1 after Cycle 1. The parameters with the highest percentage of participants with shifts to a worst grade of ≥Grade 2 were ALT increased, cholesterol high, GGT increased, hyperkalaemia, and hypertriglyceridemia for both treatment arms.

For the adjuvant part, the majority of patients had normal serum chemistry values for all parameters at all timepoints. In addition, the percentage of patients with normal or abnormal (CS or NCS) values was comparable for the EG12014, EU Herceptin/EG12014, and EU Herceptin arms for all parameters at all timepoints. The parameters with the highest percentage of patients with abnormal-CS values were the same as parameters observed during the neoadjuvant part, i.e., ALT, AST, cholesterol, and GGT.

Urinalysis

For both the neoadjuvant and adjuvant part, according to the applicant, the majority of patients had normal urinalysis values for all parameters at all timepoints and the percentage of patients with normal or abnormal values was comparable for the study drug arms for all parameters at all timepoints.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Not applicable.

2.6.8.7. Immunological events

Immunogenicity has been assessed as a secondary objective in study **EGC001** in healthy volunteers and in study **EGC002** in patients with HER2-positive EBC. The immunogenicity endpoints included incidence of ADAs and NAbs against trastuzumab. PK (peak and trough concentrations) and ADA were sampled as shown in Table 5 and Table 40.

Screening, confirmatory and characterisation assays were used to evaluate the immunogenicity of trastuzumab. Samples with signals above the screening cut point was considered positive and further analysed with the confirmatory assay. Confirmed positive ADA samples were further characterised by performing serial dilutions to determine the titre, specificity was tested, and neutralising activity was analysed by a NAb screening assay.

In study **EGC001** (healthy individuals) the contract laboratory IPM GmbH conducted and validated the ECLA assay for ADA analysis, whereas in study EGC002 (HER-2 positive EBC patients) the ECLA assay was conducted and validated by ICON Laboratory Services. However, due to an unexpectedly high number of invalid assay runs observed during study sample analysis and failed incurred sample reanalysis, data for the determination of trastuzumab used for PK-profiling were implausible and could not be used as final results. EirGenix therefore decided to transfer the PK sample analysis to ICON Laboratory Services. The latter developed and fully validated an independent PK method. Using this method for analysis, all runs fulfilled run acceptance criteria and ISR passed as well for 97.1% of samples in study **EGC001.**

In study **EGC001** and using the ADA assay developed at IPM Biotech GmbH, the incidence of baseline ADAs was 3.6% (1/28 subjects), 7.1% (2/28 subjects) and 3.6% (1/28 subjects) in the EG12014, US Herceptin and EU Herceptin treatment groups, respectively (Table 39). None of the subjects with ADA-negative results at baseline (95.2%) developed ADAs 1680 hours post-infusion, and no neutralising ADAs (NAb) were reported. Only baseline and samples at 1680h, unless positive, were analysed.

Following reanalysis of all available 415 samples from 84 subjects using the same ADA assay as for study **EGC002** (Table 40), six patients had ADAs pre-trastuzumab. Of four patients who were post-dose positive, two patients developed "de novo" (i.e. treatment-emergent ADAs in patients who were negative at baseline) ADAs post-trastuzumab (EG12014:1, EU Herceptin: 1). Samples were not tested for NAbs.

Table 40. ADA titers of samples from subjects with at least one confirmed ADA positive sample in study EGC001 (Module 2.7.2, Table 4.1.3.1-1)

Treatment Group	Time Point (hour)				
	0 (pre-infusion)	336	672	1008	1680
	ADA titer assessment				
EG12014	1:128	negative	negative	1:2	1:4
EU Herceptin	1:4	negative	negative	negative	1:4
US Herceptin	1:1	negative	negative	negative	negative
US Herceptin	1:4	negative	negative	negative	negative

Table 41. ADA status and titre of samples from subjects with at least one confirmed ADA positive result in study EGC001[1]

Pre-dose	336h	672h	1008h	1680h	Treatment-Arm
negative	1:100	negative	negative	negative	EG12014
1:100	negative	negative	negative	negative	EG12014
1:3200	negative	negative	1:200	1:100	EU Herceptin
1:100	negative	negative	1:100	negative	EG12014
1:200	negative	negative	negative	negative	US Herceptin
1:100	negative	negative	negative	negative	EG12014
negative	negative	negative	negative	1:100	EU Herceptin
1:100	negative	negative	negative	negative	US Herceptin

In the *neoadjuvant* part of study **EG002**, the incidence of baseline ADAs was 5.8% (N=23) and 4.0% (N=16) in the EG12014 and EU Herceptin arm, respectively (Table 41). Of these, 36/39 participants were ADA negative after the first administration of trastuzumab during the neoadjuvant part. Three participants (all in the EG12014 arm) showed one positive ADA result each also after the first study drug administration. Following trastuzumab administration, four versus seven patients with ADA-negative results at baseline tested positive in the EG12014 and EU Herceptin arm, respectively (Table 42). Only one patient with neutralising activity (study **EGC002**, pre-trastuzumab administration *i.e.* baseline neoadjuvant C1D1, EG12014 arm) was reported.

Table 42. Incidence of ADAs Prior to first administration of trastuzumab (SAF-neo) – Neoadjuvant Part (EGC002 study report, Table 12-28)

Timepoint	EG12014 (N=399)	Herceptin (N=398)	None (N=8)	Overall (N=805)
At least one Positive ADA[a]	23 (5.8%)	16 (4.0%)	2 (25.0%)	41 (5.1%)
Cycle 1 Day 1	17 (4.3%)	13 (3.3%)	2 (25.0%)	32 (4.0%)
Cycle 3 Day 1	10 (2.5%)	7 (1.8%)	0 (0.0%)	17 (2.1%)
Cycle 5 Day 1	9 (2.3%)	3 (0.8%)	0 (0.0%)	12 (1.5%)

Source: Table 14.3.5.1.1

Note: The table is stratified by actual treatment arm at first randomization.
Note: 'None' category includes participants who only received AC-based chemotherapy.
a. Participant had at least 1 positive ADA result at Neoadjuvant Cycle 1 Day 1, Cycle 3 Day 1, and/or Cycle 5 Day 1 visits. A participant could have 1,2 or 3 positive ADA results, but is counted only once when calculating incidence. Interim database lock: 12 Feb 2021.

Table 43. Incidence of de novo Anti-Drug Antibodies after the first study drug administration (SAF-neo) – Neoadjuvant Part (EGC002 study report, Table 12-39).

Timepoint	EG12014 (N=399)	Herceptin (N=398)	Overall (N=805)
At least one positive ADA	4 (1.0%)	7 (1.8%)	11 (1.4%)
Cycle 7 Day 1	3 (0.8%)	3 (0.8%)	6 (0.7%)
Pre-Surgery	2 (0.5%)	4 (1.0%)	6 (0.7%)

Note: The table is stratified by actual treatment arm at first randomization.
Database lock: 18 Feb 2022.

For the adjuvant part, the incidence of de novo ADAS is presented in Table 43.

[1] analysis performed at ICON Laboratory Services (D181 response)

Table 44. Incidence of de novo Anti-Drug Antibodies after the first study drug administration (SAF) – Adjuvant Part and End of Treatment (EGC002 study report, table 12-42).

Timepoint	EG12014 (N=386)	Herceptin/ EG12014 (N=188)	Herceptin (N=188)	Overall (N=762)
At least one positive ADA	7 (1.8%)	3 (1.6%)	2 (1.1%)	12 (1.6%)
Cycle 1 Day 1	2 (0.5%)	2 (1.1%)	1 (0.5%)	5 (0.7%)
Cycle 5 Day 1	3 (0.8%)	0 (0.0%)	0 (0.0%)	3 (0.4%)
Cycle 9 Day 1	4 (1.0%)	1 (0.5%)	1 (0.5%)	6 (0.8%)
Cycle 13 Day 1	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
End of Treatment[a]	1 (0.3%)	1 (0.5%)	1 (0.5%)	3 (0.4%)

Source: Table 14.3.5.1.3, Listing 16.2.39.2.2 (EOT includes participants 381913 [EG12014], 380105 [Herceptin/EG12014], and 071301 [Herceptin])[a]

Abbreviations: refer to Section 4, List of Abbreviations.

Note: The table is stratified by actual treatment arm at second randomization.

Database lock: 18 February 2022

No systematic differences in pharmacokinetics were apparent for subjects developing ADAs following trastuzumab administration in study **EGC001** and **EGC002** (data not shown), and, according to the applicant, a lack of efficacy due to antibody formation is not likely.

Overall, for the *neoadjuvant* part, the incidence of TEAEs in study **EGC002** was similar in patients who were ADA negative or ADA positive, indicating that ADAs do not have any influence on the safety profile. The four ADA positive participants in the EG12014 arm reported 32 TEAEs and the seven ADA positive participants in the Herceptin arm reported 41 TEAEs. Among participants who were ADA positive after the first study drug administration, no TEAEs of infusion reaction were reported.

Among patients who were de novo ADA positive after the first study drug administration during the adjuvant part, 3 of 4 (75.0%) patients in the EG12014 arm reported 6 TEAEs (leukopenia, neutropenia, vision blurred, metastases to central nervous system, headache, and pulmonary embolism), 1 of 3 (33.3%) patients in the Herceptin/EG12014 arm reported 4 TEAEs (lymphopenia, asthenia, COVID-19 pneumonia, and respiratory distress), and 1 of 3 (33.3%) patients in the Herceptin arm reported 1 TEAE (weight increased).

During the entire study, de novo positive ADA result after the first study drug administration was reported for a total of 28 of 805 (3.5%) patients (13 of 394 [3.3%] patients in the EG12014 arm, 5 of 185 [2.7%] patients in the Herceptin/EG12014 arm, and 10 of 210 [4.8%] patients in the Herceptin arm).

The majority of TEAEs reported in the three treatment arms during the entire study occurred in patients who were ADA negative, 3389 of 3428 (98.9%) total TEAEs in the EG12014 arm, 1731 of 1755 (98.6%) total TEAEs in the EU Herceptin/EG12014 arm, and 1712 of 1736 (98.6%) total TEAEs in the EU Herceptin arm. The most frequently reported TEAE among ADA negative patients was alopecia (89.2% of EG12014 patients, 85.7% of EU Herceptin/EG12014 patients, and 84.2% of EU Herceptin patients). The next most frequently reported TEAE was nausea (35.4%, 33.0%, and 33.7%, respectively).

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.8.9. Discontinuation due to adverse events

Phase 1 Study EGC001

Adverse events leading to study discontinuation

One SAE was reported in a subject in the EU Herceptin treatment group; the subject had a gastrointestinal bacterial infection (PT) requiring a 4-day hospitalization, which was assessed by the investigator to be of moderate intensity and to be unlikely related to EU Herceptin (onset: 36 days after administration of study medication). The SAE was initially documented as gastroenteritis acuta, with a further specification of the diagnosis to gastrointestinal bacterial infection applied in the follow-up report. The subject was treated for the SAE and the outcome of the event was reported as recovered/resolved. The subject discontinued the study as exclusion/withdrawal criteria applied.

Phase 3 Study EGC002

Adverse events leading to study discontinuation

During the neoadjuvant part, 3 patients in the EG12014 arm were discontinued from the study due to anaemia (1 event), ejection fraction decreased (1 event), and metastases to meninges (1 event) and three (3) patients in the EU Herceptin arm were discontinued from the study due to cardiac failure chronic (1 event), acute hepatitis B (1 event), and ejection fraction decreased (1 event).

During the adjuvant part, 7 patients in the EG12014 arm were discontinued from the study, 1 patient was discontinued due to myocardial infarction (1 event) and COVID-19 pneumonia (1 event), and 6 other patients were discontinued due to systolic dysfunction (1 event), acute hepatitis B (1 event), and ejection fraction decreased (4 events, 1 patient each). Four (4) patients in the EU Herceptin/EG12014 arm discontinued from the study due to cardiac failure (1 event), ventricular dysfunction (1 event), infusion-related reaction (1 event), and ejection fraction decreased (1 event). Four (4) patients in the EU Herceptin arm were discontinued from the study due to left ventricular failure (1 event) and ejection fraction decreased (3 events).

Overall, 20 (2.5%) patients had 21 TEAEs leading to study discontinuation during the entire study.

Adverse Events Leading to Trastuzumab Withdrawal

In the neoadjuvant part, TEAEs leading to study drug withdrawal were reported for 6 (1.5%) EG12014 patients (6 events) and 11 (2.8%) EU Herceptin patients (12 events). Metastases to bone was reported in 3 (0.8%) EU Herceptin patients; and metastases to the lung was reported in 2 (0.5%) EG12014 patients. No other TEAE was reported in > 1 participant in either study drug arm.

In the adjuvant part, TEAEs leading to study drug withdrawal were reported for 20 (5.2%) EG12014 patients (20 events), 5 (2.7%) EU Herceptin/EG12014 patients (5 events), and 9 (4.8%) EU Herceptin patients (10 events). *Metastases to central nervous system* was reported in 5 (1.3%) EG12014 patients, and 1 (0.5%) EU Herceptin patient; *ejection fraction decreased* was reported in 4 (1.0%) EG12014 patients, 1 (0.5%) EU Herceptin/EG12014 patients, and 3 (1.6%) EU Herceptin patients; and *metastases to the liver* was reported in 3 (0.8%) EG12014 patients, and 2 (1.1%) EU Herceptin patients; and *metastases to lymph nodes* was reported in 2 (0.5%) EG12014 patients. No other TEAE was reported in > 1 patient in any study drug arm.

2.6.8.10. Post marketing experience

EG12014 is currently not marketed in any country worldwide and therefore, no post-marketing data are available.

2.6.9. Discussion on clinical safety

Comparative safety data of EG12014 was derived from two clinical studies:

- **EGC001** – A randomised, phase 1, double-blind, single-dose study to compare pharmacokinetic characteristics and safety of EG12014 with those of EU-Herceptin and US-Herceptin, in 84 healthy male subjects.
- **EGC002** – A randomised, phase 3, multicenter, double-blind study in female HER2-positive early breast cancer (EBC) patients (n=807) with the primary objective to demonstrate therapeutic equivalence between EG12014 and EU Herceptin in terms of efficacy and to compare the safety, immunogenicity, and PK between the trastuzumab products.

Throughout the assessment, emphasis has been put on the **EGC002** study (final database lock date on 18 February 2022).

Overall, the size of the safety database is considered appropriate to evaluate the general safety profile of EG12014. However, it does not allow for characterisation and evaluation of rare events. In addition, a switch study design was chosen although it was not supported by the scientific advice, as it may confound the size of the database necessary for comparison of long-term safety.

In study **EGC001** (healthy male volunteers), Herwenda, EU-approved Herceptin, and US-licensed Herceptin were well tolerated. The overall safety profile, as reflected by the most frequently reported AEs, seems overall comparable in all treatment arms. However, the interpretation of these results should be cautious due to the very limited number of subjects (n=28 in each arm). A total of 86 TEAEs were reported: 25 TEAEs in 19/28 (67.9%) of subjects in the EG12014 treatment group, 42 TEAEs were reported in 17/28 (60.7%) of subjects in the US Herceptin treatment group and 19 TEAEs were reported in 13/28 (46.4%) of subjects in the EU Herceptin treatment group. One (1) SAE was reported in the EU Herceptin treatment group (assessed as unlikely related to study treatment).

In study **EGC002**, neoadjuvant part, the overall incidence of TEAEs was comparable between the EG12014 and Herceptin treatment arms, 99.2% vs 98.5%. The severity of TEAEs was similar between the EG12014 and Herceptin arms; Grade 1 (75.4% vs 75.1%), Grade 2 (84.2% vs 84.2%), Grade 3 or 4 (30.6% vs 25.9%) respectively. The number of patients reporting TEAEs related to chemotherapy (98.7% vs 96.5%) and to trastuzumab (22.3% and 23.6%) were comparable between the EG12014 and the Herceptin arm respectively, and so was the proportion of TEAEs reported as related to trastuzumab (229/2777 vs 240/2778).

In the adjuvant part, the overall incidence, severity, and causality of TEAEs were comparable for the three study drug arms. The severity of TEAEs for EG12014 and Herceptin were; Grade 1 (44.6% vs 45.2%), Grade 2 (31.1% vs 39.9%), Grade 3 or 4 (8.3% vs 9.0%) respectively. The incidence of TEAEs reported as related to trastuzumab was 18.9% vs 24.5% vs 21.8% for EG12014, Herceptin/EG12014 and Herceptin respectively.

The overall incidence of TEAEs by PT and SOC in the neoadjuvant part was comparable for EG12014 and Herceptin. The most frequently observed TEAEs by PT were *alopecia (88.2% vs 84.7%, nausea (34.8% vs 33.4%), asthenia (22.6% vs 26.1%), neutropenia (22.3% vs 20.6%), anaemia (17.3% vs 16.1%*, *alanine aminotransferase (ALT) increased (16.3% vs 14.1%) and arthralgia (13.3% vs 15.8%)*, for EG12014 and Herceptin respectively, and the severity of these TEAEs was similar between the treatment arms. In addition, the frequency of the most frequent treatment-related adverse events was similar between EG12014 and Herceptin. TEAEs reported for the adjuvant part, in $\geqslant$ 5% of patients in any study drug arm (by PT), were leukopenia, neutropenia, asthenia, ALT increased, ejection fraction decreased and weight increased.

During the neoadjuvant part, the incidence of AESIs was comparable for the EG12014 arm (27 (6.8%) patients (40 events)) and Herceptin arm (38 (9.5%) patients (53 events)). Cardiac disorders were reported for 1 patient (0.3%, 1 event) in the EG12014 arm and 5 patients (1,3%, 5 events) in the EU Herceptin arm. Infusion related reactions were reported in 1 patient (0.3%) in the EG12014 arm, while it was reported in 4 patients (1%) in the EU Herceptin arm. The incidence of ejection fraction decreased was numerically slightly lower in the EG12014 (3 patients, 0.8%) vs the EU Herceptin arm (6 patients, 1.5%) although it is of note that the numbers are very small.

AESIs occurring during the adjuvant part were reported in 26 (6.7%) EG12014 patients (34 events), 20 (10.6%) EU Herceptin/EG12014 patients (31 events), and 20 (10.6%) EU Herceptin patients (27 events) and were thus comparable between the treatment arms. As reported for the neoadjuvant part, the incidence of ejection fraction decreased in the adjuvant part was numerically slightly lower in the EG12014 (7 patients, 1.8%) vs the EU Herceptin arm (12 patients, 6.4%) although again, the numbers are very small.

The incidence of AESIs Grade 3 or higher (provided in the D120 response) was low; <2% in all treatment arms for both the neoadjuvant and the adjuvant part.

A total of nine deaths were reported as of the iDBL, evenly distributed in the treatment arms and according to the investigator, seven of them were considered as "not related" to trastuzumab treatment by the investigator, while two of the deaths (myocardial infarction and cerebrovascular accident) were considered "unlikely related" to trastuzumab. Four (4) of the deaths (myocardial infarction, cerebrovascular accident, hepatic failure (due to disease progression) and metastases to meninges) occurred during the neoadjuvant part (3/4 were in the EU Herceptin arm). Five (5) of the deaths occurred during the adjuvant part, 3 of which were in the EG12014 arm (metastases to central nervous system (2 patients) and pulmonary embolism), and 2 of which were in the EU Herceptin arm (metastases to peritoneum and "breast cancer metastatic"). Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting, as stated in the SmPC. However, in the patient narratives, this event of pulmonary embolism was only stated as assessed not to be related to trastuzumab treatment.

Overall, a total of 54 SAEs occurred in 48 patients during the neoadjuvant part (28 SAEs occurred in 25 patients (6.3%) in the EG12014 arm and 26 SAEs occurred in 23 patients (5.8%) in the EU Herceptin group. The incidence of SAEs was thus comparable for the treatment arms, and none of the events were considered as related to trastuzumab treatment by the investigator.

The incidence of SAEs that occurred during the adjuvant part was comparable for the treatment arms. A total of 93 SAEs occurred in 90 patients (46 SAEs occurred in 44 patients [11.4%] in the EG12014 arm, 21 SAEs occurred in 20 patients [10.6%] in the EU Herceptin/EG12014 arm, and 26 SAEs in 26 patients [13.8%] in EU Herceptin arm. Five (5) events were considered related to trastuzumab (EG12014 or EU Herceptin) treatment. Three of these events were in the SOC Cardiac disorders (myocardial infarction, cardiac failure, and angina unstable). All of the five SAEs occurred relatively late, between study day 311-472, reinforcing the importance of having the complete safety data for the final assessment of the SAEs in the adjuvant part.

For **EGC002**, overall, 20 (2.5%) patients had 21 TEAEs leading to study discontinuation during the entire study and the distribution was comparable for the treatment arms.

TEAEs leading to trastuzumab withdrawal during the neoadjuvant part was slightly numerically lower in the EGC014 arm (6 patients, 1.5%) compared to the EU Herceptin arm (11 patients, 2.8%). However, the numbers are very small and in the adjuvant part, TEAEs leading to study drug withdrawal reported were similar between EGC014 (20 patients, 5.2%) and EU Herceptin (9 patients, 4.8%).

Immunogenicity

Regarding immunogenicity, the analytical methods are adequately described, and their validations presented. In general, the methods have been acceptably validated. The applied biosimilar EG12014 appears to have a low immunogenicity potential. Overall, the incidence of treatment emergent ADAs for EG12014 was relatively low (~3.3%) and comparable to Herceptin in EBC patients irrespective of concomitant chemotherapy. No treatment-emergent NAbs were observed in baseline-negative patients with post-dose ADAs in study **EGC002**. NAbs were not tested in the pivotal PK study **EGC001**. The clinical relevance of ADAs is not known; there is no apparent impact on PK, efficacy and safety, however data are limited.

2.6.10. Conclusions on the clinical safety

Overall, the data submitted appears to support biosimilarity between EG12014 and Herceptin.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 45: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Cardiac dysfunction Administration-related reactions Oligohydramnios
Important potential risks	Medication Error (subcutaneous administration)
Missing information	None

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

Table 46: Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Cardiac Dysfunction	Routine risk minimization measures: SmPC section 4.2, 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Administration-Related Reactions	Routine risk minimization measures: SmPC section 4.2, 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None
Oligohydramnios	Routine risk minimization measures: SmPC section 4.6 and 4.8 Targeted questionnaire for follow up of any reports of pregnancy to further characterize the risk and analyse any adverse event of foetal harm for causal factors. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Medication Error (subcutaneous administration)	Routine risk minimization measures: SmPC section 4.2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable. For alignment to the reference product Herceptin in RMP Annex 4 (Specific Adverse Drug Reaction Follow-up Forms) a guided questionnaire for medication error was also added to the RMP upon request. This questionnaire should be updated as part of an upcoming regulatory opportunity.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Herceptin (trastuzumab) 150 mg (EMEA/H/C/000278) and Ziextenzo (pegfilgrastim) 6 mg (EMEA/H/C/004802). The bridging report submitted by the

applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Herwenda (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. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Herwenda is being developed as a biosimilar to the reference product Herceptin. The administration, posology, and indications are according to the reference product, as described in the Herceptin SmPC. Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2).

Herwenda is claimed for the following indications:

- treatment of adult patients with HER2 positive metastatic breast cancer
    - Monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease.
    - In combination with paclitaxel or 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.
- treatment of adult patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- In combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of adult patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anticancer treatment.

Summary of analytical comparability (quality data)

The applicant has performed extensive testing of EG12014 batches and EU Herceptin batches.

Similarity between EG12014 and EU-approved Herceptin is addressed using a wide range of analytical exercises covering physiochemical and biological properties, as well as a forced degradation study. Most of the quality attributes proved to be highly similar. The main differences between EG12014 and Herceptin include level of aggregates, oxidation, free thiols and basic variants, however, these differences do not have a significant impact on biological activities and potency assays.

Summary of non-clinical data

The EG12014 non-clinical programme consists of one pharmacodynamic xenograft mouse model study and a PK study in mice.

As indicated in EMA/CHMP/BMWP/403543/2010, a stepwise approach should be applied when evaluating non-clinical biosimilarity. Step 1 comprises a number of comparative in vitro studies.

Summary of clinical comparability data

The clinical program comprised a pivotal phase 1 pharmacokinetic (PK) similarity study (**EGC001**) in healthy males, and a phase 3 efficacy and safety study (**EGC002**) in female HER-2 positive EBC patients. Immunogenicity (incidence of ADAs and NAbs against trastuzumab) has been assessed as a secondary objective in both studies. Population pharmacokinetic (popPK) modelling of EG12014 and Herceptin in patients with HER2+ EBC is submitted as supportive PK information.

Study **EGC001** was a double blind, randomised, parallel-group, single-dose (90 minutes IV infusion of 6 mg/kg trastuzumab), three-arm, two-stage study in healthy male subjects. The primary PK endpoint was $AUC_{0\text{-}inf}$ of trastuzumab, and additional endpoints were C_{max}, $AUC_{0\text{-}t}$, AUC_{res}, $t_{1/2}$, T_{max}, Vz, λz, and CL.

The clinical efficacy and safety development program to demonstrate equivalence between EG12014 and the reference product EU-Herceptin consists of a randomised, double-blind study (**EGC002**) in 807 female HER2-positive early breast cancer (EBC) patients (405 and 402 patients in EG12014 and Herceptin arms, respectively).

The primary efficacy endpoint was pathological complete response (pCR) at time of surgery after the neoadjuvant treatment with four cycles of Anthracycline-based chemotherapy followed by four cycles with paclitaxel and trastuzumab. The pCR was defined as the absence of residual invasive cancer of the complete resected breast specimen and all sampled sentinel and/or axillary lymph nodes as assessed by central laboratory. Secondary endpoints included other histological definitions of pCR, overall response rate (ORR), event-free survival (EFS) and overall survival (OS). Up to ten blood samples per patient were collected: before start of trastuzumab therapy, pre-infusion in the trastuzumab neoadjuvant part, pre-surgery, pre-infusion at beginning of and during adjuvant therapy and three weeks after the end of study.

3.2. Results supporting biosimilarity

Quality data

Most of the quality attributes proved to be highly similar. For attributes which fail the predefined biosimilarity acceptance criteria, justifications are provided. These deviations were mostly regarded as unlikely to have an impact on safety and/or efficacy, and as the results from the orthogonal assays were within quality range, similarity can be supported.

Importantly, for the biological function parameters of EG12014 none of the deviations were considered to preclude biosimilarity.

EG12014 can thus be considered as a biosimilar to EU-Herceptin from a quality perspective.

Non-clinical data

As indicated in EMA/CHMP/BMWP/403543/2010, a stepwise approach should be applied when evaluating non-clinical biosimilarity. Step 1 comprises a number of comparative in vitro studies considered paramount for non-clinical similarity assessment. Similarity between EG12014 and EU Herceptin has been addressed in a biosimilarity exercise covering physiochemical and biological properties, and EG12014 can thus be considered as a biosimilar to EU-Herceptin from a non-clinical perspective.

Clinical data

Pharmacokinetics

In the pivotal phase I PK study **EGC001** in healthy volunteers the $AUC_{0\text{-}inf}$ point estimate (GMR) for EG12014 versus EU Herceptin was 89.81 (94.12 %CI: 82.11, 98.23). PK data obtained as secondary endpoints in the phase 1 (**EGC001**) and phase 3 study **EGC002**, also indicated similarity of the pharmacokinetics of EG12014 and Herceptin. Based on popPK modelling using neoadjuvant data from study **EGC002**, the total clearance and central volume of distribution were 0.210 and 0.234 L/day, and 3.07 and 3.08 L for EG12014 and Herceptin, respectively. Similar clearance is also indicated at steady state (adjuvant phase).

Efficacy

Similar outcomes in the two treatment groups were reported for the primary efficacy analysis (in the full analysis data set). In total, 191 subjects (47%) in the EG12014 arm and 192 (48%) subjects in the Herceptin arm were responders according to pCR (regardless of in-situ changes). The pCR risk difference (95% CI) between the two arms was -0.004 (-0.072, 0.065), which is within the pre-defined equivalence margins of ±13%. Most of the stratification subgroup- and sensitivity analyses reflect the primary endpoint.

The secondary endpoint of pCR defined otherwise than the primary endpoint (in breast tissue only and exclusive in-situ changes), had comparable findings, with the 95%CI risk difference containing 0 and within its equivalence margins. The objective response rate (95% CI) prior to surgery was in the EG12014 arm 84% (80-87%) and in the Herceptin arm 84% (80-87%). So, the ORR results support the outcome of the primary endpoint. The result is hence based on multimodal tests (i.e., pathologic, and radiologic data).

For the entire study, event-free survival was 25 subjects in the EG12014 arm and 30 in the Herceptin arm. Overall survival was 4 in the EG12014 arm and 5 in the Herceptin arm. Hazard ratios for EFS and OS were 0.775 (95% CI: 0.45, 1.33) and 0.741 (95%CI: 0.20, 2.77), respectively. So, very few survival-related events were found in total, and no indication of any differences could be seen in EG12014 and reference product. No indications of any detrimental effect are seen in the study arms.

In conclusion, a comparable efficacy profile of EG12014 to the reference product support biosimilarity.

Safety

In the Phase 1 study **EGC001**, the incidence of TEAEs was similar between the EG12014 and US Herceptin arms, 67.9% vs 60.7%, while it was slightly lower in the EU Herceptin arm, 46.4%. It is of note that these numerical imbalances are not unexpected in such a small study (28 subjects in each arm).

In the pivotal phase 3 study **EGC002**, neoadjuvant part, the overall incidence and severity of TEAEs was comparable between the EG12014 and Herceptin treatment arms, 99.2% vs 98.5% respectively. There were no obvious differences noted between the treatment arms in the frequencies of patients experiencing TEAEs within reported SOCs or PTs. Likewise, laboratory findings and cardiac assessments (LVEF and ECG) appeared balanced between the treatment arms. For the adjuvant part, the overall, incidence, severity, and causality of TEAEs were comparable for the three study drug arms.

Immunogenicity of EG12014 appears to be relatively low ("de novo" ADAs: incidence ~3.3%, no NAbs, no apparent persistence) and comparable to the reference product EU Herceptin based on available data in EBC patients.

Overall, a comparable safety immunogenicity profile has been shown between the proposed biosimilar EG12014 and the originator product, establishing biosimilarity (in combination with taxanes).

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

EG12014 can be considered as a biosimilar to EU-Herceptin from a quality point of view, a non-clinical point of view and clinical point of view. The comparability exercise has been successful and similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy has been established.

The pivotal phase I PK study **EGC001** in healthy volunteers, apparently demonstrates similarity of the pharmacokinetics of EG12014 and Herceptin. PK data obtained as secondary endpoints in the phase 3 study **EGC002**, also indicated similarity of the pharmacokinetics of EG12014 and Herceptin. Similar PK (CL and Vc) of EG12014 and Herceptin in EBC patients is indicated based on popPK modelling using sparse PK data from the neoadjuvant part of study **ECG002**.

Pathological complete response (pCR) was chosen as the primary efficacy endpoint, in accordance with CHMP guidance. The **EGC002** trial has demonstrated that the risk difference of pCR at the time of surgery was within its predefined margins. Results of secondary surgical-related and survival-related endpoints of the study, sensitivity analyses and most of the sub-group analyses reflect the primary endpoint and are also supporting therapeutic similarity.

3.5. Extrapolation of safety and efficacy

The indications granted for the reference product EU-Herceptin 150 mg are all claimed for the trastuzumab biosimilar EG12014.

The mechanism of action of trastuzumab is the same in all three indications. The dosage is also similar for all three indications, and trastuzumab is administered via the same route in all indications mentioned. Based on these points extrapolation of all originator indication can be supported given that robust evidence from the quality characterisation, functional assays, clinical pharmacokinetics, efficacy and safety including immunogenicity is demonstrated.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, EG12014 is at present considered biosimilar to Herceptin and a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Herwenda is favourable in the following indication(s):

Breast cancer

Metastatic breast cancer

Herwenda 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

Herwenda 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 Herwenda therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herwenda 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

Herwenda 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 gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herwenda 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 IHC3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

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 marketing authorisation holder (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.