18 October 2018
EMA/810499/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ogivri

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/004916/0000

Note

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

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List of abbreviations

ADA	Antidrug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR(s)	Adverse drug reaction(s)
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARR	Administration-related reaction
AST	Aspartate aminotransferase
AUC	Area under the curve
BDRM	Blinded data review meeting
BCPI	Biologics Price Competition and Innovation Act
BP	Blood pressure
BSA	Body surface area
BSSR	Blinded sample size re-estimation
BUN	Blood urea nitrogen
CDC	Complement-dependent cytotoxicity
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum drug concentration
Cmin	Minimum drug concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curricula vitae
CYP2C8	Cytochrome P2C8
CYP3A4	Cytochrome P3A4
CYP450	Cytochrome P450
DR	Duration of response
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECD	Extracellular domain (of HER2)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of study
EOT	End of treatment

ER/PgR	Estrogen receptor/Progesterone receptor
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
GCP	Good Clinical Practice
HAHA	Human antihuman antibodies
hCG	Human chorionic gonadotropin
HER2	Human epidermal growth factor receptor 2
HER2+	Human epidermal growth factor receptor 2 positive
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
ILN	Institutional level normal
IMP	Investigational medicinal product
INR	International normalized ratio
IOP	Inhibition of proliferation
IRB	Institutional Review Board
IRR(s)	Infusion-related reaction(s)
ITT	Intention-to-treat
Iv	Intravenous(ly)
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LN	Natural log
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minutes
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
N, n	Number of patients
Nab	Neutralizing antibodies
NCI	National Cancer Institute
NCS	Not clinically significant
NE	Not estimable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PEG	Polyethylene glycol
PFS	Progression-free survival
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PP	Per-protocol
PR	Partial response
PrT	Prothrombin time

PT	Preferred term
PTT	Partial thromboplastin time
QT	interval Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	interval Corrected QT interval
RA	Regulatory authorities
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SE	Standard error
SmPC	Summary of Product Characteristics
SOC	System organ class
SPR	Surface plasmon resonance
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
36M/240D	The study time point when 36 months have passed since the last patient was randomized into the study or the 240th death has occurred, whichever occurred first
T1/2	Terminal elimination half-life
TK	Toxicokinetics
TLFs	Tables, Listings, and Figures
TOST	Two one-sided tests
TTP	Time to tumour progression
ULN	Upper limit of normal
US	United States
Vd	Volume of distribution
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S submitted on 3 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Ogivri, 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 indication:

Breast cancer

Metastatic breast cancer

Ogivri 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

Ogivri is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Ogivri therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter

Ogivri should only be used in patients with metastatic or EBC whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay

Metastatic gastric cancer

Ogivri in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Ogivri should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

The legal basis for this application refers to:

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

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 6/8/10 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 comparability tests and studies have been conducted:

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

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received Scientific Advice from the CHMP on 15 March 2012. The Scientific Advice pertained to quality, pre-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Koenraad Norga Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	3 November 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 September 2018
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	20 September 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 September 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 October 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ogivri on	18 October 2018

2. Scientific discussion

2.1. Problem statement

About the product

Trastuzumab is a humanized recombinant IgG 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 (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.

The applicant's trastuzumab (Ogivri) has been developed as a biosimilar product to Herceptin which is the reference product in this application. The claimed indications are the same as the ones approved for the reference product Herceptin:

Breast Cancer

Metastatic breast cancer

Ogivri 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

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

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

Metastatic gastric cancer

Ogivri in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Ogivri should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see SmPC sections 4.4 and 5.1).

The posology and method of administration are the same as the ones approved for Herceptin 150 mg powder for concentrate for solution for infusion. The applicant did not claim subcutaneous use.

Ogivri is for intravenous infusion and contains 150 mg of trastuzumab as a lyophilized powder for concentrate for solution for infusion. In addition to the drug substance, the formulation contains L-histidine hydrochloride and L-histidine, sorbitol and Macrogol 3350. The formulation is identical to the reference medicinal product with the exception of the substitution of sorbitol for α-trehalose dehydrate, and Macrogol 3350 for polysorbate-20.

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. This is an application for a biosimilar trastuzumab. 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.

The clinical programme was initiated with the aim to show biosimilarity between both products in the setting of metastatic breast cancer (MBC), and extrapolating similarity to the other indications in case biosimilarity was confirmed in MBC in regards to quality, non-clinical, PK, pharmacodynamic and clinical aspects.

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

2.2. Quality aspects

2.2.1. Introduction

Ogivri is a proposed biosimilar to Herceptin (trastuzumab, Roche Registration Limited) indicated for the treatment of human epidermal growth factor receptor 2 (HER-2) overexpressing cancers.

The finished product is presented as a powder for concentrate for solution for infusion containing 150 mg of trastuzumab as active substance.

Other ingredients are: histidine hydrochloride, histidine, sorbitol, macrogol 3350, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment). The product is available in a 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film.

2.2.2. Active Substance

General Information

The active substance (INN: trastuzumab) is a recombinant deoxyribonucleic acid (DNA)-derived humanized monoclonal antibody directed against human epidermal growth factor receptor type 2 (HER2). It belongs to the immunoglobulin G subclass 1 kappa isotype and contains human framework regions with the complementary-determining regions of a murine antibody (4D5) that binds to HER2.

Trastuzumab consists of 1328 amino acids and is comprised of two identical heavy chains (HCs) and two identical light chains (LCs). Each HC is comprised of 450 amino acid residues and each LC is comprised of 214 amino acids. The HCs are fully glycosylated at Asn300.

The formulated bulk active substance is a clear to slightly opalescent non-turbid liquid.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The facility responsible for the manufacture and testing of the active substance is Biocon Limited, Plot No. 2-5, Phase IV, Bommasandra-Jigani Link Road, Bangalore, India.

The active substance is manufactured using a fed-batch process in a production bioreactor. Following cell culture and harvest, active substance is purified from the harvest culture fluid through a series of filtration and chromatography steps. The process includes steps to inactivate/remove potential contaminating viruses. Excipients are added to generate the formulated active substance.

Process control classifications and acceptance ranges are considered acceptable. The process parameters are controlled by acceptable ranges

Control of materials

Raw materials are sufficiently described and controlled. The details regarding the origin of materials, pharmacopoeial reference or internal specification, and the stage of the manufacturing process, where the material is used, are provided.

Recombinant CHO cells expressing the monoclonal antibody trastuzumab were established. A 2-tiered cell banking system of MCB and WCB was established and qualified. The MCB complies with ICH Q5A and Q5D. A post-production cell bank (PPCB) was prepared and tested for identity, purity, and contamination by adventitious agents such bacteria, fungi, mycoplasma, and viruses according to ICH Q5A and ICH Q5D. Genetic stability up to and beyond the generation number needed for routine production was investigated.

Control of critical steps and intermediates

Input critical process parameters (CPPs) have been defined during process characterization. The output attributes are classified into critical and non-critical output attributes. In-process controls (IPCs) are performed at each stage during the manufacture of active substance to ensure that the process is controlled. The definition of the critical IPCs along with justification for limits, are acceptable.

Process validation

The process validation (PV) was performed on three full scale active substance batches. The batches were manufactured using the final commercial process. The data demonstrate that the commercial process, when operated within the specified ranges, consistently produces active substance that meets the predetermined specification. Clearance of process-related impurities has been found to be consistent. The impurity levels obtained at the end of the manufacturing process are considered acceptable. Overall the manufacturing process is considered appropriately validated.

A hold time stability study was conducted to support the hold time of the in-process product pools.

Chromatographic column resin reusability was evaluated.

Manufacturing process development

The process development, including several process versions, has been described. Changes introduced during development include scale up and process optimisations. The applicant has performed comparability studies (including verification of process performance, release test results, characterisation test results and stability test results) to show that batches from the different process versions can be considered as comparable.

Characterisation

Characterisation studies were performed to verify primary structure, disulphide bonds, higher order structure, glycosylation pattern, oxidation, purity and biological function of the active substance.

The intact mass, reduced mass, N and C terminal analysis as well as > 95% coverage of the protein sequence by peptide mass fingerprinting using two endo-proteinases demonstrated that the active substance had the expected primary structure.

For the secondary structure analysis and tertiary, while a direct quantitative measurement of the structure aspect was possible only for Far-UV CD analysis, for other techniques comparison with the reference product Herceptin was used a tool to elucidate the structure of the protein. In Far UV-CD analysis, the protein was identified to be a predominant β sheet structure. From the UV profile of the disulphide and peptide map analysis, it could be ascertained that the disulphide linkages and the protein fold was in the correct orientation as verified by comparing with Herceptin. Similarity in free cysteine content added to this conclusion. The tertiary structure analysis was completely evaluated in comparison to Herceptin.

Product-related variants like high molecular weight protein (HMWP), low molecular weight protein (LMWP), fragments, surface charge and net charge based were all analyzed with various techniques and it was found in all cases that the major structural form was the intact monoclonal antibody with the appropriate molecular weight, surface and net charge.

The glycoforms were found to be consistent from batch to batch and comparable with EU Herceptin. Also, the sialic acid was of the N-acetylneuraminic acid (NANA) type with no evidence of the N-glycolylneuraminic acid (NGNA) type being present.

Functional analysis of the protein was performed by means of SKBr3 cell proliferation, HER2 binding kinetics, ADCC and complement-dependent cytotoxicity (CDC) analysis. In all the biological assays the activity was found to be comparable to the reference indicative of the fact that protein was structurally intact and in the required conformation.

Levels of product-related impurities were very low and within acceptable limits.

Process-related impurities are controlled and/or removed at different steps of the purification process during manufacture of the active substance Levels of process-related impurities were very low due to efficient clearance by the process purification steps.

Specification

Specifications are set in accordance with ICH Q6B and include tests for appearance, identity, purity and impurities, content, potency, microbiological safety and general tests. The specifications are considered sufficient in order to control the quality of the active substance. However, some of the limits should be re-assessed once release data from further commercial batches are available. Regarding afucosylated species, the lower limit has been revised to a level that can be considered as clinically qualified and representative of the normal EU Herceptin quality range.

Analytical methods

The analytical methods used for active substance testing have been described in detail. Potency is determined by cell proliferation and binding to HER-2 expressing cells.

The validation of the analytical methods was described in detail. The results are deemed sufficient and acceptable. Consequently, the methods are appropriately validated.

Batch analysis

The applicant has provided batch data for several active substance lots from different versions of the manufacturing processes.

Reference materials

The applicant provided detailed information on the current and previous reference standard lots. For qualification, each of these lots was extensively tested according to the release specifications as well as by additional characterisation testing. For future internal reference standards the same panel of release and characterisation tests will be used for qualification.

Container closure

The formulated bulk active substance is stored in a Celsius-Pak bag. The container closure system was described and adequately qualified; leachables and extractables studies were performed.

Stability

Stability data have been provided for batches stored under long-term and accelerated storage conditions. The stability data provided for the different processes, show that all results were compliant with the specifications and no significant trending has been observed.

The stability samples were stored in Celsius bags made of the same material as used for the proposed commercial primary packaging.

The stability data support the proposed shelf-life of 24 months, when the active substance is stored at the recommended long-term storage condition.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is presented as 150 mg powder for concentrate for solution for infusion and is supplied in a single use vial (15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film). The finished product is intended for reconstitution with 7.2 mL of sterile water for injections (not supplied with the pack) to yield a solution containing approximately 21 mg/mL trastuzumab. Other ingredients are histidine hydrochloride, histidine, sorbitol, macrogol 3350, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

There is no overage in the manufacturing process. An overfill of 4% is included in order to assure that the labelled dose of 150 mg can be withdrawn from each vial.

The pharmaceutical development was focused on developing a formulation that was highly similar to the reference product, Herceptin, from a quality and stability perspective. The reference product contains trehalose dihydrate (which functions as a lyoprotectant, cryoprotectant, and bulking agent) and polysorbate 20 (which functions as a surfactant). To circumvent patent protection, macrogol 3350/PEG 3350 was selected as an alternative cryoprotectant and D-sorbitol was selected as a lyoprotectant and bulking agent for Ogivri.

Changes made to the finished product manufacturing process during the development have been described and aimed at improving control of the process, with no impact to the quality of the finished product. The comparative analytical data of the finished product used in the manufacture of Phase I, Phase III and process validation batches were provided.

The container closure system was described and adequately qualified; leachables and extractables studies were performed. The container closure system for the finished product remained unaltered during process development.

Manufacture of the product and process controls

The facility responsible for manufacture and QC testing of the finished product is Biocon Limited, Plot Nos. 2, 3, 4 & 5, Phase IV, Bommasandra-Jigani Link Road, Bangalore, India. The batch release site for EU is McDermott Laboratories T/A Mylan Dublin Biologics (Dublin, Ireland).

The manufacturing process consists of thawing of formulated active substance, pooling of individual active substance bags followed by mixing, pre-filtration, sterile filtration, aseptic filling, lyophilization, and sealing of vials containing the lyophilized product. The manufacturing steps have been appropriately described. The definition and classification of critical and non-critical process parameters is acceptable. The in-process controls and acceptance criteria have been described and found acceptable.

The finished product manufacturing process has been validated by three consecutive full scale production batches using the same manufacturing facilities, process and equipment as intended for commercial use. All process parameters as well as performance parameters monitored during the process validation study were maintained within their specified ranges. Based on the data provided, it can be concluded that the finished product manufacturing process is under control and can be considered as validated.

The aseptic process used for the sterilization has been validated through media fills.

Product specification

The release specification for the finished product includes tests for appearance, identity, purity and impurities, content, excipient, potency, determination of pH, general pharmacopeial tests, and safety testing.

The finished product specifications are considered adequate and in accordance with ICH Q6B. Upon request by the CHMP, the applicant aligned the shelf life specification limits for purity by SEC-HPLC and Biological activity by inhibition of SK-BR-3 proliferation with those for release as lower requirements for shelf life are not considered acceptable in the absence of any trends during shelf life.

Analytical methods

The analytical methods used for routine testing of the finished product have been appropriately described and non-compendial methods have been validated in accordance with ICH Q2(R1).

Batch analysis

The applicant has provided batch data for finished product lots manufactured using active substance from different processes. The results confirm the consistency of the manufacturing process.

Reference materials

Please refer to the active substance section. The reference standards for finished product are the same as those used for the active substance.

Stability of the product

Real time (5°C ± 3°C), accelerated (25°C± 2°C) and stressed (40°C± 2°C) stability studies have been performed according to ICH Q5C. No decrease or trends were observed for potency or purity at 2-8°C or 25°C± 3°C.

An in-use stability study was performed and supports the stability of the reconstituted finished product as indicated in the SmPC. An infusion study showed compatibility with infusion bags/systems of polyvinyl chloride (PVC), polypropylene (PP) or polyethylene (PE) materials at 30°C for a period of 24 hours.

A temperature excursion study showed that the product was stable after being exposed to a temperature excursion (25°C) of 48 hours.

Based on available stability data, the proposed shelf life of 48 months for the finished product when stored at 5°C ± 3°C, as stated in the SmPC, is acceptable.

Post-Approval Change Management Protocol (PACMP)

In preparation for Brexit, the applicant included a PACMP covering the addition of test sites for finished product release to ensure uninterrupted EU importation testing. The data from the analytical method transfer will be submitted as a Type IB variation.

The proposed PACMP is deemed acceptable.

Biosimilarity

The applicant has performed an extensive comparability analysis to demonstrate biosimilarity to the reference product Herceptin. Comprehensive analyses of the proposed biosimilar and reference medicinal product were

carried out using sensitive and orthogonal methods. This included batches of EU-approved Herceptin, US licensed Herceptin and Ogivri finished product. US-licensed Herceptin has been used as part of a global development and was included as supportive data, however the pivotal clinical data was generated with EU-approved Herceptin. The number of lots chosen for the biosimilarity analysis was based on the criticality of attribute, availability of an orthogonal technique, assessment of analytical method variability, complexity and suitability of method for large number of assays and availability of material.

Most of the quality attributes proved to be highly similar between Ogivri and EU-approved Herceptin. Nevertheless for some structural parameters, which might impact clinical performance, differences were observed, such as for high mannose and afucosylated glycoforms, sialic acid content and non-glycosylated species. These are further discussed below.

The overall level of non-glycosylated species is very low and the small difference observed is therefore not expected to have any meaningful impact.

The total high mannose content is higher for Ogivri as compared to EU-approved Herceptin. The applicant has however provided *in vitro* bioactivity assay data dependent on Fc function (ADCC, FcγRIIIa, C1q and other Fc binding assays) for Ogivri which indicate a high similarity with EU-approved Herceptin lots. In addition, data were provided to show that the higher mannose content most probably has no impact on PK.

As the overall content of total non-glycosylated heavy chain (NgHC) and sialic acid is very low, the slight differences are not considered to have an impact on PK and biological activity.

Afucosylated content for Ogivri is somewhat higher as compared to EU-approved Herceptin. However, the *in vitro* bioactivity assay data of Ogivri dependent on Fc function (ADCC, FcγRIIIa, C1q and other Fc binding assays) indicate similarity with EU-approved Herceptin lots.

Ogivri lots showed slightly higher main peak content and slightly lower acidic peak content estimated by ion exchange HPLC as compared to EU-approved Herceptin. Similar results were observed with cIEF. This has been justified. It is acknowledged that C-terminal lysine is not expected to have an impact on biological activity.

Taken together, the data provided indicate that Ogivri can be considered as biosimilar to EU-approved Herceptin at quality level and the small differences observed have been appropriately justified. A tabular summary of the analytical similarity assessment is provided below.

Table 1: Tabular summary of analytical similarity assessment results

Quality attribute	**Methods/Tests**	**Analytical similarity summary**
Protein content	UV 280 absorption	Highly similar
Amino acid sequence	Peptide mapping	Identical
	Intact mass	Highly Similar
Conformation (Secondary and higher order structure)	Peptide mass finger printing	Highly Similar
	Far UV CD	Highly Similar
	Fourier transform infrared spectroscopy	Highly Similar
	Free cysteine	Highly Similar
	Disulfide bridging	Highly Similar
	Near UV CD	Highly Similar
	Differential scanning calorimetry	Highly Similar
	Intrinsic fluorescence	Highly Similar
	Hydrophobic interaction chromatography	Similar
Aggregates	SEC UV	Highly Similar

Quality attribute		Methods/Tests	Analytical similarity summary
		Analytical ultracentrifugation	Highly Similar
		SEC – MALS	Highly Similar
Fragments		CE-SDS (non-reduced)	Highly Similar
Glycoform variants	Afucosylated	NP-HPLC linked with liquid chromatography-mass spectrometry	Afucosylated content for MYL-1401O is marginally higher as compared to EU-approved Herceptin. All the *in vitro* bioactivity assay data of MYL-1401O dependent on Fc function (ADCC, FcγRIIIa, C1q and other Fc binding assays) indicate a high similarity with EU-approved Herceptin lots. Furthermore, afucosylated content in US-licensed Herceptin when tested *in-vitro* has shown to have no measurable impact on ADCC activity or binding to FcγRIIIa. Additionally, clinical studies with these levels of afucosylated species have not shown any impact on pharmacokinetics and demonstrated bioequivalence within a very narrow confidence
	High mannose	Normal phase HPLC	Total mannose content for MYL-1401O is marginally higher as compared to EU-approved Herceptin. All the *in vitro* bioactivity assay data of MYL-1401O dependent on Fc function (ADCC, FcγRIIIa, C1q and other Fc binding assays) indicate a high similarity with EU-approved Herceptin lots. Furthermore, high mannose content in US-licensed Herceptin when tested *in vitro* has shown to have no measurable impact on ADCC activity or binding to FcγRIIIa. Additionally, clinical studies with these levels of total mannose content have not shown any impact on pharmacokinetics and demonstrated bioequivalence within a very narrow confidence.
	Terminal galactose	Normal phase HPLC	Highly similar
	Terminal sialic acid	Reverse phase HPLC	The level of total sialic acid content was observed to be marginally higher for most of MYL-1401O lots compared to EU-approved Herceptin. Literature data report that high levels of sialylated forms can potentially impact ADCC and PK. The narrow range of sialyation of MYL-1401O lots when tested *in vitro* has shown to have no detectable impact on ADCC activity or binding to FcγRIIIa and thus there is a low risk that this minimal difference in sialic acid content will have an impact. Additionally, clinical studies with these levels of sialic acid content have not shown any impact on pharmacokinetics and demonstrated bioequivalence within a very narrow confidence.
	Aglycosylated	Reduced CE SDS	The total NgHC content of MYL-1401O lots is marginally lower as compared to EU-approved Herceptin. Although the Ng-HC content of MYL-1401O is observed to be marginally lower this minor difference is not expected to have a meaningful impact as the overall level of impurity is very low (<1.0%). This is substantiated by the ADCC and FcγRIIIa binding data of MYL-1401O vs EU-approved Herceptin, which are highly similar. Additionally, clinical studies with these levels of Ng-HC content have not shown any impact on pharmacokinetics and demonstrated bioequivalence within a very narrow confidence

Quality attribute	Methods/Tests	Analytical similarity summary
Glycation	Boronate affinity chromatography	Highly similar
Charge variants (deamidation, isomerization, and C-terminal lysine)	Ion exchange HPLC Capillary isoelectric focusing	MYL-1401O lots showed a marginally higher main peak content and slightly lower acidic peak content estimated by ion exchange HPLC as compared to EU-approved Herceptin. Similar results were observed in cIEF as well. This could be attributed to the carboxypeptidase treatment included in the manufacturing process of MYL-1401O which removes the C-terminal lysine residues and changes the distribution of the charge variants potentially leading to increase in main peak content. C-terminal lysine variants have been reported to have no impact on biological activity. Additionally, the charge variants from MYL-1401O as well as EU-approved Herceptin have been extensively characterized and found to be comparable.
HER2 binding	SKBr3 based binding assay	Highly Similar
Inhibition of proliferation	SKBr3 cell based assay	Highly Similar
ADCC	SKBr3 and PBMC based ADCC assay	Highly Similar
FcγRIIIa	FcγRIIIa binding Biacore based assay	Highly Similar
FcRn	FcRn binding Biacore based assay	Highly Similar
Other effector/ Fc functions	FcγRIa binding Biacore based assay	Highly Similar
	FcγRIIa binding Biacore based assay	Highly Similar
	FcγRIIb binding Biacore based assay	Highly Similar
	FcγRIIb binding Biacore based assay	Highly Similar
	C1q binding ELISA assay	Highly Similar

Adventitious agents

Raw materials are sufficiently controlled for possible contaminating viruses. In-process testing is performed on the active substance harvest to screen for possible virus, retrovirus, mycoplasma or microbial contamination. The MCB and sMCB were adequately qualified and tested for possible viral contamination. The active substance manufacturing process contains validated virus removal/inactivation steps.

Compliance with the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.3) has been sufficiently demonstrated. The active substance is produced in a serum-free medium and no materials of animal or human origin are used during manufacturing.

2.2.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

A major objection was raised during the procedure relating to the GMP status for the finished product manufacturing site. Following a positive outcome of a re-inspection of the site, the major objection was resolved.

With regard to the biosimilarity analysis, the applicant has performed an extensive analytical comparability assessment. The data provided indicate that Ogivri can be considered as biosimilar to EU-approved Herceptin at the quality level and the small differences observed have been appropriately justified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

In the context of the obligation of MAHs to take due account of technical and scientific progress, the CHMP recommended some additional points for investigation, relating to review of some specification limits once data from further commercial batches becomes available.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical studies submitted consist of *in vitro* pharmacodynamic studies, a single-dose pharmacokinetic (PK) study in cynomolgus monkeys, and a combined 28-day repeat-dose toxicokinetic study in cynomolgus monkeys. Only the repeat-dose toxicity study with toxicokinetics in cynomolgus monkeys was conducted in accordance with Good Laboratory Practices (GLP) regulations.

The initial formulation was developed to have the same composition as that of intravenous Herceptin. This formulation was referred to as the Bmab 200-reference product formulation (Bmab 200-RPF), however, Macrogol 3350/PEG 3350 was then selected as an alternative cryoprotectant and D-sorbitol was selected as a lyoprotectant and bulking agent. The resulting formulation is referred to as “MYL-1401O” or Bmab 200-PGS formulation is proposed for the current Marketing Authorisation Application.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Trastuzumab binding 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 animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of ADCC. *In vitro*, trastuzumab-mediated ADCC has been shown to preferentially exert its effect on HER2 overexpressing cancer cells compared with cancer cells that do not

overexpress HER2. Finally, the presence of trastuzumab has also been shown to mediate macrophages and cancer cell killing through phagocytic engulfment (ADCP) (see Herceptin EPAR).

The *in vitro* assays performed for the biosimilarity assessment were: target (HER2) binding assay, ADCC assay, Antibody dependent cellular phagocytosis (ADCP), surface plasmon resonance (SPR) kinetic assays on the Biacore instrument platform for Fc gamma receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa and FcγRIIIb), and C1q binding as determined by an enzyme-linked immunosorbent assay (ELISA), FcRn binding by SPR, CDC assay, and MYL-1401O inhibition of proliferation (IOP) assay.

All the studies supporting biosimilarity assessment were performed with MYL-1401O, except the initial complement dependent cytotoxicity assay, which was performed with the previous Bmab200 formulation. Additional CDC data were provided with a lot from a different process (see further below).

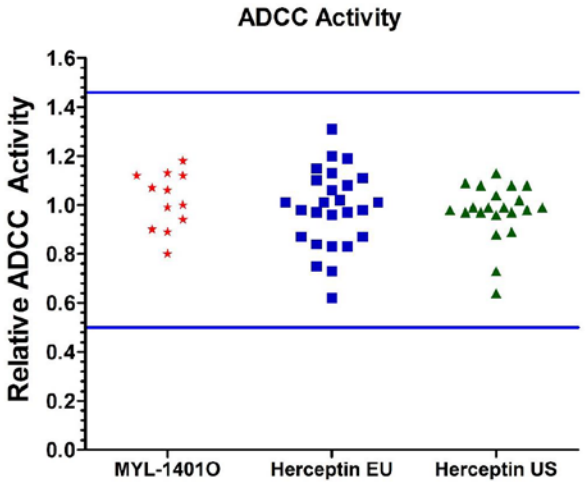
A number of batches of MYL-1401O (current formulation) were compared to the reference medicinal product, Herceptin (European Union [EU]-approved [EU-Herceptin], and United States [US]-licensed [US-Herceptin]).

ADCC Assay (Cell-Based Assay) (study number(s): BDL/TR/1168/13/003 V002, BDL/TR/BR.14.5002/16/002 and BDL/TR/BR.14.5002/15/006)

Twenty-six batches of EU-Herceptin, 21 batches of US-Herceptin, and 12 batches of in-house MYL-1401O with concentrations from 0.0001 to 1000 ng/mL were pre-incubated with SK-BR-3 cells. Following incubation, peripheral blood mononuclear cells (PBMCs) were added. The resulting cell death due to ADCC mediated cytolysis was detected by measuring protease release with CytoTox Glo reagent. The relative potency compared to the reference standard ranged from 0.62 to 1.31, 0.64 to 1.13 and 0.80 to 1.18, respectively.

The result distribution and the quality range limits are represented in Figure 3 below:

Figure 1: Scatter plot distribution of Relative ADCC activity of MYL-1401O, EU approved HERCEPTIN, and US Licensed HERCEPTIN Lots



FcγRIIIa Kinetics Assay (Biacore Kinetics) (Study Number(s): BDL/SAR.BR.14.5002/16/001 and BDL/TR/BR.14.5002/16/003)

FcyRIIa receptor is subject to polymorphism: 2 forms exist for FcγRIIIA: 158V and 158 F depending on valine or a phenylalanine at amino-acid position 158. Since binding of IgG depends on the isoform of the receptor used in the assays and to ascertain that biosimilarity applies for polymorphic forms of FcYIIIA receptors, comparative

binding data for isoforms 158V / 158F were provided. The binding kinetics (ka and kd) and dissociation constant (KD) of MYL-1401O and Herceptin to FcγRIIIa 158V and 158 F were compared by SPR.

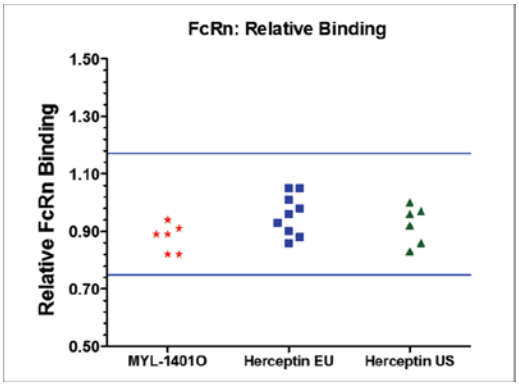
Results FcγRIIIa-V158: Ten batches of EU-Herceptin, 10 US-Herceptin and 6 MYL-1401O batches were analyzed; the dissociation constant (KD) ranged from 85.7 to 147.7 nM, 90.3 to 150.3 nM, and 102.5 to 114.3 nM, respectively.

Results FcγRIIIa-F158: Five batches of EU-Herceptin, 4 US-Herceptin and 3 MYL-1401O batches were analyzed; the KD ranged from 76.09 to 125.12 nM, 67.48 to 144.53 nM, and 76.21 to 93.51 nM, respectively. An updated data set including data from 7 lots of EU-Herceptin and 5 lots of MYL-1401O was provided. The FcYRIIIa-F158 K_D values of the 5 MYL-1401O lots tested were found within the Mean ± 2SD range of the EU-Herceptin lots.

FcRn Binding Assay (Study Number(s): BDL/TR/BR.14.5002/16/007)

The relative binding affinity to the FcRn receptor was compared between MYL-1401O and Herceptin using SPR. Nine EU-Herceptin, 6 US-Herceptin and 6 in-house MYL-1401O samples were analyzed; the average relative binding compared to the reference standard ranged from 0.86 to 1.05, 0.83 to 1 and 0.82 to 0.94, respectively.

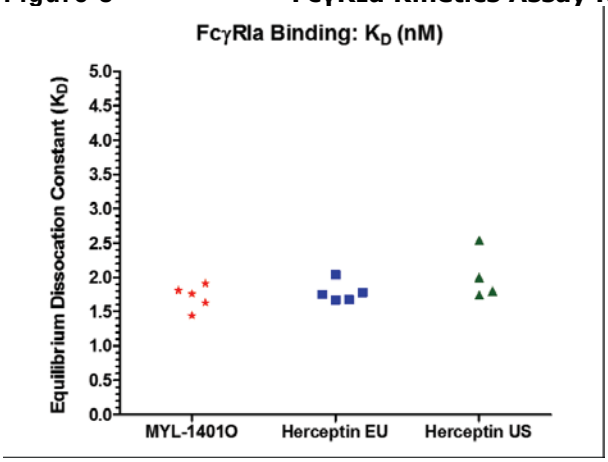
Figure 2 FcRn relative binding



FcγRIa Kinetics Assay (Study Number(s): BDL/TR/BR.14.5002/16/004)

The binding kinetics (ka and kd) and dissociation constant (KD) of MYL-1401O and Herceptin to FcγRIa were compared by SPR. Five EU-Herceptin, 4 US-Herceptin and 5 MYL-1401O samples were analyzed; the KD ranged from 1.67 to 2.04 nM, 1.74 to 2.54 nM and 1.44 to 1.91 nM, respectively.

Figure 3 **FcγRIa Kinetics Assay Results**



FcγRIIa Kinetics Assay (Study Number(s): BDL/HER/SAR/16/001)

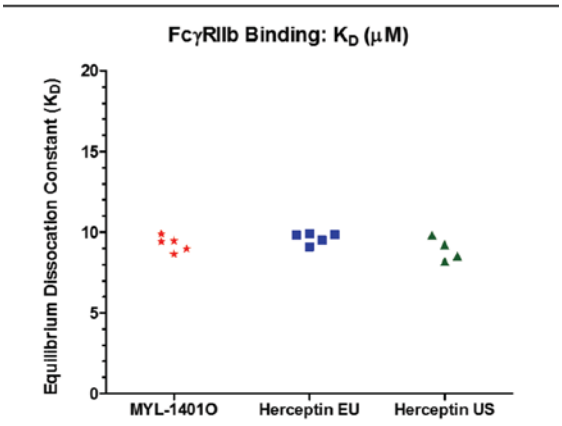
SPR was used to determine the binding kinetics (ka, kd and KD) of MYL-1401O and Herceptin to FcγRIIa. FcγRIIa receptors are subject to polymorphism: 2 forms exist for FcγRIIa: 131H and H131R depending on histidine or arginine at position 131. Since binding of IgG depends on the isoform of the receptor used in the assays and to ascertain that biosimilarity applies for polymorphic forms of FcγRIIa, comparative binding data for isoforms 131H / H131R were provided.

For the FcγRIIa-R131 form, 5 EU-Herceptin, 4 US-Herceptin and 5 MYL-1401O batches were analyzed; the KD ranged from 4.95 to 6.34 µM, 5.05 to 5.95 µM and 5.04 to 5.25 µM. For the FcγRIIa-H131 form, 5 EU-Herceptin, 4 US-Herceptin and 3 MYL-1401O batches were analyzed; the KD ranged from 2.75 to 4.18 µM, 2.10 to 2.46 µM and 2.71 to 2.94 µM. An updated data set including data from 7 lots of EU-Herceptin and 5 lots of MYL-1401O was provided. The FcYRIIa-H131 K_D values of the 5 MYL-1401O lots tested were found within the Mean ± 2SD range of the EU-Herceptin lots.

FcγRIIb Kinetics Assay (Study Number(s): BDL/HER/SAR/16/002)

The binding kinetics (ka and kd) and dissociation constant (KD) to FcγRIIb were compared between MYL-1401O and Herceptin using SPR. Five EU-Herceptin, 4 US-Herceptin and 5 MYL-1401O samples were analyzed; the KD ranged from 9.10 to 9.92 µM, 8.19 to 9.81 µM and 8.65 to 9.89 µM.

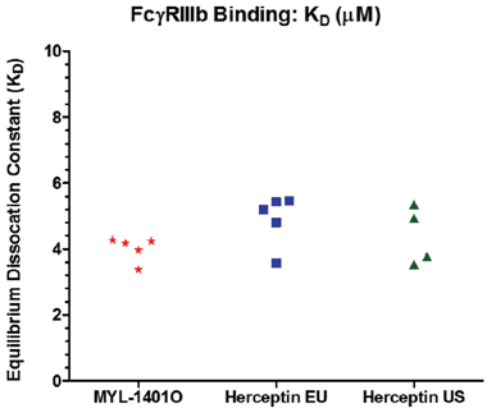
Figure 4: FcγRIIb Kinetics Assay Results



FcγRIIIb Kinetics Assay (Study Number(s): BDL/HER/SAR/16/003)

The study assessed binding of MYL-1401O and Herceptin to FcγRIIIb by SPR using Biacore instrument in the kinetic mode. Five EU-Herceptin, 4 US-Herceptin and 5 MYL-1401O samples were analyzed; the KD ranged from 3.58 to 5.46 μM, 3.54 to 5.35 μM and 3.38 to 4.27 μM, respectively.

Figure 5: FcγRIIIb Kinetics Assay Results



C1q Binding Assay (ELISA method) (Study Number(s): BDL/TR/BR.14.5002/16/005)

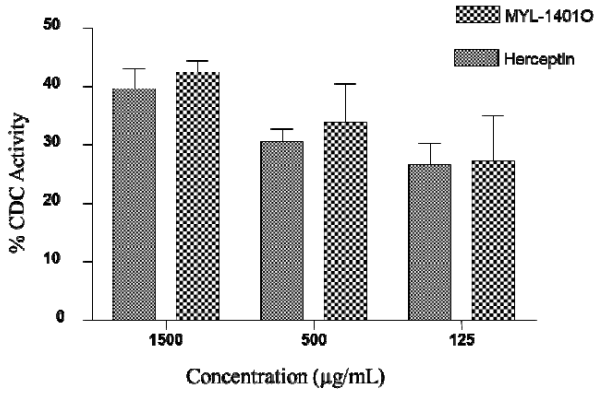
This study assessed the relative binding affinity of MYL-1401O and Herceptin to C1q (complement) employing a sandwich ELISA relative to the reference standard (QC/Q8/LS/001/03). Five EU-Herceptin, 4 US-Herceptin and 5 in-house MYL-1401O samples were analyzed, the relative potency compared to the reference standard ranged from 0.64 to 1.04, 0.76 to 0.96 and 0.93 to 1.04.

Complement-Dependent Cytotoxicity Assay (Cell-Based Assay) (Study Number(s): BRL/TR/1168/11/061)

This assay used a fluorescence based method that detects the live (SK-BR-3) cells after CDC activity of trastuzumab. It is based on the reduction of an oxidized, blue, non-fluorescent Alamar Blue (resazurin), to a pink fluorescent dye (resorufin) in the medium by live cell activity.

Measurements were taken as percentage CDC activity at varying concentration of MYL-1401O and Herceptin. The data obtained from the CDC assay for MYL-1401O and reference product was analyzed using student's T-test.

Figure 6 Percentage of CDC activity of MYL-1401O (QC/Q8/LS/001/02) and Herceptin (H0745).



Similar CDC activity was observed for the internal reference standard (QC/Q8/LS/001/02) and EU-sourced Herceptin (H0745B01). T-test analysis indicated no statistical difference between results for MYL-1401O and Herceptin at all concentrations assayed.

This assay was initially performed using the first formulation developed (Bmab200 formulation). Following request, additional results were provided on one lot of MYL-14O10 produced according to the current commercial process (lot #BS15003580 produced in August 2015 according to the 2000 L- Process C). That lot was compared to 1 lot of Herceptin sourced from EU and 1 lot of Herceptin sourced from US. Three trastuzumab concentrations were pre-incubated with SK-BR-3 cells, i.e. 250, 500, & 1500 µg/mL. After pre-incubation, undiluted or 10-fold diluted human plasma was added and incubated. The resulting cell death due to CDC was determined by comparing the fluorescence of SK-BR-3 cells pre-incubated with trastuzumab to that of SK-BR-3 cells incubated with plasma alone. The results showed that no CDC activity was observed at any of the three concentrations tested when the cells were treated with either Herceptin or MYL-1401O.

SK-BR-3 Inhibition of Proliferation Assay (Study Number(s): DDL/TR/BR.14.5002/16/005)

The SK-BR-3 cell proliferation is inhibited by trastuzumab. SK-BR-3 cells were incubated for 5 days with varied concentrations of test article in Poly-LLysine coated 96 well flat bottom plates. Fluorescence was measured after incubation for an additional 8 hs. Proliferation was indicated by increased fluorescence.

Ten EU-Herceptin, 10 US-Herceptin and 07 in-house MYL-1401O samples were analyzed, the relative potency compared to the reference standard ranged from 0.90 to 1.28, 0.899 to 1.22 and 0.965 to 1.24, respectively.

Her 2 Target binding study (Study Number(s): DDL/TR/BR.14.5002/16/004)

The immortalized breast cancer cell line SK-BR-3 expresses HER2 receptor tyrosine kinase on its surface. Trastuzumab binds to this receptor, suppresses its associated signalling cascade, and thereby causes antibody dependent cellular cytotoxicity, as well as inhibition of proliferation. Varying the concentrations of trastuzumab enables a dose dependent inhibition receptor binding of SK-BR-3 cells and is comparable to the internally qualified MYL-1401O reference standard.

Trastuzumab binds to HER2 receptor in SK-BR-3 cells and the extent of this binding is measured using an antibody based flow cytometry method.

Twenty two EU-Herceptin, ten US-Herceptin and seven MYL-1401O samples were analyzed; compared to the reference standard the relative affinity ranged from 0.84 to 1.20, 0.91-1.05 and 0.89 to 1.06, respectively.

Antibody dependent cellular phagocytosis (ADCP) (Study number :BDL/HER/MDR/17/002)

Antibody-dependent cell-mediated phagocytosis (ADCP) is an important mechanism of action of therapeutic antibodies designed to recognize and mediate the elimination of virus-infected or diseased (e.g., tumour) cells.

Engineered effector cells that stably express the human FcγRIIa-H variant receptor, and an NFAT (nuclear factor of activated T-cells) response element driving expression of firefly luciferase are co-cultured with SK-BR-3 cells and either MYL-1401O or Herceptin. Binding of trastuzumab, which is itself bound to the SK-BR-3 cells, to the FcγRIIa receptor on the effector cells activates the NFAT pathway, which in turn increases expression of luciferase. The increase in luciferase can be quantified with luminescence readout. Five batches of EU-Herceptin, 4 batches of US-Herceptin, and 5 batches of MYL-1401O batches were analyzed; the relative potency compared to the reference standard ranged from 70 to 102, 60 to 123 and 91 to 115, respectively.

Qualification summary of in vitro assays

The following assays were qualified: HER2 binding, inhibition of proliferation, FcRn, ADCC, and FCyRIIIa.

Secondary pharmacodynamic studies

The applicant did not submit secondary pharmacodynamic studies (see non-clinical discussion).

Safety pharmacology programme

Safety pharmacology endpoints were included in the repeat dose toxicology study conducted in cynomolgus monkeys (see toxicology section).

To examine the relative cardiotoxic potential of MYL-1401O, the applicant submitted two comparative *in vitro* studies investigating the effect of Herceptin and MYL-1401O on human and rat cardiomyocytes. The mitochondrial toxicity assessment and comparison between EU Herceptin and MYL-1401O is provided in Table 6 below.

Table 2: Summary of Comparative Measurements of Mitochondrial Toxicity for Herceptin and MYL-1401O Treated Human and Rat Cardiomyocytes

Measurement	Technique	Positive control	Substrates/Enzymes
Viability loss†	MTT‼ assay/Spectrofluorometry	Doxorubicin and vinblastine	NA
Mitochondrial membrane delta potential ΔΨm	Flow cytometry /JC-1 and DIOC-6 dyes	ClCCP; carbonyl cyanide 3-chlorophenyl hydrazine or staurosporin	Propidium iodide
Reactive oxygen species (ROS)	Flow cytometry/MitoSOX dye	Antimycin A	NA
Cytochrome C release†	Flow cytometry/Alexa Fluor 488 dye	Staurosporine	NA
Respiration Complex I and Complex II activity by consumption of oxygen in presence of ADP‡	Spectrofluorimetry/LUX-MitoXpress dye	Complex I - Rotenone Complex II - Oligomycin A	ADP Complex I - malate + glutamate Complex II - Succinate
ATP, ADP and ADP/ATP ratio	Differential luminescence	Antimycin A and staurosporin	Luciferin/luciferinase, ADP converting enzyme

† Only performed in Part A studies with human cardiomyocytes.
‡ Only measured Complex I in rat cardiomyocytes, in human assessed both Complex I and Complex II.
‼ - (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide
For human cardiomyocyte studies
Test Product - MYL 1401O (Biocon, India), Batch DEVBV10-0001 for Part B
Reference Product - Herceptin (Roche, EU sourced)Batch H0696B01 for Part A and Batch H7013B01 for Part B
For rat cardiomyocyte studies
Test Product: MYL 1401O (Biocon, Bangalore, India), Batch V10DEVB-0005 for Part B
Reference Product: Herceptin (Roche, EU sourced) Batch H0745B01 for Parts A and B

For all studies, the positive controls used in Part A and Part B studies gave statistically significant ($P<0.05$) changes in the parameters being assessed relative to untreated controls, with the exception of ATP and ADP levels at the 72 h time point where differences were not statistically significant.

In the cell viability assay, MTT was more reduced at 48 h in cells treated with Herceptin and MYL-1401O than in untreated cells, consistent with increased mitochondrial activity, as evidenced by increased ATP levels at this time-point.

Neither test article had any measurable effect on transmembrane potential (ΔΨm) or cell viability for human (up to 2 mg/mL) or rat (up to 0.2 mg/mL) cardiomyocytes. Similar, statistically significant increased adenosine diphosphate/ adenosine triphosphate (ADP/ATP) ratios were observed for both products in both cell lines with recovery to baseline after 24 to 48 hours. Additionally, a similar statistically significant inhibition of oxygen consumption was observed with both test articles in both human and rat derived cardiomyocytes; with recovery by 48 hours.

The results suggested that Herceptin and MYL-1401O mediated comparable and reversible levels of mitochondrial toxicity in cardiomyocytes. No significant differences were observed between MYL-1401O and Herceptin.

Pharmacodynamic drug interactions

The applicant did not submit pharmacodynamic drug interaction studies (see non-clinical discussion).

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) of MYL-1401O were determined in cynomolgus monkeys in a single-dose study (MYL-Her-PC-02) in comparison with European Union (EU) sourced Herceptin (EU-Herceptin) after a single 30-minute intravenous (IV) administration of 25mg/kg. Test articles were administered by IV infusion over 30 minutes. The animals were monitored for 6 weeks post-dose (3 to 4 serum half-lives). Blood samples for PK analysis were collected from all monkeys on the day of dose administration (Day 1), pre-dose, post infusion and at 1, 2, 4, 8, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 216 (Day 10), 312 (Day 14), 504 (Day 22), 672 (Day 29), 840 (Day 36), and 1008 (Day 43) h after dosing. The study also included observations of skin at the injection site, clinical observations, and body weight. The plasma levels of trastuzumab were determined using a validated enzyme linked immunosorbent assay.

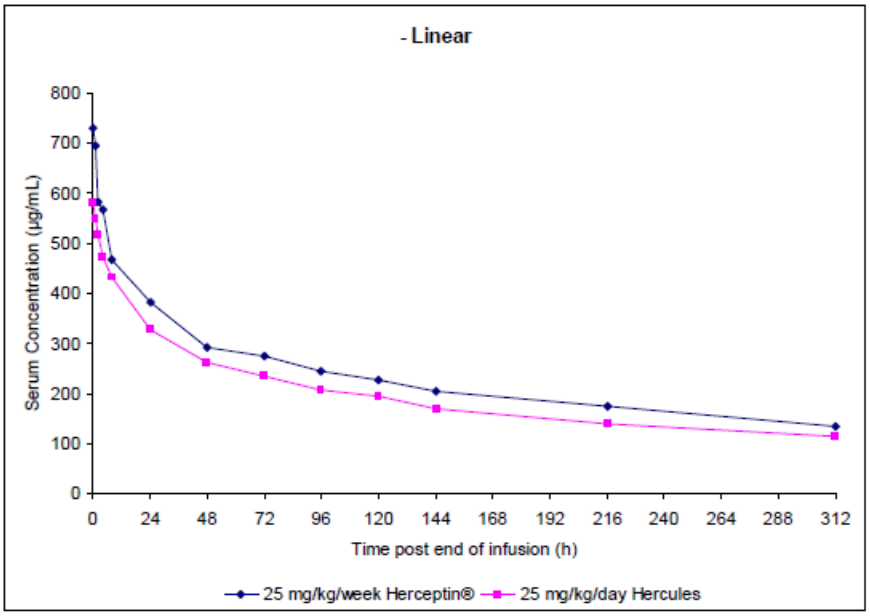
The results are presented below:

Table 3 Pharmacokinetics of Herceptin and MYL-1401O in Female Cynomolgus Monkeys Following a Single Intravenous Infusion of 25 mg/kg Trastuzumab

Parameter	$AUC_{0-\infty}$ (µg.h/mL)	C_{max} (µg/mL)	$t_{1/2}$ (h)	CL (mL/hr/kg)	V_{ss} (L/kg)
Herceptin					
N°	6	6	6	6	6
Arithmetic mean	131000	783	280	0.195	0.0731
CV%	17.0	14.0	24.8	17.1	16.0
Geometric mean	130000	777	274	0.192	0.0724
Geometric CV%	17.2	14.2	22.3	17.2	15.5
MYL-1401O					
N	5	5	5	5	5
Arithmetic mean	102000	600	233	0.247	0.0793
CV%	10.6	8.5	24.0	9.8	16.3
Geometric mean	102000	598	227	0.246	0.0785
Geometric CV%	10.2	8.4	24.8	10.2	16.1
F_{rel} (on geometric mean)	79.7%	78.2%			

Animal 10 was not included in calculation of means due to significantly lower exposure (AUC) observed in this animal compared to all other animals on study. AUC0-∞ - area under the serum concentration-time curve from time zero to infinity; CL - clearance; Cmax – maximum observed serum concentration; CV – coefficient of variation; Frel - bioavailability of MYL-1401O relative to Herceptin (based on AUC0-∞ and Cmax); t1/2 – terminal elimination half-life; Vss - volume of distribution at steady state.

Figure 7 Geometric Mean Serum Concentrations (µg/mL) of Herceptin and MYL-1401O Following Single Intravenous (Infusion) Administration at a Target Dose of 25 mg/kg (Excluding Animal 10)



ADA were evaluated in one animal (number 10, a female from group 2 administered 25 mg/kg of MYL-1401O) removed from the calculations following consistently low serum concentrations. No underlying disease condition that could explain this low drug exposure was found and no ADA were detected.

2.3.4. Toxicology

Single dose toxicity

The applicant did not submit single dose toxicity studies (see non-clinical discussion).

Repeat dose toxicity

The toxicology program for MYL-1401O consisted of one pivotal GLP-compliant 2-way comparative repeat-dose toxicity study performed in cynomolgus monkeys administered weekly 25 mg/kg or 50 mg/kg iv for 5 weeks.

This study was designed to evaluate differences between MYL-1401O and EU-sourced Herceptin in terms of clinical signs, changes in weight, food consumption, blood pressure and electrocardiography (ECG), mortality, changes at the injection site (local tolerance), ophthalmology, toxicokinetics (TK), clinical pathology, and anatomical pathology. Delayed toxicity and reversibility of toxic effects were not assessed; histological examination at the end of treatment was used to ascertain potential toxicity differences between the test articles.

The objective of the toxicokinetic component of this study was to compare the serum concentration versus time profiles of MYL-1401O and Herceptin following a single IV infusion and following weekly IV infusions (days 1 and 22). The objective was also to test the final formulation containing Macrogol 3350/PEG 3350 used as alternative cryoprotectant and D-sorbitol used as a lyoprotectant and bulking agent. No recovery groups were included in this study.

A summary of the main study is provided in Table 8 below:

Table 4 Summary of study Myl-Her-PC-03

Study ID	Species/Sex/ Number/Group	Dose per week (mg/kg) Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
MYLHer-PC-03	Cynomolgus Monkey 3M/3F Tot.:15/15	0/control* 25 Herceptin EU 25 MYL-1401O 50 Herceptin EU 50 Myl-1401O IV	4 weeks (5 injections)	NOEL : 50 mg/kg	no notable differences between MYL-1401O and Herceptin; no treatment related findings

* Vehicle formulation : 1.93 mM L-histidine, 2.22 mM L-histidine HCl, 0.01% w/v polysorbate 20 and 50 mM sorbitol at PH 5.56; water for injection; 3% sterile saline

The toxicokinetic results indicated there were no notable differences in MYL-1401O and EU-approved Herceptin exposure or bioavailability to monkeys.

Genotoxicity

The applicant did not submit genotoxicity studies (see non-clinical discussion).

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction Toxicity

The applicant did not submit reproduction toxicity studies (see non-clinical discussion).

Toxicokinetic data

See repeat dose toxicity section.

Local Tolerance

Local tolerance was assessed in the single-dose PK (MYL-Her-PC-02) and repeat-dose toxicity (Myl-Her-PC-03) studies in cynomolgus monkeys. In the single-dose study, erythema and desquamation were reported at the injection sites with similar frequency and severity for MYL-1401O and Herceptin. There was no microscopic examination performed. In the repeat-dose study, no signs of erythema, oedema, atonia, desquamation, or fissuring were evident in any animal. Histopathology was performed around the site of injection at the end of the study for group 1 (controls), 4 (Herceptin 50 mg/kg) and 5 (MYL-1401O 50 mg/kg). The findings are summarised in the table below.

Table 5 Microscopic finding description around the injection site (saphenous vein) and incidence amongst study groups:

Organ and finding description	Group					
	Males			Females		
	1	4	5	1	4	5
Number Examined	3	3	3	3	3	3
Left Saphenous						
- Phlebitis/periphlebitis	2	2	**3**	2	2	**3**

Organ and finding description	Group					
	Males			Females		
	1	4	5	1	4	5
- Intimal proliferation	1	0	1	1	0	0
- Medial hypertrophy	0	1	0	0	0	0
- Haemorrhage	0	0	**1**	3	1	2
- Agonal congestion/haemorrhage	1	0	0	0	0	0
Right Saphenous						
- Folliculitis	0	1	0	0	0	0
- Fasciitis/fibrosis	1	0	1	1	1	**2**
- Phlebitis/periphlebitis	1	2	0	1	1	**3**
- Intimal proliferation	1	0	**2**	2	0	2
- Myositis	0	0	**1**	0	0	0
- haemorrhage	0	1	1	1	1	0

2.3.5. Ecotoxicity / environmental risk assessment

The applicant submitted a justification for not providing an environmental risk assessment. Trastuzumab is already used in existing marketed products and no significant increase in environmental exposure is anticipated with Ogivri. Furthermore, the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMENCHMP/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. Therefore, considering that Ogivri is a protein and there is no expected increased environmental exposure, the absence of formal environmental risk assessment studies for Ogivri is considered justified.

2.3.6. Discussion on non-clinical aspects

The biological and functional similarity of MYL-1401O performed in accordance with the EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issue (EMA/CHMP/BMWP/403543/2010) was compared with EU- and US-approved Herceptin using multiple assays to measure both the Fab and Fc functionality.

Those *in vitro* assays were: target (HER2) binding assay, ADCC and ADCP assays, SPR kinetic assays on the Biacore instrument platform for Fc gamma receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa and FcγRIIIb), and C1q binding as determined by an ELISA, FcRn binding by SPR, Complement-Dependent Cytotoxicity Assay (CDC assay), and MYL-1401O IOP assay. Since both FcyRIIa and FcyIIIa receptors are subject to polymorphism with two forms described depending on histidine or arginine at position 131 (131H and H131R) and 2 forms 158V and 158F depending on valine or a phenylalanine at amino-acid position 158 respectively, the binding of trastuzumab to each 131H / H131R and 158V / 158F isoforms was also compared and the results showed comparative binding independent of the isoform tested. The applicant also submitted a summary of qualifications for the above tests, showing their suitability for the biosimilarity exercise.

From the results obtained it is concluded that MYL-1401O does not differ from the reference product Herceptin.

The applicant has not provided any *in vivo* PD studies, secondary pharmacodynamic studies or pharmacodynamic drug interactions studies with MYL-1401O which is deemed acceptable for a biosimilar product application.

In line with ICH guideline S6 (R1) 'Preclinical safety evaluation of biotechnology-derived pharmaceuticals', functional indices related to safety pharmacology were incorporated to toxicity studies. The applicant examined further the mechanism behind the relative cardiotoxic potential of MYL-1401O, in two comparative *in vitro* studies investigating the effect of Herceptin and MYL-1401O on human and rat cardiomyocytes. The results showed that the toxicity originated from reversible impact on inhibition of respiration complex I and II and by mobilization of energy over adenosine diphosphate in mitochondria. The results also showed a comparable effect for both MYL-1401O and Herceptin.

The pharmacokinetics (PK) of MYL-1401O were determined in cynomolgus monkeys in a single-dose study (MYL-Her-PC-02) in comparison with European Union (EU) sourced Herceptin (EU-Herceptin) after a single 30-minute intravenous (IV) dosing. The results showed similar t1/2 observed for MYL-1401O and Herceptin, while MYL-1401O had a slightly higher CL rate and volume of distribution at steady-state (Vss). The relative bioavailability (Frel) of MYL-1401O vs. Herceptin was approximately 80%. The pharmacokinetic comparison was however performed on a limited number of animals therefore the applicant does not claim comparative pharmacokinetic between Herceptin and MYL-1401O and refers to comparative pharmacokinetic studies provided in human (healthy volunteers and patients).

ADA was assessed in one animal removed from the calculations following consistently low serum concentrations. No underlying disease condition that could explain this low drug exposure was found. No ADA were detected. ADA studies were not conducted because the applicant did not observe any differences in toxicity profiles, TK, or injection site reactions. ADA was assessed during the clinical development programme (see clinical safety).

Information on distribution, metabolism, excretion and pharmacokinetic interactions were not provided but those studies are not required for a biosimilar medicinal product.

The toxicology program for MYL-1401O consisted of one pivotal GLP-compliant 2-way comparative repeat-dose toxicity study performed in cynomolgus monkeys administered weekly 25 mg/kg or 50 mg/kg iv on 5 occasions for 4 weeks. This species is considered suitable to assess the toxicological profile of MYL-1401O. The same species was used in the toxicological development programme of the reference product. This study was designed to evaluate differences between MYL-1401O and Herceptin in terms of clinical signs, changes in weight, food consumption, blood pressure and electrocardiography (ECG), mortality, changes at the injection site (local tolerance), ophthalmology, toxicokinetics (TK), clinical pathology, and anatomical pathology. The claimed NOEL was 50 mg/kg. The toxicokinetic results indicated there were no notable differences in MYL-1401O and EU-approved Herceptin exposure or bioavailability to monkeys. However, the number of animals is limited.

Single dose toxicity study, reproductive and developmental, carcinogenicity, genotoxicity studies were not performed. This is considered acceptable for an application for a biosimilar product.

No specific local tolerance studies were conducted, but tolerance was evaluated in the repeat-dose toxicity study. A slight trend for phlebitis/periphlebitis was noted in the high dose group administered MYL-1401O. However, no firm conclusion as regards this finding can be made, given the low number of animals present in each group.

The excipients (D-sorbitol and Macrogol 3350/PEG 3350) in the MYL-1401O drug product are different from the reference product and are said to be commonly used in injectable dosage forms and to comply with applicable European Pharmacopoeial standards. It is acknowledged that sorbitol is contained in other intravenous products. Relevant information about sorbitol has been included in the product information including a warning for patients with the rare genetic disorder of hereditary fructose intolerance (HFI), in accordance with the guideline for excipients labelling (see discussion on clinical safety). Macrogol 3350 included in MYL-1401O was qualified for use at the proposed levels based on animal studies reported in the scientific literature, a

repeat-dose toxicity study in cynomolgus monkeys and previous clinical experience with MYL-1401O. Additional information provided by the applicant and mainly consisting of literature data (data not shown) gave some assurance that Macrogol is considered as safe and poses no greater risk of toxicity or immune reactions compared to the polysorbate 20 used in the reference product (see also clinical safety section). Macrogol 3350 is reflected in the product information under the list of excipients.

2.3.7. Conclusion on the non-clinical aspects

Overall, the nonclinical data indicated that MYL-1401O has a similar activity to the reference product Herceptin with an acceptable safety profile.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Number	Study Objective(s)	Study Design	Test Product(s), Dosage, Regimen, Route of Administration	Number of Subjects/ Diagnosis	Duration of Treatment
Pivotal Studies						
PK bioequiv-alence, PD, safety, immuno-genicity	MYL-Her-1001	• To confirm PK bioequivalence between MYL-1401O and EU-Herceptin® • To assess comparative safety and tolerability • To investigate PD parameters	Single-center, single-dose, 2-period, double-blind, crossover study	MYL-1401O, EU-Herceptin 8 mg/kg single dose IV	22 randomized, 19 completed/ Healthy male subjects	Single IV dose administered over 90 min
PK, safety, immuno-genicity	MYL-Her-1002	• To demonstrate PK similarity of MYL-1401O vs EU-Herceptin and US-Herceptin along with EU-Herceptin vs US-Herceptin • To further assess	Single-center, single-dose, randomized, double-blind, 3-arm, parallel-group study	MYL-1401O, EU-Herceptin, US-Herceptin 8 mg/kg single dose IV	132 randomized, 121 completed/ Healthy male subjects	Single IV dose administered over 90 min

Type of Study	Study Number	Study Objective(s)	Study Design	Test Product(s), Dosage, Regimen, Route of Administration	Number of Subjects/ Diagnosis	Duration of Treatment
		similarity of PK among MYL-1401O, EU-Herceptin, and US-Herceptin • To assess comparative safety				
Confirmatory efficacy and safety, immuno-genicity	MYL-Her-3001	• To compare the independently assessed best ORR at Week 24 • To compare independently assessed clinical activity at Week 24 (TTP, PFS, OS) • To descriptively compare safety, tolerability, and immunogenicity • To compare population PK • To assess impact of shed ECD fragments on HER2 receptor on PK and efficacy parameters	Multicenter, double-blind, randomized, parallel-group study	MYL-1401O, EU-Herceptin 8 mg/kg loading dose followed by 6 mg/kg maintenance, every 3 weeks for 8 cycles IV	500 randomized, 356 completed Part 1/ Patients with HER2+ MBC	48 weeks
Supportive Study						
PK, comparative efficacy and safety, immuno-genicity	BM200-CT3-001-11	• To evaluate and compare the single-dose PK parameters of Bmab-200 and EU-Herceptin • To evaluate and compare ORR • To evaluate and compare the multi-dose PK • To assess comparative safety and immunogenicity • To correlate secondary efficacy parameters with shed HER2 ECD	Multicenter, double-blind, randomized, parallel-group study	Bmab-200, EU-Herceptin 8 mg/kg loading dose followed by 6 mg/kg maintenance, every 3 weeks for 8 cycles IV	135 randomized, 103 completed /Patients with HER2+ MBC	24 weeks

2.4.2. Pharmacokinetics

Pivotal pharmacokinetics data were available from two studies in healthy volunteers (Studies MYL-Her-1001 and MYL-Her-1002). A population PK analysis conducted in patients with HER-2+ MBC in the phase III study MYL-Her-3001 was also submitted. In addition, supportive data were provided from study BM200-CT3-001-11.

Bioanalytical methods

Analytical methods applied during the clinical development include: Assays for quantitative determination of total trastuzumab in human serum (ELISA); Assays for detection of ADA in human serum (ELISA); Quantitative determination of HER2/neu Oncogene in human serum; Quantitative determination of trastuzumab coating of infusion pouch and infusion lines.

In Studies MYL-Her-1001 and MYL-Her-1002, an ELISA using anti-idiotypic antibody was used for quantitation of MYL-1401O/Herceptin in human serum. The concentrations of MYL-1401O/Herceptin were determined by spectrophotometric measurements and were then back-calculated from their respective validation/calibration curves. In the phase 3 study MYL-Her-3001, the concentration of MYL-1401O/Herceptin in human serum samples were also determined using ELISA.

In Study BM200-CT3-001011, a single analytical method was used for the quantitation of both Bmab-200 and EU-approved Herceptin in human serum. Designated samples from Study BM200-CT3-001011 were analysed for the detection of Bmab-200 and Herceptin in human serum using an ELISA.

Immunogenicity was detected using an electro-chemiluminescence ligand binding assay involving biotinylated and s-tagged drug (MYL-1401O or Herceptin) with the MesoScale Discovery (MSD) platform. This technology uses acid dissociation to release any anti-drug (anti-MYL-1401O or anti- Herceptin) antibodies complexed with free drug. Samples were then bound to corresponding biotinylated-drug and to sulfo-tagged drug to form an antibody complex bridge.

A multi-tiered sample analysis approach was used to evaluate the immunogenic potential of Ogivri in studies MYL1010-Her-1001, MYL1010-Her-1002 and MYL-Her-3001.

In the study MYL-Her-3001, samples that were confirmed as ADA-positive were further analysed for Nab using the validated cell-based assay. For the first round of NAb analysis, study samples were subjected to the screening assay (Tier 1) for the presence of NAb against MYL-1401O and Herceptin using a statistically determined assay cut-point. For the second round of NAb sample analysis, study samples were subjected to 2 additional analytical tiers (no inducer and confirmatory assays). The no inducer assay (Tier 2) eliminated samples that demonstrated non-specific cell growth factors that could interfere with assay performance. The confirmatory assay (Tier 3) determined whether the neutralizing activity was specific to MYL-1401O/Herceptin or due to non-specific neutralization of cell growth. Samples were taken before administration of MYL-1401O or Herceptin since elevated serum levels of trastuzumab can interfere with the antibody assays.

Immunogenicity data are presented and discussed in the section on clinical safety.

Clinical PK Study Myl-Her 1001

Study Myl-Her 1001 was a Phase I, single-center, single-dose, 2-period, randomized, double-blind, cross-over study.

The primary objective of Study MYL-Her-1001 was to confirm bioequivalence between MYL-1401O (Ogivri) and Herceptin administered at a dose of 8 mg/kg, administered as a single intravenous (IV) infusion over 90 minutes

in healthy male volunteers. The secondary objective was to assess comparative systemic safety and tolerability including local tolerance, and to evaluate immunogenicity with anti-drug antibody (ADA) formation.

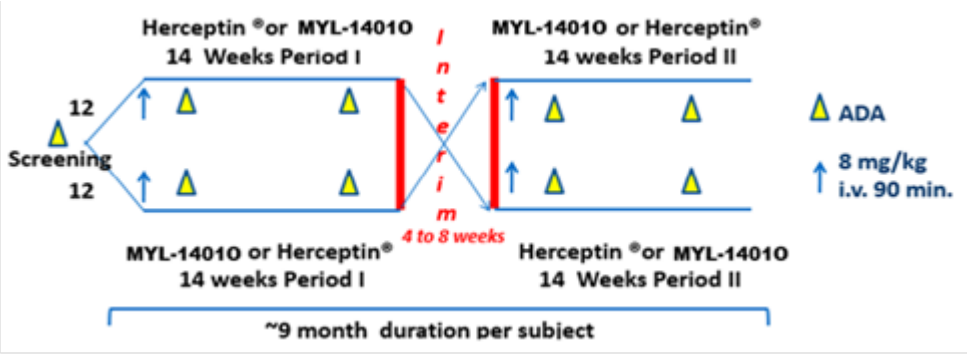


Figure 8: MYL-Her-1001 study design

The following PK parameters were determined for Herceptin and for MYL-1401O, using noncompartmental analysis.

Table 6: PK parameters determined for Herceptin and MYL-1401O using non-compartmental analysis

Parameter	Unit	Definition
$AUC_{0\text{-last}}$	µg.h/mL	Area under the serum concentration-time curve from time zero to the last quantifiable concentration post-start of infusion
$AUC_{0\text{-}\infty}$	µg.h/mL	Area under the serum concentration-time curve from time zero to infinity
$AUC_{\%extrap}$	µg.h/mL	Percentage of the $AUC_{0\text{-}\infty}$ extrapolated to infinity (should be <10%)
C_{max}	µg/mL	Maximum observed serum concentration
t_{max}	h	Time of maximum observed serum concentration
$t_{1/2}$	day	Apparent terminal elimination half-life
CL	L/day	Total serum clearance
V_z	L	Apparent volume of distribution during the terminal elimination phase
V_{ss}	L	Apparent volume of distribution at steady-state
F_{rel}	%	Bioavailability of Hercules relative to Herceptin® (based on $AUC_{0\text{-}\infty}$ and C_{max})

Primary PK parameters were C_{max} and $AUC_{0\text{-}\infty}$.

The subjects either received the test drug (MYL-1401O also referred as Hercules) or the reference drug (Herceptin) in Period I and the alternate treatment in Period II. The study drugs (MYL-1401O and Herceptin) were administered under medical supervision as i.v. infusions of 8 mg/kg body weight (BW) over a 90 min period (total volume infused of 250 mL).

Healthy male subjects aged between 18 and 45 years, with body weight (BW) range between 60 and 95kg, providing body mass index (BMI) was between 18 and 29 kg/m^2 were included in the study.

The PK population included all subjects included in the ITT Set who completed both mAb treatments (Herceptin and MYL-1401O) without a major protocol deviation, for which at least primary PK criteria ($AUC_{0-\infty}$ and C_{max}) were available for both mAb treatments.

In total, 22 subjects were randomized to either MYL-1401O (11 subjects) or Herceptin (11 subjects). Three of the 22 subjects were withdrawn from the study after receiving Herceptin in Period I: 2 due to personal reasons and 1 by the Safety Committee after Period I as a precaution due to raised values for liver function tests (transaminases) in Period I.

The main demographic and baseline characteristics of subjects in the ITT and PP populations are shown in the table below.

Table 7: Baseline characteristics in study MYL-Her-1001

Characteristic	ITT population (N=22)	PP population (N=19)
Age, mean ± SD (years)	28.0 ± 7.1	27.4 ± 7.0
Weight, mean ± SD (kg)	78.2 ± 12.79	78.1 ± 13.74
BMI, mean ± SD (kg/m^2)	23.8 ± 3.16	23.6 ± 3.19
Race, N (%)		
Asian/Oriental	1 (4.5)	1 (5.3)
Black	4 (18.2)	3 (15.8)
Caucasian	16 (72.7)	14 (73.7)
Multiracial	1 (4.5)	1 (5.3)

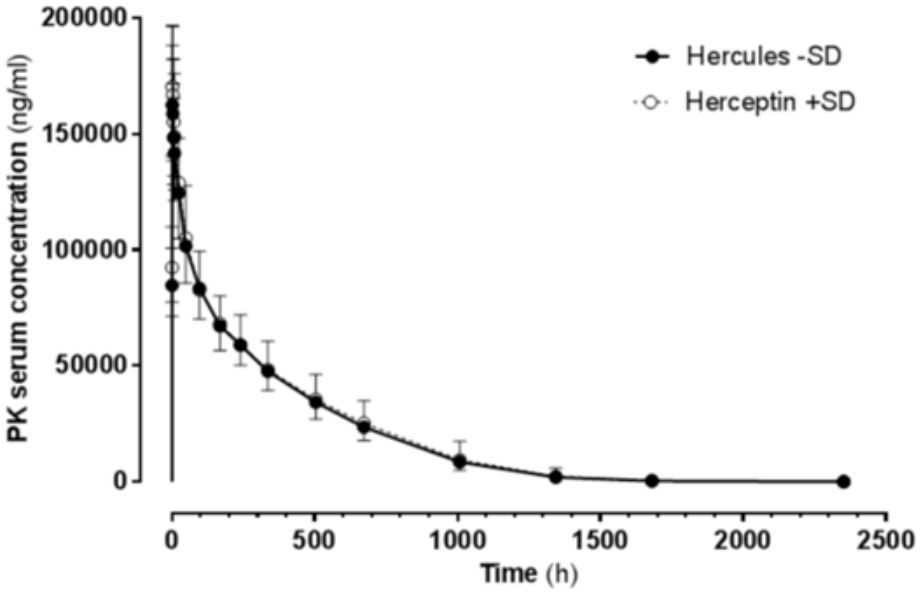
BMI = Body mass index; ITT = Intention-to-treat; N = Number of subjects; PP = Per-protocol; SD = Standard deviation.
Source: Appendix 16.3, Tables 5.1 and 5.2

Blood samples were collected at 0, 45 (mid infusion), and 90 minutes (just prior to the end of infusion); and at 3, 6, 9, 24, 48, and 96 hours on Days 8, 11, 22, 29, 43, 57, 71, and 99. Blood samples were analysed by ELISA.

Serum was collected from treated subjects for ADA screening on a regular basis (0 h, 48 h, 2 weeks, and 10 weeks after treatment) and assayed with the corresponding validated assay. The 48 h samples were collected as reserves only, to be assayed only in case of a severe reaction during infusion or thereafter.

Pharmacokinetics Results

The time plot of geometric means averaged over all 19 subjects who received both formulations shows that the concentration/time profiles for the 2 study drugs were essentially super-imposable.



geoSD: geometric standard deviation; PP: per-protocol; PK: pharmacokinetic.
Hercules= MYL-1401O (MYL-1401O was referred to as Hercules before the company code was generated).
Data Source: CSR MYL-Her-1001 Figure 1

Figure 9: Geometric Mean Serum Concentrations (Linear/Linear) ± GeoSD of MYL-1401O and Herceptin (PP Population; Study MYL-Her-1001)

Table 8: Primary and Secondary PK Parameters (PP Population; Study MYL-Her-1001) – Statistical analysis

Parameter	MYL-1401O (N=19)	EU-Herceptin (N=19)	Point Estimate (90% CI)
Primary parameters			
C_{max} normalized (µg/mL)	165 (15.7)	178 (15.6)	0.9218 (0.8760; 0.9699)
$AUC_{0-\infty}$ normalized (µg.h/mL)	45486 (22.7)	48350 (28.5)	0.9368 (0.8874; 0.9889)
Secondary parameters			
C_{max} native (µg/mL)	167 (14.7)	175 (15.8)	0.9417 (0.8997; 0.9858)
$AUC_{0-\infty}$ native (µg.h/mL)	45802 (23.0)	47547 (28.6)	0.9571 (0.9048; 1.0123)
AUC_{0-last} (µg.h/mL)	45747 (23.0)	47496 (28.5)	NA
T_{max} (h) (median [range])	1.5 (1.4-9.0)	1.5 (1.3-9.0)	NA
$t_{1/2}$ (day)	6.94 (22.6)	7.02 (26.3)	0.9880 (0.9428 ; 1.0353)
V_z[a] (L)	2.96 (18.0)	2.81 (18.0)	1.0547 (1.0126; 1.0985)
V_{ss}[a] (L)	4.38 (17.6)	4.30 (15.1)	1.0190 (0.9681; 1.0726)
CL[a] (L/day)	0.296 (22.7)	0.278 (28.5)	1.0675 (1.0112; 1.1269)

Data is presented as Geo Mean (Geo CV%) unless otherwise specified.
[a]Parameters adapted to 70 kg body weight.
Point estimate as a ratio of geometric means of MYL-1401O versus Herceptin (difference of adjusted means after back transformation).
Normalized $AUC_{0-\infty}$area under the serum concentration-time curve from time zero to infinity (normalized to a dose of 8.0 mg/kg); Normalized C_{max}=maximum observed serum concentration (normalized to a dose of 8.0 mg/kg); CI=confidence interval; CL=total serum clearance; PK=pharmacokinetic; PP=per-protocol; NA=not applicable.
Data Source: CSR MYL-Her-1001 Table 7

For AUC_{0-inf} normalized or native and Cmax normalized or native, the 90% confidence interval for the ratio of the test and reference products fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing Ogivri to the reference product from EU. The other secondary parameters were within the acceptance range of 80-125% as well. Tmax and terminal half-life were also similar.

Clinical PK study Myl-Her 1002

This study was a single-centre, single-dose, randomized, double-blind, 3-arm parallel-group study investigating the bioequivalence of MYL-1401O versus EU-approved Herceptin and US-licensed Herceptin as well as EU-approved Herceptin versus US-licensed Herceptin after 8 mg/kg as single dose administered as IV infusion over 90 minutes in healthy male subjects under fasting conditions.

The primary objective of study Myl-Her-1002 was to demonstrate pharmacokinetic similarity of Ogivri (MYL-1401O) versus EU-approved Herceptin and US-licensed Herceptin and between EU-approved Herceptin and US-licensed Herceptin. The study was conducted in the US and was completed (last subject's visit) on 27 February 2014.

GCP inspections were carried out by the FDA or other regulatory agencies at the clinical site where the study was carried out. No critical finding was found.

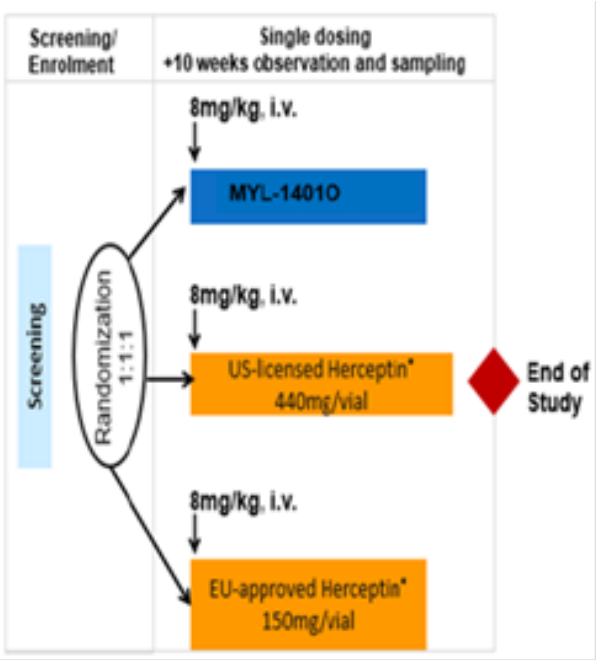


Figure 10: MYL-Her-1002: study design

The primary pharmacokinetic variables for assessment of similarity were dose-normalized Cmax, AUC0-last, and AUC0-∞.

The PK population included all subjects who had received treatment and for whom the PK data were considered to be sufficient and interpretable. Subjects who did not complete through Day 43 or who had been deemed to have insufficient data points for meaning analysis or who did not complete the study due to noncompliance or withdraw consent were excluded from PK population.

In each study period, PK blood samples were collected just immediately prior to dose administration (0 hour) and at 45 and 90 minutes (just prior to end of infusion). PK blood samples were collected post-dose at 3, 6, 9, 24 and 48 hours, relative to the start of infusion. Subjects returned to the clinical facility for the scheduled blood sample collections post-dose on Day 5, 8, 11, 15, 22, 29, 43, 57, and 71 (over a period of 10 weeks). Blood samples for anti-drug antibodies (ADA) were collected prior to dosing on Day 1 and on Day 71.

One hundred thirty-two volunteers were enrolled in the study. Eleven (11) subjects withdrew consent prior to the Day 43 blood draw. Therefore, one hundred twenty-one subjects completed the study. One subject was discontinued after study completion from the bioanalytical analysis by the pharmacokinetist because the subject did not receive the correct dose amount due to a dose preparation error. Therefore, one hundred twenty subjects are included in the pharmacokinetic analysis.

A summary of mean demographic data (± SD) is presented below:

	All Subjects Dosed (N=132)	Hercules (N=44)	Herceptin-EU (N=44)	Herceptin-US (N=44)
Age (years)	32.9 (± 9.77)	31.9 (± 9.51)	33.0 (± 9.97)	33.9 (± 9.94)
Weight (kg)	80.1 (± 11.39)	82.0 (± 10.87)	79.2 (± 11.09)	79.2 (± 12.19)
Height (cm)	177.2 (± 7.79)	177.8 (± 7.81)	176.6 (± 8.40)	177.2 (± 7.25)
BMI (kg/m^2)	25.5 (± 2.66)	25.9 (± 2.76)	25.3 (± 2.67)	25.1 (± 2.55)

Pharmacokinetics Results

Mean Graphical Presentation of Dose-Normalized Trastuzumab Serum Concentrations is presented below.

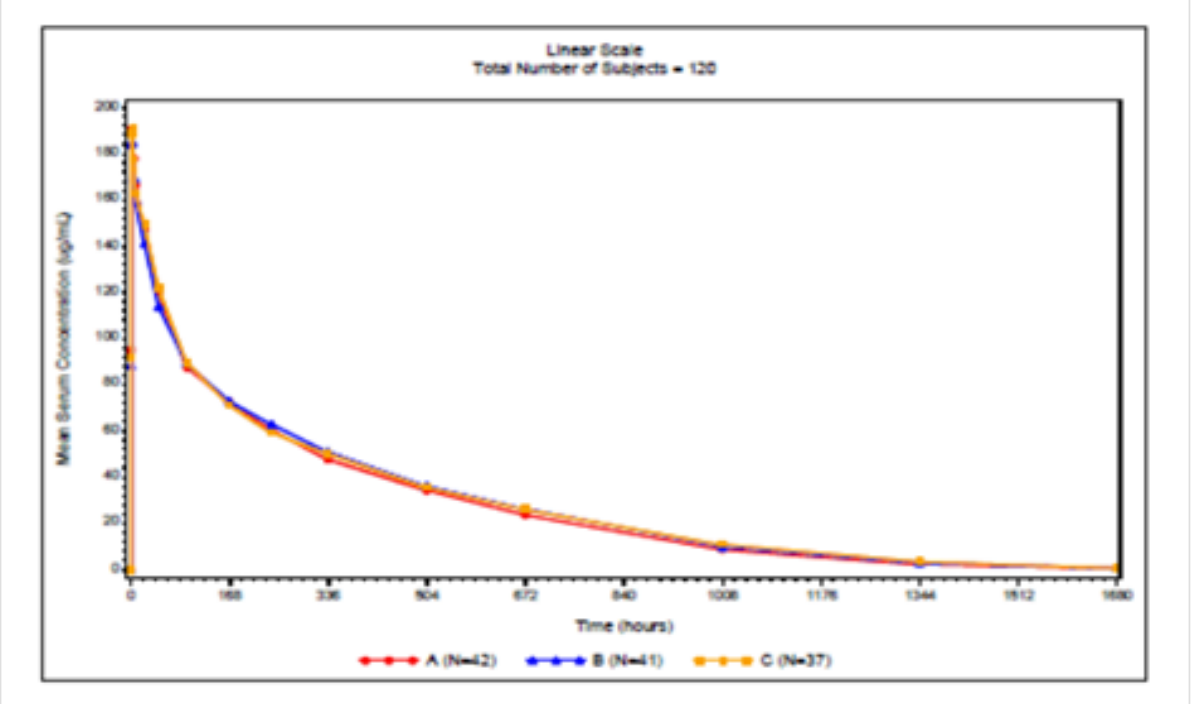


Figure 11: Geometric Mean Serum Concentrations of MYL-1401O, EU-approved Herceptin 150 mg in vial and US-licensed Herceptin 440 mg in vial (dose-normalised analysis, Study MYL-Her-1002)

Table 9: Mean (%CV) Dose-Normalized Trastuzumab Pharmacokinetic Parameters in Healthy Adult Male Subjects Following a Single 8 mg/kg Intravenous Infusion Over Ninety Minutes. Protocol number Myl-Her 1002 (EU-Herceptin)

Parameter	Arithmetic Mean A = Hercules N=42	Arithmetic Mean B = Herceptin-EU N=41	LSMEANS Ratio (A/B)	90% Confidence Interval**
$AUC_{0\text{-last}}$ (mcg•hr/mL)	48055 (15.92)	49823 (19.61)	0.97	91.31% – 103.05%
$AUC_{0\text{-}\infty}$ (mcg•hr/mL)	48241 (16.19)	50075 (19.81)	0.97	91.17% – 102.97%
C_{max} (mcg/mL)	200.4 (12.34)	192.6 (14.13)	1.04	99.00% – 109.82%
λ_z (hr^{-1})	0.0046 (22.80)	0.0044 (27.14)		
$t_{½}$ (hr)	160.0 (28.39)	173.8 (32.92)		
t_{max} (hr)	2.880 (54.83)	3.028 (118.2)		

Treatment A: Trastuzumab Powder Concentrate for Intravenous Infusion, 150 mg/vial, (Lot No.: DBBMPTV12-0003) – (Hercules)
Treatment B: Herceptin® (trastuzumab) Powder for Concentrate for Solution for Infusion, 150 mg/vial, (Lot No.: H4078B02) – (Herceptin-EU)

* Ratio (A/B) = $e^{[LSMEANS\ of\ (LNA - LNB)]}$
**Used Natural Log Transformed Parameter

The ratios (90% CI) of geometric means for both primary PK endpoints AUC0-last, AUC0-inf and Cmax were within the acceptability range of 80-125%. In addition, the mean secondary PK endpoints show to be similar for the MYL-1401O and Herceptin treatment groups.

Table 10: Mean (%CV) Dose-Normalized Trastuzumab Pharmacokinetic Parameters in Healthy Adult Male Subjects Following a Single 8 mg/kg Intravenous Infusion Over Ninety Minutes. Protocol number Myl-Her 1002 (EU-Herceptin)

Mean (%CV) Dose-Normalized Trastuzumab Pharmacokinetic Parameters in Healthy Adult Male Subjects Following a Single 8 mg/kg Intravenous Infusion Over Ninety Minutes PROTOCOL NUMBER Myl-Her 1002

Parameter	Arithmetic Mean A = Hercules N=42	Arithmetic Mean C = Herceptin-US N=37	LSMEANS Ratio (A/C)	90% Confidence Interval**
$AUC_{0\text{-last}}$ (ng•hr/mL)	48055 (15.92)	49826 (13.98)	0.96	90.34% – 102.29%
$AUC_{0\text{-}\infty}$ (ng•hr/mL)	48241 (16.19)	50181 (13.86)	0.96	89.96% – 101.94%
C_{max} (ng/mL)	200.4 (12.34)	197.9 (16.25)	1.02	96.42% – 107.26%
λ_z (hr^{-1})	0.0046 (22.80)	0.0042 (23.45)		
$t_{½}$ (hr)	160.0 (28.39)	176.4 (29.85)		
t_{max} (hr)	2.880 (54.83)	2.625 (53.37)		

Treatment A: Trastuzumab Powder Concentrate for Intravenous Infusion, 150 mg/vial, (Lot No.: DBBMPTV12-0003) – (Hercules)
Treatment C: Herceptin® (trastuzumab) Intravenous Infusion, 440 mg/vial, (Lot No.: 516558) – (Herceptin-US)
* Ratio (A/C) = $e^{[\text{LSMEANS of (LNA - LNC)}]}$
**Used Natural Log Transformed Parameter

Source: Appendix 16.2.6.1.3 and Appendix 16.2.6.2.2

Clinical Study BM200-CT3-001-11

This study is a supportive study. The objective was to evaluate and compare the single dose pharmacokinetic parameters of Bmab-200 and Herceptin in terms of AUC0-t and Cmax in patients with Her2+ metastatic breast cancer.

This was a double-blind, randomized, active-controlled, parallel-group, comparative study (BEAT MBC Study) in patients with HER2-positive metastatic breast cancer to evaluate the comparative PK, efficacy, safety, and immunogenicity of Bmab-200 with EU-approved Herceptin. This study was conducted to meet the requirements for marketing authorization in the country of origin (India) and the formulation used (Bmab-200) was slightly different from that used in the pivotal studies.

During this study, up to 8 cycles of Bmab-200 and Herceptin were administered over 24 weeks with 8 mg/kg as the loading dose and 6 mg/kg as the maintenance dose.

Pharmacokinetic parameters Cmax, AUC0-t, Tmax, t1/2, Kel , and AUCExtrapolated (%) were calculated using plasma concentration vs. time profile (actual time of sample collection) data of the investigational products in individual subjects. Descriptive statistical analysis was performed on primary pharmacokinetic parameters i.e. AUC0-t and Cmax. All other PK parameters were summarized as summary statistics.

A total of 135 patients were randomized to two arms; the Bmab-200 arm (n=67) and the Herceptin arm (n=68). Of these 135 patients, 134 patients were dosed and 103 patients completed all 8 cycles of the study (Bmab-200, n=51; Herceptin, n=52). The study included female patients who had a confirmed histopathological diagnosis of breast cancer and confirmed metastatic disease by biopsy or radiology.

Table 11: Bioequivalence Analysis of Bmab-200 vs. Herceptin for Single Dose PK Parameters (PK-Population), Study BM200-CT3-001-11

Measures	Primary PK Endpoints	
	Ln C_{max} (ng/mL)	Ln AUC_{0-t} (ng.hr/mL)
ANOVA p-value:	0.6705	0.0321
Geometric Mean		
Bmab-200	241880.690	26499087.198
Herceptin®	247869.326	29964020.824
Ratio (%) of Geometric Means (Bmab-200/ Herceptin®)	97.58	88.44
90% Confidence Interval - (Bmab-200/ Herceptin®)	(88.74 , 107.31)	(80.51 , 97.15)
Total Subject variability (%)	33.45	33.05
Power	98.64	98.78

Source: Table 14.2.7a
ANOVA: Analysis of variance
Note: Patient Numbers [redacted] excluded from the analysis as the C_{max} is observed at 504 hrs (the cycle-2 pre-dose time point). The cycle-2 pre-dose concentration was several-fold higher than post-dose concentrations.

Formal statistical analysis using ANOVA confirmed that the 90% CIs around the point estimates of the geometric means of the test/reference (Bmab-200/Herceptin) for the PK parameters Cmax and AUC0-t were within the predefined interval of 74%-135%, and also within the classical bioequivalence interval of 80%-125%. The 90%CI for Cmax was 88.74% to 107.31%; and for AUC0-t, 80.51% to 97.15%.

Population PK

In Study MYL-Her-3001 (see clinical efficacy section), MYL-1401O and Herceptin minimum drug concentration (Cmin) (pre-infusion samples) were assessed in all patients for Cycles 1, 2, 4, 6, 8, and 9. One sample at the end of infusion (Cmax) was collected from all patients for Cycle 1 and Cycle 6.

The PK population included all randomly assigned patients who received at least 1 complete dose of MYL-1401O or Herceptin, and who provided at least 1 post-dose sample for PK analysis.

Model development included assessment of covariate effects on the inter-individual variability in PK parameters. A bootstrap analysis and goodness-of-fit plots, including visual predictive checks, were presented to evaluate the robustness of the final model. Observed Cmin values at the end of Cycle 1 and Cycle 6 were used to assess the similarity of MYL-1401O versus Herceptin using the two 1-sided t-tests statistical approach for bioequivalence. Individual patient empiric Bayesian parameter estimates were used to estimate PK measures reflecting exposure to drug and were compared qualitatively between treatments.

Treatment was not a significant covariate of clearance (p=0.176) or volume of the central compartment (p=0.567) using the likelihood ratio Chi-square test. Model-based exposure measures were similar between treatments. The test-to-reference mean ratios for Cycle 1 and Cycle 6 Cmin values were 103.11% and 103.88%, respectively, and their 90% CIs were 90.61% to 117.33% and 93.75% to 115.11%, respectively. Thus, observed trough concentrations were not different between treatments at the end of the first dosing interval or at Cycle 6.

It was also shown in the POP PK analysis that the model based assessment of ADA as a covariate of CL was inconclusive due to the low frequency of ADA development with each treatment. The presence of ADA was

modeled as a time-variant, proportional covariate of clearance. The proportionality parameter was estimated to reduce clearance by approximately 9% in the presence of ADA (see discussion on pharmacology).

2.4.3. Pharmacodynamics

Mechanism of action

See discussion on clinical pharmacology.

Primary and Secondary pharmacology

Although currently there is no validated PD marker that is predictive of the efficacy for trastuzumab, PD was evaluated in Study MYL-Her-1001. This study assessed PD parameters to support the biosimilarity assessment of MYL-1401O and Herceptin.

Phamacodynamics for MYL-1401O were evaluated in Study MYL-Her-1001, encompassing 22 healthy subjects of which 19 completed the study.

The following PD variables were assessed in Study MYL-Her-1001:

- Proliferation inhibition (antiproliferative activity)
    - *Ex vivo* serum anti-proliferative activity on breast tumor cell line (BT-474) overexpressing HER2.
- Clinical variables
    - Body temperature, C-reactive protein, and immunoglobulins.
- Immunomodulation
    - *Ex vivo* release of 8 cytokines in serum (interleukin [IL]-1, IL-2, IL-6, IL-10, IL-12, tumor necrosis factor-alpha, granulocyte-macrophage colony stimulating factor, interferon-gamma).
    - *Ex vivo* mononuclear cell subset modulation (frequency and activation of various populations).
    - *Ex vivo* production of the same panel of 8 cytokines by peripheral blood mononuclear cells (PBMCs) in response to a 6-day stimulation with recall antigens and mitogen (phytohemagglutinin).
- Apoptosis
    - Markers of apoptosis in PBMCs (caspase-3, caspase-3 activation), DNA fragmentation, Akt phosphorylation, and HER2 labeling.
- Baseline *in vitro* stimulation
    - *In vitro* production of the same panel of 8 cytokines (see immunomodulation) by PBMCs collected pre-treatment in response to a 20 h culture in presence of 4 immobilized monoclonal antibodies (MYL-1401O, Herceptin, Avastin, and OKT3) at 3 selected doses.

Results showed that there were no significant differences between MYL-1401O and Herceptin for any of the PD parameters, although many showed marked changes over time for both groups (see table below).

Table 12: Exploratory pharmacodynamic investigations

Variable	Treatment Difference	Time Effect	
		comparison	direction of time effect
Proliferation Inhibition			
Proliferation inhibition index	NS	p<0.0001	↑1.5h
Clinical Variables			
Body temperature	NS	p<0.0001	↑9h
CRP	NS	p<0.0001	↑24h
IgA	NS	p<0.0001	↑168h
IgM	NS	0.0058	↑168h
IgG	NS	p<0.0001	↑168h
Immunomodulation: Cytokines in serum			
IL-6	NS	p<0.0001	↑6h
IL-2, IL-10, GM-CSF; IFNg; TNFa; IL-1b; IL-12p70	NS	NS	-
Immunomodulation: Mononuclear cell subset modulation			
T Cells	NS	0.0066	↓48h
B Cells	NS	0.0035	↑3h
NK cells	NS	p<0.0001	↓3h ↑48h
Monocytes	NS	0.015	↓3h ↑48h
T cells CD8+	NS	0.0043	↑3h
NKT cells CD8+	NS	p<0.0001	↓3h
NKT cells CD4+	NS	p<0.0001	↓3h ↑48h
T cells CD4+	NS	p<0.0001	↓48h
Mono CD16+CD14-	NS	p<0.0001	↓3h ↑48h
Mono CD16+CD14+	NS	p<0.0001	↓3h ↑48h
Mono CD16-CD14-	NS	NS	-
Mono CD16-CD14+	NS	NS	-
CD69+ T cells	NS	0.0006	↑48h
CD69+ B cells	NS	NS	-
CD69+ NK cells	NS	p<0.0001	↑48h
CD69+ Monocytes	NS	NS	-
CD69+ CD8+ T cells	NS	0.012	↑48h
CD69+ CD8+ NKT cells	NS	p<0.0001	↓3h ↑48h
CD69+ CD4+ NKT cells	NS	0.0001	↑48h
CD69+ CD4+ T cells	NS	0.0012	↑48h
CD25+ T cells	NS	0.013	↓3h
CD25+ B cells	NS	NS	-
CD25+ NK cells	NS	NS	-
CD25+ Monocytes	NS	NS	-
CD25+ CD8+ T cells	NS	NS	-
CD25+ CD8+ NKT cells	NS	NS	-
CD25+ CD4+ NKT cells	NS	NS	-
CD25+ CD4+ T cells	NS	NS	-

Variable	Treatment	Time Effect	
	Difference	comparison	direction of time effect
Immunomodulation: PBMC 6 day culture - non stimulated			
Non Stim. IL-2; Non Stim. IL-6; Non Stim. IL-10; Non Stim. GM-CSF; Non Stim. IFNg; Non Stim. TNFa; Non Stim. IL-1b; Non Stim. IL12p70	NS	NS	-
Immunomodulation: PBMC 6 day culture - MM stimulation			
MM IL-2	NS	0.0021	↑3h
MM IL-10	NS	0.043	↓3h
MM GM-CSF	NS	0.036	↑3h ↓48h
MM IFNg; MM TNFa; MM IL-1b; MM IL12p70; MM IL-6	NS	NS	-
Immunomodulation: PBMC 6 day culture - PHA Stimulation			
PHA GM-CSF	NS	0.0025	↑48h↓192h
PHA TNFa	NS	0.0002	↓3h ↓192h
PHA IL-1b; PHA IL12p70; PHA IL-2; PHA IL-6; PHA IL-10; PHA IFNg	NS	NS	-
Apoptosis			
Her-2	NS	NS	-
Caspase-3	NS	NS	-
Cleaved caspase-3	NS	0.0498	↑48h
Akt	NS	NS	-
Phosph Akt	NS	NS	-
DNA fragmentation	NS	NS	-

↑↓ = time of noticeable increase or decrease;
Akt = serine/threonine kinase; CRP = c-reactive protein; GM-CSF = granulocyte-macrophage colony stimulating factor; IFN-γ = interferon γ; Ig = immunoglobulin; IL = interleukin; MM = memory mix; NK = natural killer; NS = not significant; Non stim = non stimulated; PBMC = peripheral blood mononuclear cells; PHA = phytohemagglutinin; Phosph = phosphorylated Akt; TNF-α = tumor necrosis factor α

2.4.4. Discussion on clinical pharmacology

The Applicant's development program to demonstrate the similarity between Ogivri (MYL-1401O) and Herceptin with respect to the pharmacokinetic (PK) is considered adequate and was performed according to the guidance on similar biological products and the recommendations given in the national and CHMP Scientific Advice. The comparability exercise was performed between EU sourced reference product and the Ogivri formulation intended to be marketed in the European Union (EU). In addition, comparability with US licensed and Indian Herceptin formulations were used as supportive data.

The Ogivri (MYL-1401O) PK program consisted of two pivotal studies carried out in healthy subjects (Clinical Study Reports MYL-Her-1001 and MYL-Her-1002) and one supportive study in combination with docetaxel in patients with Her2+ metastatic breast cancer (Clinical Study Report BM200-CT3-001-11).

Several ELISA analytical methods to quantify the concentration of MYL-1401O and Herceptin in human plasma in volunteers and in patients with Her2+ Metastatic Breast Cancer were submitted. In general, the ELISA methods used in Study MYL-Her-1001 and MYL-Her-1002 have been adequately validated before study sample analysis and during all accepted runs for MYL-1401O and Herceptin. The analyses were substantially carried in accordance with the current Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). The validation of the method included assessment of precision and accuracy of the standard curve,

the assay range (defined by the LLOQ and ULOQ), intra-assay precision and accuracy, inter-assay precision and accuracy, selectivity, dilutional linearity, minimum required dilution, pro-zone effect, and short-term, long-term and freeze/thaw stability.

With regards to study MYL-Her-1001, the cross-over design is acceptable because it allows reducing the variability and a higher sensitivity to detect differences between both products. The selected dose (8 mg/kg body weight) corresponds to a frequently applied regimen in patients with metastatic breast cancer, although the use of a lower dose (6 mg/Kg) would equally allow establishing biosimilarity and would have been preferable from the safety point of view. In addition, given that the clearance is independent of dose in the therapeutic range, any dose in this range is suitable for this study. Based on the half-life value of trastuzumab in healthy subjects (approx. 22 days) the length of each study period of 14 weeks (corresponding to 4.5 half-lives) is adequate to full characterisation on the elimination phase and allow covering at least 80% of the AUC. This proposal was endorsed in the CHMP Scientific advice (EMA/CHMP/SAWP/153458/2012).

In the context of a cross-over design, based on a terminal $T_{1/2}$ to be around 22 days in healthy male subjects on the basis of known half-life for endogenous IgG1, a carry-over effect could have been observed in several subjects at baseline of period II for serum concentrations despite the long interim period and the 14 week follow-up. Therefore, the applicant proposed a sensitivity analysis to correct measured concentrations during period II if needed. Finally, two samples at baseline of Period II were slightly above the LOQ (75 ng/mL): before Herceptin (114.2 ng/mL for one subject) and before MYL-1401O (99.4 ng/mL for another subject) administration. These concentrations were <0.1% of Cmax and no further analysis was judged needed.

Duration of wash-out period was extended from 0-4 weeks in original protocol to 0-8 weeks to accommodate a few subjects for whom the 4 week interim period may not be achievable for personal or for professional reasons. This change was based on the need for flexibility and not on pharmacokinetics (PK) considerations, and this extension has no impact on study quality. This is considered acceptable.

The study was conducted in healthy Caucasian males with a very small group of subjects with other ethnicity. This difference between ethnic groups would not be expected to cause systemic bias in the biosimilar comparison exercise. In addition, healthy subjects represent a homogeneous population and reduce the inherent variability. Proposed PK and statistical methods are the standard methods recommended in the guideline on the Investigation of bioequivalence.

The design of the second PK study MYL-Her-1002 is also considered acceptable. In the case of a monoclonal antibody with per definition a long half-life and a potential of immunogenicity, a parallel design is accepted. Volunteers are the most sensitive population for initial investigation of PK with the aim of minimizing variability and permitting detection of differences between pharmaceutical products. This proposal was endorsed in the CHMP Scientific Advice. A single dose is sufficient to detect any difference in clearance. The single dose of 8mg/kg in intravenous infusion (over 90 minutes) is considered adequate as discussed further above. A sufficient number of samples to adequately characterise the whole profile were collected, with sufficient sampling around predicted Tmax to provide reliable estimate of peak exposure. Based on the half-life values of trastuzumab in healthy subjects, the length of each study period is adequate for characterisation of the elimination phase.

The submitted primary PK analysis showed PK comparability of the test and reference products at the dose of 8 mg/kg body weight given that the 90% confidence intervals for the ratios of both primary parameters (Cmax and AUC0-t/AUC0-∞) were well contained within the standard bioequivalence interval of 0.80–1.25 in study Myl-Her-1001 and in study Myl-Her-1002. In addition, the terminal half-life, Vz and CL parameters were also similar across the groups.

Likewise, the study performed in patients (BM200-CT3-001-11) with the other formulation supports the conclusion of similarity given that the 90% confidence intervals for the ratios of both primary parameters (Cmax and AUC0-t) were well contained within the standard bioequivalence interval of 0.80–1.25.

A population pharmacokinetic (PopPK) analysis was carried out for protocol MYL-HER 3001. Data supporting the appropriateness of using a linear PK model was provided. At clinical doses, trastuzumab was shown to follow linear pharmacokinetics, with nonlinear behaviour being more substantial at low concentrations and at Km values well below the trough concentrations observed at clinical doses. The use of a linear PK model was considered justified.

The inclusion of healthy data would have been informative to unravel target-mediated effects. However, as the primary aim of the PopPK exercise was to show similarity in (patient) pharmacokinetics of Ogivri and the reference product Herceptin, thus the model can be considered fit for purpose. The model showed that observed trough concentrations were not different between treatments at the end of the first dosing interval or at Cycle 6.It was also shown in the POP PK analysis that the model based assessment of ADA as a covariate of CL was inconclusive due to the low frequency of ADA development with each treatment. The presence of ADA was modeled as a time-variant, proportional covariate of clearance. The proportionality parameter was estimated to reduce clearance by approximately 9% in the presence of ADA, but the parameter was poorly estimated.

Analyses in the special populations were not submitted but are not relevant in the Ogivri MAA as the biosimilar relies on the information already known of the reference product. No formal drug-drug interaction studies are needed.

In conclusion, pharmacokinetic data provided support the biosimilarity of Ogivri (MYL-1401O) and Herceptin.

Regarding pharmacodynamics, a wide range of exploratory PD markers were analysed in study MYL-Her-1001. PD investigation was done *ex vivo* as there are no quantifiable PD endpoints that can be investigated in healthy subjects. Therefore *ex vivo* serum samples and peripheral blood mononuclear cells were isolated from treated healthy subjects and used for exploratory investigation. All *ex vivo* and *in vitro* exploratory PD variables showed similar responses to MYL-1401O and Herceptin. Findings in this large PD panel support the assessment of MYL-1401O as being highly similar to Herceptin.

There were no significant differences between MYL-1401O and Herceptin for any of the PD parameters, though some of the individual tests making up the broader parameters did deviate between both products (CD8+ T-cell counts, IgG expression and cleaved caspase-3). However, given the low number of individuals, and given that none of the other parameter markers went out of bound it is not possible to ascribe any relevant meaning to these limited differences.

Findings in this large PD panel, consisting of 72 variables, constitute supportive results for the assessment MYL-1401O similarity to Herceptin. Studies on the mechanism of action were not provided which is acceptable for a biosimilar.

2.4.5. Conclusions on clinical pharmacology

From a pharmacokinetic perspective, the data provided support demonstration of biosimilarity of MYL-1401O and Herceptin. The pharmacodynamics investigation results also support biosimilarity.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response study was provided (see discussion on clinical efficacy).

2.5.2. Main study

Study MYL-Her-3001

Methods

The pivotal confirmatory efficacy and safety study MYL-Her-3001 aimed to evaluate biosimilarity between MYL-1401O and EU-approved Herceptin.

There were two parts to the study, with Part 1 being the main comparative part and Part 2 evaluating the continued safety and immunogenicity of MYL-1401O with Herceptin administered as a single agent. A schematic of the study design is provided in Figure 14. Note that in contrast to the implied regimens on the figure, patients were allowed to continue concomitant Taxane treatment if it was the investigator's opinion that they would benefit from this.

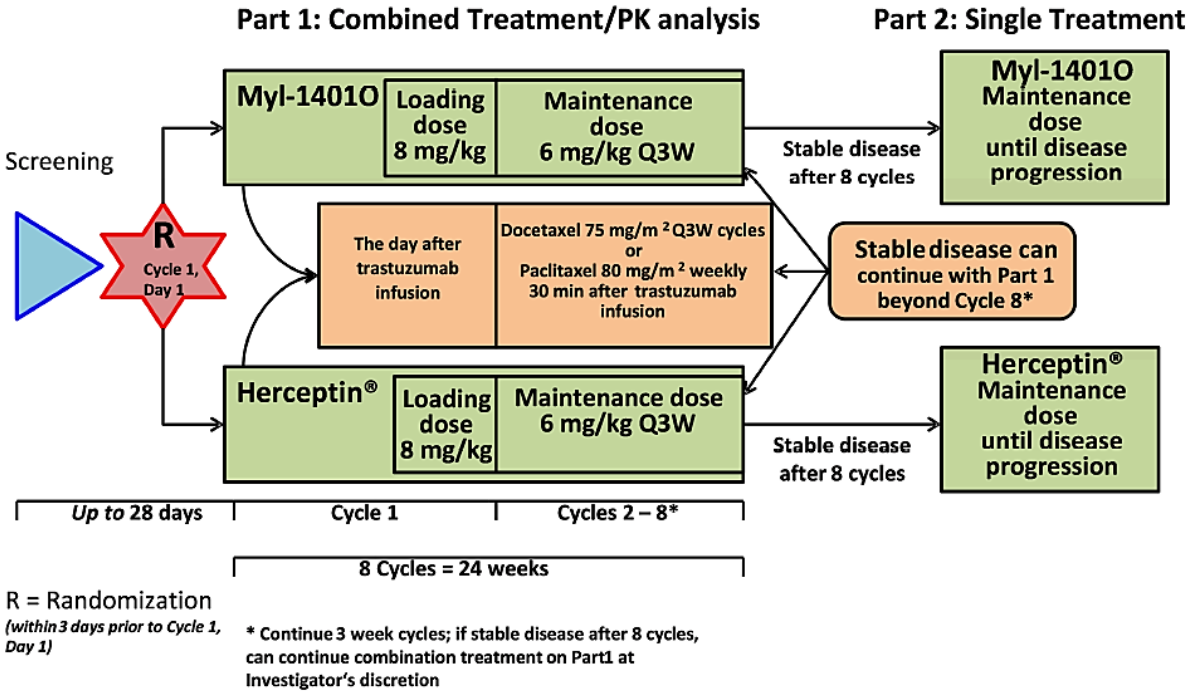


Figure 12: Schematic of the Design of Study MYL-Her-3001

Study Participants

Key inclusion criteria

1. At least 18 years of age.
2. Histologically confirmed diagnosis of breast cancer.
3. Locally recurrent or MBC that was not amenable to curative surgery and/or radiation.
4. Documentation of HER2 gene amplification by fluorescent in situ hybridization (FISH) (as defined by a ratio > 2.0) or documentation of HER2-overexpression by immunohistochemistry (IHC) (defined as IHC3+, or IHC2+ with FISH confirmation) based on Sponsor-identified central laboratory before randomization. Archival tumour tissue samples could have been used.
5. Documentation of ER/PgR status (positive or negative) based on either a local or central laboratory report must have been available before randomization.
6. Pathologically confirmed breast cancer with at least 1 measurable metastatic target lesion (based on RECIST 1.1 criteria). Bone, central nervous system (CNS), and skin lesions, as well as lesions that were irradiated, biopsied, or had any form of local intervention or surgical manipulation, were only to be assessed as non-target lesions. Baseline imaging studies and submitted for central confirmation of target lesions must have been performed in the 4 weeks preceding randomization.
7. Patients with a history of CNS metastases or cord compression were eligible if they had been successfully treated and were off steroids for at least 4 weeks before first dose of investigational product. Patients with newly detected CNS metastases had to have been successfully treated (e.g., radiotherapy, stereotactic radiosurgery) before being considered for the trial. Patients with known or suspected brain metastases had to have undergone a baseline brain computed tomography (CT) scan or magnetic resonance imaging (MRI) scan.
8. Patients previously treated with trastuzumab or lapatinib in the adjuvant setting were allowed if metastatic disease was diagnosed at least 1 year after the last dose of treatment.
9. Prior treatment with hormonal agents or bisphosphonates/denosumab was allowed. Bisphosphonates/denosumab could have been given simultaneously with study drug but could not have started after randomization and was considered an indication of progressive disease (PD). Hormonal agents had to have been discontinued before beginning study therapy.
10. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2.
11. Screening laboratory values within the following parameters: Absolute neutrophil count (ANC) ≥ 1.5 × 109/L (1500/mm3); Platelet count ≥ 100 × 109/L (100,000/mm3); Hemoglobin ≥ 9.0 g/dL (90 g/L), without a prior transfusion in the last 2 weeks; Serum creatinine ≤ 1.5 × upper limit of normal (ULN); Total bilirubin ≤ 1.0 × ULN (> 1 ULN if documented Gilbert's disease); Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × ULN; AST and/or ALT < 1.5 × ULN, if alkaline phosphatase > 2.5 × ULN; Alkaline phosphatase > 2.5 × ULN, if bone metastases present and no liver dysfunction present.
12. Left ventricular ejection fraction (LVEF) within institutional range of normal as measured by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO).

Key exclusion criteria

1. Prior systemic therapy in the metastatic disease setting. This included: chemotherapy, signal transduction inhibitors (e.g., lapatinib), HER2 targeted therapy (e.g., trastuzumab), or other investigational anticancer therapy.
2. Prior treatment with neoadjuvant or adjuvant anthracyclines with a cumulative dose of doxorubicin of > 400 mg/m2 or epirubicin of > 800 mg/m2.
3. Participation in the active treatment part of an investigational drug study ≤ 28 days before randomization. Patients with bone or skin as the only site of disease. Patients with skin lesions measurable by CT scans or MRI scan as only site of measurable disease were allowed.
4. Surgery or radiotherapy ≤ 2 weeks preceding Day 1. Target lesions had to be outside the irradiated fields and the patient had to have fully recovered from surgery or radiotherapy.
5. Presence of unstable angina or a history of CHF according to the New York Heart Association criteria, history of myocardial infarction < 1 year from randomization, clinically significant valvular disease, serious cardiac arrhythmia requiring treatment, uncontrolled hypertension, or known pulmonary hypertension.
6. Peripheral sensory or motor neuropathy Grade 2 or higher according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
7. Any other cancer, including contralateral breast cancer, within 5 years before screening with the exception of adequately treated ductal carcinoma in situ, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin.
8. Immunocompromised patients, including known seropositivity for human immunodeficiency virus, or current or chronic hepatitis B and/or hepatitis C infection (as detected by positive testing for hepatitis B surface antigen or antibody to hepatitis C virus with confirmatory testing).
9. Patients with documented severe hypersensitivity reaction to trastuzumab, paclitaxel, docetaxel, or excipients used in their formulations, including murine protein remnants and patients with heredity fructose intolerance.
10. Evidence of significant medical illness or abnormal laboratory finding (including dyspnea at rest or serious pulmonary illness) that, in the Investigator's judgment, substantially increased the risk associated with the patient's participation in, and completion of, the study, or could preclude the evaluation of the patient's response.

Treatments

Both MYL-1401O and Herceptin were administered by continuous IV infusion over 90 min (±10 min) for the Cycle 1, Day 1 loading dose and then by continuous IV infusion over 30 min (±10 min) as the corresponding maintenance doses on subsequent cycles.

In combination with the above the patients also received taxane-treatment, with the choice of taxane to be made by the Investigator at each study site prior to the start of screening. Said choice was then to be applied to all patients enrolled by that particular site.

Since MYL-1401O was developed with biosimilar intent compared to Herceptin, treatments were dosed according to the latter's SmPC, with a starting dose of 8 mg/kg trastuzumab over 90 min by continuous iv infusion followed by 6 mg/kg trastuzumab over 30 min continuous iv infusion every 3 weeks.

For docetaxel, a dose of 75 mg/m^2 of BSA administered iv over 1 hour (±10 min) every 3 weeks throughout the study was selected based on docetaxel being used in previous different clinical trials as well as in clinical practice in a dose range of 30 to 100 mg/m^2. Furthermore, published literature suggests that a large proportion of studies and Investigators favour dosing patients with docetaxel at 75 mg/m^2.

For paclitaxel, a weekly schedule of 80 mg/m^2 was selected based on a phase 3 study comparing weekly paclitaxel to every-3-week paclitaxel which showed an improvement in response rate and TTP of weekly administration over of the standard paclitaxel schedule.

Dose modification of all the above was possible for selected reasons.

After the first part of the study (eight cycles) those with CR and PR proceeded to Part 2 of the study, wherein single-agent MYL-1401O or Herceptin was administered. Those with SD continued with a combination of MYL-1401O or Herceptin and the taxane therapy beyond 24 weeks at the investigator's discretion in Part 1 or stopped the taxane therapy and continued in Part 2 with monotherapy (after a minimum of 8 completed taxane cycles), though exceptionally taxane combination treatment could be temporarily continued if the investigator deemed this necessary for the patient's benefit.

Those who were intolerant to the combination therapy during Part 1 or who had responded to therapy and declined participation in Part 2 were discontinued from the study, treated at the investigator's discretion, and followed for long-term survival. In Part 2 of the study, all patients with at least SD continued with the trastuzumab product that they were originally allocated to as a single agent until disease progression, unacceptable toxicity, or death, whichever occurred first. Dosing was done according to the EU SmPC of Herceptin.

Concomitant drugs or treatments that were forbidden included:

- Immunotherapy for the treatment of breast cancer
- Any tumour-directed therapy from study screening until the completion of study treatment.
- IMP or experimental procedure
- Non-study drug therapy for MBC, with the exception of hormonal therapy (permitted in Part 2 of the study for ER/PgR-positive patients).

Objectives

The primary objectives for part 1 and 2 were respectively comparison of the independently assessed best ORR at Week 24 and the descriptive comparison of the safety, immunogenicity, and tolerability profile of single-agent MYL-1401O and Herceptin.

Secondary objectives encompassed comparison of independently assessed clinical activity at Week 24 between treatment arms by measuring TTP, PFS, OS and DR, as well as a descriptive comparison of the safety, immunogenicity, and tolerability profiles and a PopPK comparison. In part 2 the secondary objective was to compare the clinical activity at Week 48 between treatment arms by measuring PFS, OS and DR, and OS at 36 months or after 240 deaths.

Finally, exploratory objectives were the assessment of the impact of shed ECD fragments of the HER2 receptor (HER2/ECD) in serum on PK and efficacy parameters.

Outcomes/endpoints

The primary endpoint was the best ORR where objective response was defined as a CR or PR according to RECIST 1.1 criteria based on central tumour evaluation (taking as reference for PD the smallest measurements recorded since the treatment started) achieved at 24 weeks after start of treatment. Objective response was based on the best overall response recorded from the start of treatment (Day 1) until centrally assessed PD, death, or first administration of anti-tumour treatment (other than study drug), whichever occurred first.

Secondary endpoints were: Time to progression (TTP) defined as the time from randomization to date of first documentation of objective progression; Progression-free survival (PFS) defined as the time from randomization to first documentation of objective progression or to death due to any cause; Overall survival (OS) defined as the time from date of randomization to date of death due to any cause; Duration of response (DR) defined as the time from the first documentation of objective tumour response (CR or PR) to the date of first documentation of objective tumour progression or to death due to any cause, whichever occurred first.

Exploratory endpoints were: Disease control rates (sum of CR, PR, and SD) at Week 24; Baseline HER2/ECD evaluated as a predictor for the efficacy endpoints of ORR, OS, and TTP at Week 24 and Week 48; General Descriptive Summaries of HER2/ECD (elevated HER2/ECD defined as a HER2/ECD value of 15 ng/mL or greater; significant Percent Change From Baseline in HER2/ECD defined as a decrease of 55% or more).

In Part 1 of the study, tumour assessments were conducted every 6 weeks (±3 days) independent of delays in taxane administration. In Part 2 of the study (for patients with at least documented SD, based upon local radiographic tumour assessments and clinical evaluation as per RECIST 1.1 criteria), tumour assessments were conducted every 12 weeks (±3 days) independent of delays in MYL-1401O or Herceptin administration.

Sample size

A sample size of 410 patients (205 per treatment group) was required to provide at least 80% power to declare MYL-1401O equivalent to Herceptin in the analysis of ORR at Week 24 within the respective primary endpoint analyses. Given an estimated 10% attrition rate the required sample size of 410 was then adjusted to the final needed number of 456 persons.

Randomisation

Randomization was done in a 1:1 proportion to MYL-1401O (also referred as Hercules) plus taxane (docetaxel or paclitaxel) or Herceptin plus taxane within 3 days prior to Cycle 1, Day 1.

Patients were stratified based on the following baseline covariates:

- Tumour progression into metastatic part ≥ 2 years OR < 2 years after primary diagnosis (calculated as time from primary tumour surgery until randomization). Patients diagnosed with primary metastatic disease were classified together with the patients who progressed < 2 years, regardless of the date of tumour surgery.
- ER/PgR status (ER- and/or PgR-positive/ER- and PgR-negative).
- Type of taxane received (i.e., paclitaxel or docetaxel).

Blinding (masking)

Treatment assignment was not disclosed to the Investigator, site or study personnel, or any Sponsor Representative, except for the designated site monitor responsible for unblinded monitoring. An unblinded pharmacist was identified at each centre, but this person's role was limited to handling the study drug, which was provided them to the Investigator in a blinded manner.

Study unblinding was performed at the end of Part 1 when the final analysis of the primary efficacy endpoint occurred. Only individuals fulfilling select roles at the sponsor and the contract research organization (CRO) were unblinded. For both parties, blinded and unblinded teams were established prior to the completion of study Part 1. Blinded teams at the sponsor and the CRO remained blinded for the duration of the study.

For Parts 1, 2 and the period of time until the final OS analysis, investigators and patients remained blinded to the treatment that the patient received. The Coordinating Investigator remained blinded throughout the study.

Independent oversight of this study was provided by a DSMB who reviewed partially unblinded interim and cumulative safety and blinded efficacy data, on a quarterly basis and reviewed partially unblinded efficacy data at the a priori declared interim analysis.

Statistical methods

Statistical analysis sets

ITT1 population was the one on which both primary endpoint analysis were conducted. It consisted of all patients who were randomized into the study under Protocol Amendment 2 (version 5.0; 11 Oct 2013) and beyond. ITT2 population set consisted of all randomized patients (i.e., included patients enrolled under Protocol Amendment 1 [version 2.0; 02 Jul 2012]). This early protocol version allowed randomization of patients who would receive second-line treatment for MBC. In total 42 patients were randomized under Protocol Amendment 1, and these are not part of the ITT1 population.

The Per-Protocol (PP) population was defined at the end of Part 1 and was a subset of ITT1 and included patients who met the following additional criteria: (1) received the treatment to which they were randomized; (2) absence of any major protocol deviations in Part 1 which precluded the evaluation of the patient including, for example, the lack of measurability of the lesions; the absence of violation of entry criteria which completely precluded the assessment of efficacy and safety; (3) had at least 1 post-baseline tumour assessment if a progression disease; and at least 2 if CR, PR, or SD; (4) had received at least 2 complete cycles of treatment; however, if a progression, death, or discontinuation occurred before the end of the first 2 cycles, the patient was retained in the PP population.

The safety population included all patients who received at least 1 dose of study drug MYL-1401O or Herceptin, in any amount, with treatment assignments designated according to actual study drug received were included in the safety population.

The PK population included all randomized patients who received at least 1 complete dose of MYL-1401O or Herceptin, and had at least 1 post-dose sample for PK analysis.

Primary analysis

Equivalence of MYL-1401O and Herceptin was analysed using pre-specified equivalence intervals, based on the ratio of ORRs. A 2-sided 90% confidence interval (CI) for the ratio of the best ORRs at Week 24 was calculated

based on the method of logarithmic transformation. Equivalence was declared if the 90%-CI was within the equivalence range of (0.81, 1.24).

Based on scientific advice from the CHMP (EMA/CHMP/SAWP/153458/2012), an additional equivalence analysis was conducted using the difference in best ORRs (sensitivity analysis). A 2-sided 95% CI for the difference of the best ORRs at Week 24 was calculated. Equivalence was declared if the CI was within the equivalence range of (-15%, 15%), the details of which were discussed and amended following the EMA Scientific Advice received March 15, 2012 (EMA/CHMP/SAWP/153458/2012). This equivalence margin was based on review of literature and study reports, and by linking the ORR with PFS/TTP.

The outcome of said linking found that for a TTP of 12 months the model predicts an ORR of 65.3%. The value (65.3% - 15%) is 50.3% and the value (65.3% + 15%) is 80.3%. These values equate to 10.10 and 13.52 months, respectively, which is less than ± 1.90 months from the median TTP of 12 months. This deviation of 1.9 months is not considered a clinically meaningful difference.

Secondary analysis

For TTP, PFS, OS, and DR, Kaplan-Meier plots by treatment were presented and the log-rank test of the 2 treatment groups unadjusted for any covariates was performed. For TTP, PFS, OS, and DR, Cox's proportional hazards model was used to analyse for treatment effects, adjusting for subgroup. Univariate analysis and multivariate analysis with forward selection were performed. Hazard ratios and 95% CIs were presented. Forest plots were produced for subgroups (stratification factor).

Sensitivity analysis

The following sensitivity analyses were performed on the primary endpoint, ORR:

• Subgroup analyses for ORR ratio by stratification factor, age, race, previous adjuvant/neoadjuvant chemotherapy or HER2-targeted treatment, visceral metastases, number of metastatic sites, CNS as first site of metastasis, and geographic region.

Forest plots were produced for subgroups.

• Univariate analysis and multivariate logistic regression analysis with forward selection were performed based on the factors and covariates indicated above.

• Cochran-Mantel-Haenszel analysis for ORR ratio stratified by the stratification factors was performed. Estimates of the relative risk and the odds ratio, and their 90% and 95% CIs were presented.

• Logistic regression analysis of the treatment odds ratio adjusted for the stratification factors were performed.

• The primary efficacy analysis was replicated in the PP population for both ORR ratio and difference in ORR.

• The primary efficacy analysis was replicated in the ITT2 population for both ORR ratio and difference in ORR.

The primary efficacy analysis was conducted with the Investigator assessments of disease response and progression in the ITT1, ITT2, and PP population for ORR ratio.

• The difference in ORR (with two-sided 90% and 95% CIs) was calculated with no covariate adjustment in the ITT1, ITT2, and PP population. Equivalence was evaluated within the equivalence region of ±15%.

Sensitivity Analyses for TTP, PFS and OS were also performed by the applicant in addition to exploratory analyses.

Results

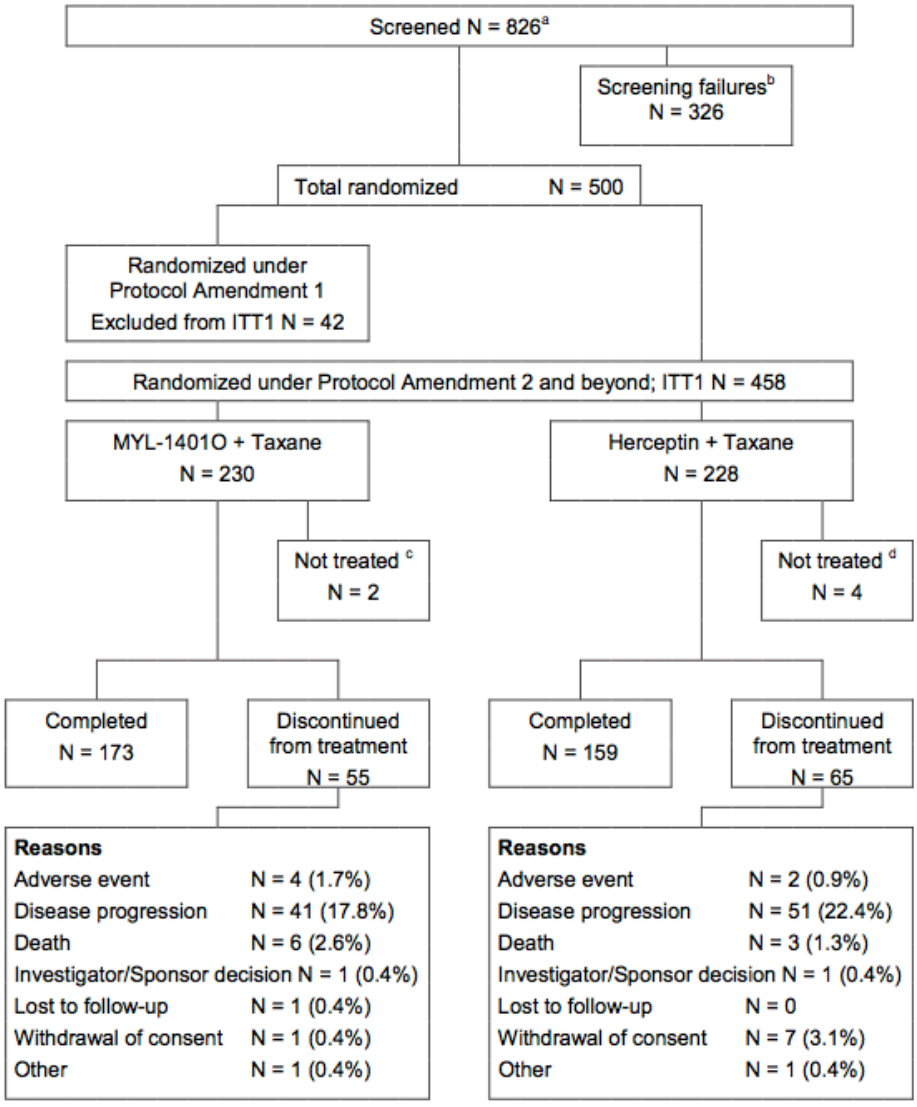
Participant flow

In total 826 patients were screened, of which 39.5% (n = 326) failed the screening (the majority by lack of HER2+ confirmation).

Figure 15 below gives an overview of the patient flow in Part 1, whereas

Figure 16 provides the patient flow in Part 2.

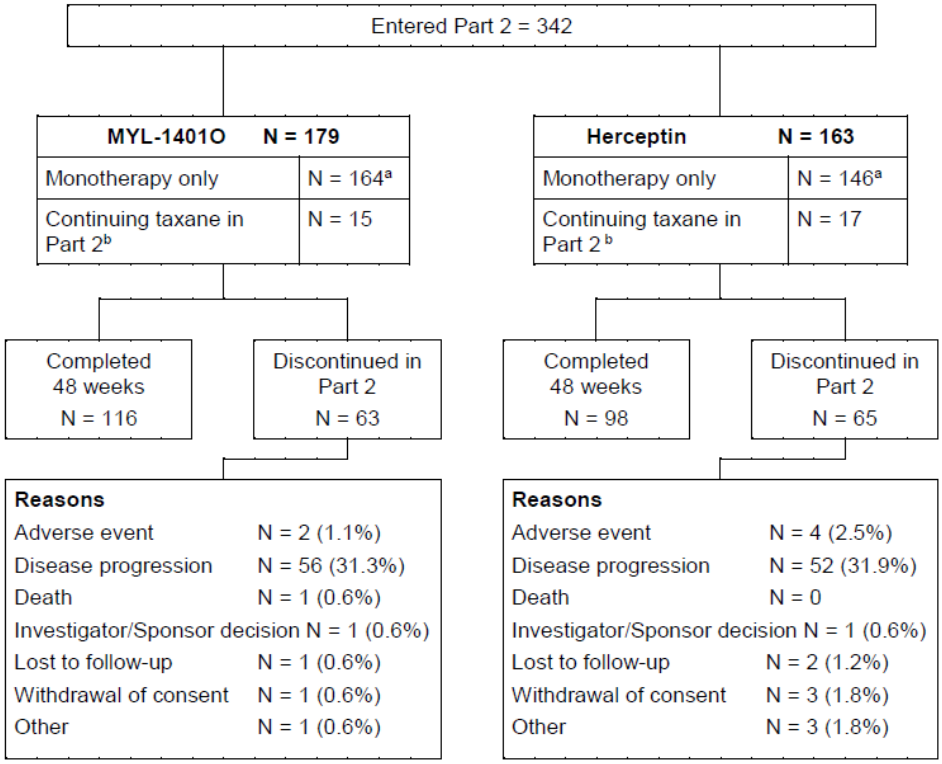
Figure 13: Participant flow in Part 1 of the study, ITT1 population



ITT: intent-to-treat, N: number of patients; Percentages are based on the number of patients randomized. Note, the first 42 patients who were randomized under Protocol Amendment 1 were included in the ITT2 population (all randomized patients) but excluded from the ITT1 population used for the primary efficacy analysis, as Protocol Amendment 1 allowed randomization of patients who would receive second-line treatment for MBC.

[a] 9 patients were re-screened; [b] Screening failures patients were not randomized in the study;
[c] Reason: death, lost to follow-up (1 patient each); [d] Reason: withdrawal of consent (2 patients), other (2 patients).

Figure 14: Participant flow in Part 2 of the study, Safety population



ITT: intent-to-treat, N: number of patients
Percentages are based on the number of patients entering Part 2.
Note, the first 42 patients who were randomized under Protocol Amendment 1 were included in the ITT2 population (all randomized patients) but excluded from the ITT1 population used for the primary efficacy analysis, as Protocol Amendment 1 allowed randomization of patients who would receive second-line treatment for MBC.
22 patients randomized under Protocol Amendment 1 continued into Part 2 of the study (MYL-1401O 10, Herceptin 12) and 13 patients (5/8) completed Week 48.
9 patients (5/4) discontinued in Part 2.
Reasons for discontinuation were: MYL-1401O: disease progression (4), other (1); Herceptin: AE (2), disease progression (1), lost to follow-up (1).
[a] *Number calculated by author.*
[b] *All 32 patients continuing taxane in Part 2 switched to receiving trastuzumab monotherapy during Part 2 as per the protocol.*

The study protocol initially allowed the recruitment of patients receiving trastuzumab as both first- and second-line treatment for metastatic breast cancer (MBC). Forty-two patients were randomized under these conditions (henceforth referenced to as Protocol Amendment 1). Later recruitment was limited to patients receiving trastuzumab as first-line treatment, with the objective of increasing the homogeneity of the study population and the reliability of the study results, and to more closely reflect the standard of care. These patients, randomized under Protocol Amendment 2; are included in the intent-to treat-1 (ITT1) population, which is also the efficacy analysis population.

The ITT-2 population (ITT2) consisted of all randomized patients, including 42 patients enrolled under protocol Amendment 1. This population was used in sensitivity analyses to investigate the rigor of the results attained with the ITT1 population.

Recruitment

A total of 500 patients were enrolled at 95 sites in Bulgaria, Chile, Czech Republic, Georgia, Hungary, India, Latvia, Philippines, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Thailand, and Ukraine.

Date of first enrollment: 10 Dec 2012

Date Last Patient's Last Assessment in Part 1 of the Study (Date of Data Cut-Off): 25 Jan 2016

Date Last Patient's Last Assessment in Part 2 of the Study (Date of Data Cut-Off): 13 Jul 2016

Conduct of the study

Protocol amendments

The protocol was finalized on 07 Feb 2012 and was amended on 02 Jul 2012 (Amendment 1; version 2.0), 05 Sep 2013 (Amendment 2; version 3.0), 26 Sep 2013 (Amendment 2; version 4.0), 11 Oct 2013 (Amendment 2; version 5.0). An errata (version 1.1) to Protocol Amendment 2 (version 5.0) was issued on 21 Nov 2013. Three country-specific amendments issued on (Amendment 3, version 6.0, dated 28 May 2014; Amendment 4, version 7.0, dated 10 Jul 2014, and Amendment 5, version 8.0, dated 19 Aug 2014) were produced. A global protocol amendment (Amendment 6; version 9.0) was issued on 10 Apr 2015. The latest global protocol amendment Protocol Amendment 7 (version 10.0) was issued on 3 March 2017 to include the analysis of the ORR difference as a sensitivity analysis in alignment with the SAP. The protocol was primarily written for the US regulatory authority (US FDA) with a dual scope on the European regulatory authority (EMA)'s requirement on equivalence. Since EMA has requested to use the difference in best ORRs as the primary efficacy analysis, the analysis on difference of ORRs was carried out as a sensitivity analysis, without type I error adjustment.

No patients were enrolled under the original protocol (07 Feb 2012). On 10 Dec 2012, the first patient was enrolled into the study under Protocol Amendment 1 (02 Jul 2012; version 2.0). In total, 42 patients were enrolled under Protocol Amendment 1 (02 Jul 2012; version 2.0) with the last patient enrolled under this amendment on 28 Aug 2013. Protocol Amendment 2 (version 3.0; 05 Sep 2013) was related to a change in CRO. No patients were enrolled under Protocol Amendment 2 (version 3.0 [05 Sep 2013]) or Protocol Amendment 2 (version 4.0 [26 Sep 2013]). All other patients were enrolled under Protocol Amendment 2 (version 5.0; 11 Oct 2013) and beyond (n = 458). A summary of the key changes between Protocol Amendment 1 (version 2.0; 02 Jul 2012) and Protocol Amendment 2 (version 5.0; 11 Oct 2013) is detailed below:

- Clear exclusion of patients who had received a previous chemotherapy as first-line therapy of MBC.
- For the primary objective in Part 1 of the study, details of the variable assessed (best ORR), the method of assessment (the RECIST 1.1. criteria), and the time point (Week 24) of the assessment were added.
- A primary objective to "descriptively compare the safety, immunogenicity, and tolerability profile of single-agent MYL-1401O and Herceptin and; to compare the immunogenicity of MYL-1401O and Herceptin by examining clinical immunogenic response" was added for Part 2 of the study.
- Clarification that clinical activity (i.e., TTP [Part 1 only], PFS, OS, and DR) would be assessed as a secondary objective for Part 1 and Part 2 of the study was added.
- A descriptive comparison of the immunogenicity profile of MYL-1401O and Herceptin given in combination with a taxane was added to the secondary objectives for Part 1 of the study.

- The exploratory objective was amended to be assessed in Part 2 of the study as well as Part 1 of the study. It was clarified that the impact of shed ECD fragments of the HER2 receptor (HER2/ECD) in serum assessed the impact on PK and efficacy parameters.
- The number of planned global sites was increased from approximately 150 sites to approximately 200 sites. In addition, the number of anticipated male and female patients to be included in this study was increased from up to 470 patients to up to 600 patients
- Protocol Amendment 2 (version 5.0) added paclitaxel as a possible type of taxane to be used in this study, and as such, details of the paclitaxel dosing schedule were added. In Protocol Amendment 1 (version 2.0), the only taxane available for use was docetaxel
- Protocol Amendment 2 (version 5.0) deleted the following stratification factor: "Previous adjuvant/neoadjuvant chemotherapy or HER2 targeted treatment (yes/no)."
- A number of the inclusion and exclusion criteria were changed between protocol amendment versions. This included the addition of inclusion criterion 5): "documentation of ER/PgR status (positive or negative) based on either a local or central laboratory report must have been available before randomization." This was required as it was a stratification factor for randomization.

The SAP (version 1.0) was finalized on 12 Dec 2013 and was amended on 23 Mar 2015 (version 2.0), which aligned with the Protocol Amendment 6 (version 9.0, 10 Apr 2015). A summary of the key changes between Protocol Amendment 2 (version 5.0; 11 Oct 2013) and Protocol Amendment 6 (version 9.0; 10 Apr 2015) is detailed below.

- The sample size was re-calculated based on a new meta-analysis and planned to randomize 456 patients in the study.
- The hypothesis of the primary efficacy analysis was updated to "Ho: RT/RC $\leq$ 0.81 or RT/RC $\geq$ 1.24, H1: 0.81 RT/RC < 1.24". Two-sided 90% CI for the ratio of the best ORRs was to be calculated instead of two-sided 95% CI. The equivalence range was updated to (0.81, 1.24).
- Interim analysis was re-scheduled be performed when at least 30% information target was available to ensure that sufficient study information was obtained.

Protocol deviations

All patients who were randomized under Protocol Amendment 2 and beyond (230 patients in the MYL-1401O and 228 patients in the Herceptin arm), irrespective of protocol deviations, were included in efficacy analysis of the ITT1 population. Pre-defined rules were applied to exclude patients from the PP population. A total of 20 patients were excluded from the PP population (8 patients in the MYL-1401O arm; 12 patients in the Herceptin arm, per BDRM minutes). The most common protocol deviation in both arms was the lack of a post-baseline tumour assessment (MYL-1401O 4 patients, Herceptin 8 patients). Reason for lack of post-baseline data in these 12 patients was withdrawal of consent in 6 patients (all randomized to Herceptin), death (3 patients, all MYL-1401O), withdrawal per Investigator or Sponsor decision (2 patients; MYL-1401O and Herceptin), and AE not due to disease progression (1 patient, Herceptin).

Baseline data

Table 13: Demographic Characteristics by Treatment Group: ITT1 Population

	MYL-1401O + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Age [years]		
n	230	228
Mean (SD)	54.3 (10.97)	52.9 (11.22)
Median	55.0	54.0
Range	26, 79	26, 82
Age category [n (%)]		
< 50 years	74 (32.2)	86 (37.7)
≥ 50 years	156 (67.8)	142 (62.3)
Race [n (%)]		
Asian	70 (30.4)	72 (31.6)
Black/African American	1 (0.4)	2 (0.9)
Caucasian	159 (69.1)	154 (67.5)
Height [cm]		
n	221	217
Mean (SD)	159.0 (7.07)	159.3 (7.61)
Median	160.0	160.0
Range	143, 177	131, 176
Weight [kg]		
n	229	226
Mean (SD)	68.37 (14.977)	68.90 (16.029)
Median	67.00	67.00
Range	41.0, 110.0	36.0, 120.0
Body surface area [m^2]		
n	229	226
Mean (SD)	1.73 (0.206)	1.73 (0.220)
Median	1.73	1.73
Range	1.3, 2.3	1.1, 2.4

ITT: intent-to-treat, N: number of patients in treatment group, n: number of patients with data available, SD: standard deviation
Percentages are based on the number of patients in the ITT1 population.

Table 14: Disease History and Baseline Characteristics by Treatment Group: ITT1 or Safety Population

	MYL-1401O + Taxane	Herceptin + Taxane
	n (%)	n (%)
ECOG performance status (safety population)	(N = 247)	(N = 246)
0	127 (51.4)	107 (43.7)
1	115 (46.6)	132 (53.9)
2	5 (2.0)	6 (2.4)
Missing	0	1
ITT1 population	(N = 230)	(N = 228)
Assigned taxane		
Docetaxel	193 (83.9)	192 (84.2)
Paclitaxel	35 (15.2)	32 (14.0)
No treatment	2 (0.9)	4 (1.8)
Tumor endocrine status		
Estrogen- and progesterone-receptor-negative	128 (55.7)	127 (55.7)
Estrogen- or progesterone-receptor-positive	102 (44.3)	101 (44.3)
HER2/ECD status		
< 15 ng/mL	60 (27.0)	46 (21.0)
≥ 15 ng/mL	162 (73.0)	173 (79.0)
Missing	8	9
IHC status		
Equivocal	41 (17.8)	24 (10.5)
Positive	187 (81.3)	203 (89.0)
Negative	2 (0.9)	1 (0.4)
FISH status		
Positive	42 (18.3)	24 (10.5)
Equivocal	0	1 (0.4)
Negative	0	0
Missing	188 (81.7)	203 (89.0)
Tumor progression into metastatic phase		
< 2 years	146 (63.5)	153 (67.1)
≥ 2 years	75 (32.6)	71 (31.1)
Missing	9 (3.9)	4 (1.8)
Previous trastuzumab treatment		
Yes	22 (9.6)	16 (7.0)
No	207 (90.0)	212 (93.0)
Missing	1 (0.4)	0 (0.0)
Previous taxane treatment		
Yes	46 (20.0)	42 (18.4)
No	183 (79.6)	186 (81.6)
Missing	1 (0.4)	0 (0.0)

	MYL-1401O + Taxane	Herceptin + Taxane
	n (%)	n (%)
Previous lapatinib treatment		
Yes	2 (0.9)	1 (0.4)
No	228 (99.1)	227 (99.6)
Previous hormonal treatment		
Yes	47 (20.4)	43 (18.9)
No	182 (79.1)	185 (81.1)
Missing	1 (0.4)	0 (0.0)
Previous bone disease treatment		
Yes	18 (7.8)	20 (8.8)
No	211 (91.7)	208 (91.2)
Missing	1 (0.4)	0 (0.0)
Previous CNS disease treatment		
Yes	4 (1.7)	3 (1.3)
No	225 (97.8)	225 (98.7)
Missing	1 (0.4)	0 (0.0)

CNS: central nervous system, ECOG: Eastern Cooperative Oncology Group, FISH: fluorescent in situ hybridization, HER2/ECD: human epidermal growth factor receptor 2 extracellular domain, IHC: immunohistochemistry, ITT: intent-to-treat, N: number of patients in treatment group, n: number of patients with data available
Percentages are based on the number of patients in the ITT1 population, except for ECOG performance status where percentages are based on the number of patients in the safety population.

Table 15: Tumour Characteristics at Baseline: ITT1 Population

	MYL-1401O + Taxane (N = 230)	Herceptin + Taxane (N = 228)
	n (%)	n (%)
Number of metastatic sites		
1	58 (25.2)	61 (26.8)
2	87 (37.8)	67 (29.4)
3	44 (19.1)	57 (25.0)
≥ 4	41 (17.8)	43 (18.9)
Presence of visceral metastases		
Yes	172 (74.8)	185 (81.1)
No	58 (25.2)	43 (18.9)
CNS first site of metastasis		
Yes	1 (0.4)	2 (0.9)
No	229 (99.6)	226 (99.1)

CNS: central nervous system, ITT: intent-to-treat, N: number of patients in treatment group, n: number of patients with data available
Percentages are based on the number of patients in the ITT1 population.
Note: CNS first site of metastasis includes brain.

The most frequent concomitant conditions were hypertension (MYL-1401O 25.2%, Herceptin 22.4%) and menopause (MYL-1401O 22.6%, Herceptin 18.0%) in both treatment groups followed by uterine leiomyoma (9.1%), hysterectomy (7.4%), back pain, myocardial ischemia, and cholecystitis chronic (7.0% each) in the MYL-1401O group, and by back pain and biopsy breast (8.3% each) and diabetes mellitus (7.5%) in the Herceptin group.

Concomitant and prior medicine use

Prior medicine use was comparable between both treatment arms, with the most common ones in the pooled subject group being analgesics (3.7% overall) and drugs for treatment of bone diseases (3.0% overall). No patients in either treatment group used an excluded prior medication.

Almost 100% of patients used concomitant medicine. Most commonly used medicines were part of pre- or post-chemotherapy treatment: corticosteroids for systemic use, antiemetics and antinauseants, drugs for acid-related disorders and antihistamines for systemic use.

In Part 2 a total of 32 patients (15 patients in the MYL-1401O arm, 17 patients in the Herceptin arm) still received taxane when entering Part 2, but all moved on to receive monotherapy later on. Continuation of combination therapy and switch to monotherapy, based on potential benefit for the patient, was at the discretion of the Investigator.

The most commonly used concomitant medications in both treatment groups were similar to Part 1 and equal in both treatment arms: corticosteroids for systemic use, antiemetic and antinauseants, drugs for acid-related disorders and antihistamines for systemic use. Less patients on monotherapy used concomitant medications compare to those on combination therapy in Part 1.

Numbers analysed

Table 16: Analysis sets

Number of patients	**MYL-1401O + Taxane (N = 249)**	**Herceptin + Taxane (N = 251)**	**Total (N = 500)**
Part 1	**n (%)**	**n (%)**	**n (%)**
Randomized for Part 1	249 (100.0)	251 (100.0)	500 (100.0)
Safety population	247 (99.2)	246 (98.0)	493 (98.6)
ITT1 population	230 (92.4)	228 (90.8)	458 (91.6)
ITT2 population	249 (100.0)	251 (100.0)	500 (100.0)
PP population	222 (89.2)	216 (86.1)	438 (87.6)
PopPK population	245 (98.4)	240 (95.6)	485 (97.0)
	MYL-1401O (N = 179)	**Herceptin (N = 163)**	**Overall (N = 342)**
Part 2	**n (%)**	**n (%)**	**n (%)**
Entering Part 2	179 (100.0)	163 (100.0)	342 (100.0)
Entering Part 2 and receiving monotherapy[a]	164 (91.6)	146 (89.6)	310 (90.6)
Entering Part 2 and still receiving taxane for at least 1 cycle	15 (8.4)	17 (10.4)	32 (9.4)
Safety population entering Part 2	179 (100.0)	163 (100.0)	342 (100.0)
ITT1 population entering Part 2	169 (94.4)	151 (92.6)	320 (93.6)
ITT2 population entering Part 2	179 (100.0)	163 (100.0)	342 (100.0)
PP population entering Part 2	166 (92.7)	150 (92.0)	316 (92.4)

ITT: intent-to-treat, N: number of patients randomized (for Part 1) or number of patients entering Part 2 (for Part 2), n: number of patients in respective analysis set, PopPK: population pharmacokinetics, PP: per-protocol
Percentages are based on N of the respective part.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
A patient could be excluded from a dataset/population for more than 1 reason.
Safety population included all patients who received at least 1 dose of study medication. ITT1 population included all patients randomized under Protocol Amendment 2 and beyond. ITT2 population included all randomized patients. PP population was a subset of the ITT1 population who met the per-protocol criteria. PopPK population included all patients who received at least 1 dose of study medication and provided at least 1 concentration sample.
[a] Numbers calculated by author.

Outcomes and estimation

Primary efficacy results

Table 17: ORR and Ratio of Best ORR at Week 24 (ITT1 Population; Study MYL-Her-3001)

Response		MYL-1401O + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Complete response (CR)	n (%)	3 (1.3)	0 (0.0)
Partial response (PR)	n (%)	157 (68.3)	146 (64.0)
Stable disease (SD)	n (%)	48 (20.9)	49 (21.5)
Progressive disease (PD)	n (%)	9 (3.9)	20 (8.8)
N/A	n (%)	13 (5.7)	13 (5.7)
Overall response rate	n (%)	160 (69.6)	146 (64.0)
90% CI		(64.57, 74.56)	(58.81, 69.26)
95% CI		(63.62, 75.51)	(57.81, 70.26)
Ratio MYL-1401O:Herceptin		1.09	
90% CI		(0.974, 1.211)	
95% CI		(0.954, 1.237)	

CI: confidence interval, ITT: intent-to-treat, N: number of patients in treatment arm, n: number of patients with data available, N/A: not applicable

Sensitivity analysis

Table 18: Difference of Best Overall Response Rate (ORR) at Week 24 (ITT1 Population; Study MYL-Her-3001)

Response	MYL-1401O + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Overall response rate, n (%)	160 (69.6)	146 (64.0)
90% CI	(64.57, 74.56)	(58.81, 69.26)
95% CI	(63.62, 75.51)	(57.81, 70.26)
Difference MYL-1401O:Herceptin (%)	5.5	
90% CI	(-1.70, 12.69)	
95% CI	(-3.08, 14.04)	

CI: confidence interval, CR: complete response, ITT: intent-to-treat, N: number of patients in treatment arm, n: number of patients with data available, PR: partial response

The efficacy sensitivity analysis for difference in best ORR was replicated using the PP and ITT2 population. The difference between both treatment arms for the PP population was 4% with a 95% CI of (-4.59%, 12.61%). For the ITT2 population this difference between treatments was 4.1% with a 95% CI of (-4.17%, 12.34%). Both were thus well within the pre-defined equivalence boundaries of -15% and 15%, supporting the primary analysis.

Table 19: Differences in ORR (MYL1401O – Herceptin) for the analysis populations in study MYL-Her-3001

	Week 24		Week 48	
Population	ORR Difference	95% CI	ORR Difference	95% CI
ITT1	5.5%	(-3.08%, 14.04%)	3.3%	(-5.16%, 11.77%)
PP	4.0%	(-4.59%, 12.61%)	1.7%	(-6.77, 10.18)
ITT2	4.1%	(-4.17%, 12.34%)	2.1%	(-6.07, 10.30)

The primary efficacy analysis of ORR was also conducted based on the Investigator assessments of disease response and progression in the ITT1 population. The ratio between both treatment groups in this case was 1.08 with a 90% CI of (0.968, 1.202), and thus within the pre-defined equivalence boundaries of 0.81 and 1.24. A similar analysis was also performed in the PP and ITT2 populations showing ratios of 1.05, 90% CI (0.942, 1.162) and 1.06, 90% CI (0.958, 1.183) respectively.

Secondary efficacy results

Time to Tumour Progression

In the first 24 weeks there were 35 patients (15.2%) in the MYL-1401O group whom had tumour progression compared to 44 patients (19.3%) in the Herceptin group. According to the log-rank test, the time-to-event curves for both treatment groups were not statistically significantly different (p = 0.192). Note that for the Kaplan-Meier estimates for TTP the median was not reached due to the relatively small number of patients with tumour progression.

The average hazard ratio remained slightly lower with a longer TTP in benefit of MYL-1401O, though the difference was less pronounced at week 48 than at week 24, and thus remained statistically insignificant.

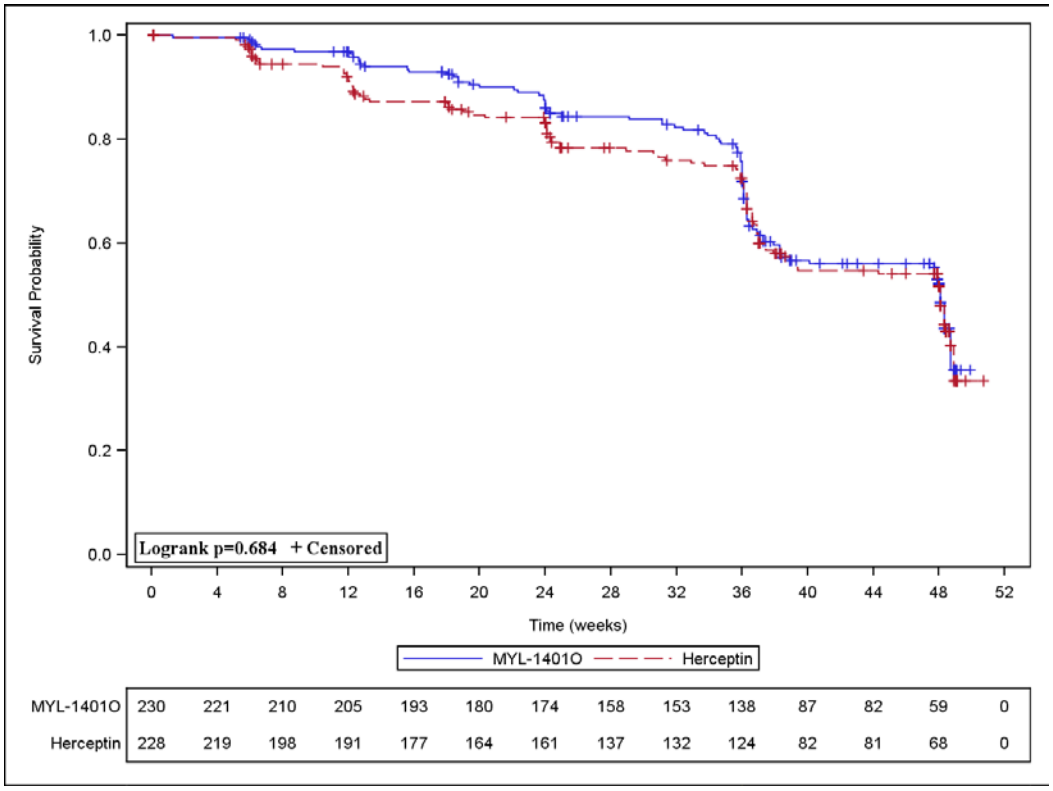
Table 20: Time to Tumour Progression (TTP) at Week 48, ITT1 Population

	MYL-1401O (N = 230)	**Herceptin (N = 228)**
Patient status		
Number of patients	230	228
Events, n (%)	95 (41.3)	98 (43.0)
Censored,[a] n (%)	135 (58.7)	130 (57.0)
Log-rank test: p-value	0.684	
Kaplan-Meier estimates [months]		
N	230	228
Mean (95% CI)	9.2 (8.82, 9.58)	8.8 (8.37, 9.26)
SE	0.19	0.23
Median (95% CI)	11.1 (8.83, 11.20)	11.1 (8.88, 11.20)
Q1, Q3	8.3, NE	7.8, NE
Min, Max	0.0, 11.5	0.0, 11.7
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
N	230	228
Hazard ratio (95% CI)	0.94 (0.712, 1.254)	
p-value	0.694	
Stratified hazard[c] (95% CI)		
N	220	220
Hazard ratio (95% CI)	0.92 (0.692, 1.231)	
p-value	0.584	

CI: confidence interval, ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, Q: quartile, SE: standard error, TTP: time to tumour progression defined as the time from randomization to date of first documentation of objective progression, divided by (365.25/12)
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] *Events occurring after the data cut-off were censored at the date of cut-off.*
[b] *The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average hazard rate and a longer TTP for MYL-1401O relative to Herceptin.*

[c] *Stratified by assigned taxane, tumour progression, and tumour endocrine status.*

Figure 15: Kaplan-Meier Plot of Time to Tumour Progression at Week 48: ITT1



Progression-Free Survival

In the MYL-1401O arm, 189 patients (82.2%) had PFS until Week 24 compared with 180 patients (78.9%) in the Herceptin arm the time-to-event curves for both treatment groups were not statistically significantly different.

The average hazard rate for progression or death was slightly lower and PFS was slightly longer for MYL-1401O compared with Herceptin but the difference was not statistically significant.

Until Week 48, 55.7% of MYL-1401O and 55.3% of Herceptin subjects still did not have progression of the disease (see Table below). Log-rank testing showed that the time-to-event curves for both treatment groups were not different in a statistically significant way.

K-M estimate of median time for PFS was 11.1 months in both treatment arms.

Table 21: Progression-Free Survival (PFS) at Week 48, ITT1 Population

	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	230	228
Events, n (%)	102 (44.3)	102 (44.7)
Censored,[a] n (%)	128 (55.7)	126 (55.3)
Log-rank test: p-value	0.842	
Kaplan-Meier estimates [months]		
N	230	228
Mean (95% CI)	9.0 (8.56, 9.38)	8.7 (8.25, 9.16)
SE	0.21	0.23
Median (95% CI)	11.1 (8.81, 11.20)	11.1 (8.60, 11.20)
Q1, Q3	8.2, NE	7.1, NE
Min, Max	0.0, 11.5	0.0, 11.7
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
N	230	228
Hazard ratio (95% CI)	0.97 (0.740, 1.282)	
p-value	0.851	
Stratified hazard[c] (95% CI)		
n	220	220
Hazard ratio (95% CI)	0.95 (0.714, 1.251)	
p-value	0.694	

CI: confidence interval, ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, PFS: progression-free survival defined as the time from randomization to first documentation of objective progression or to death due to any cause, divided by (365.25/12), Q: quartile, SE: standard error

Percentages are based on the number of patients in the ITT1 population.

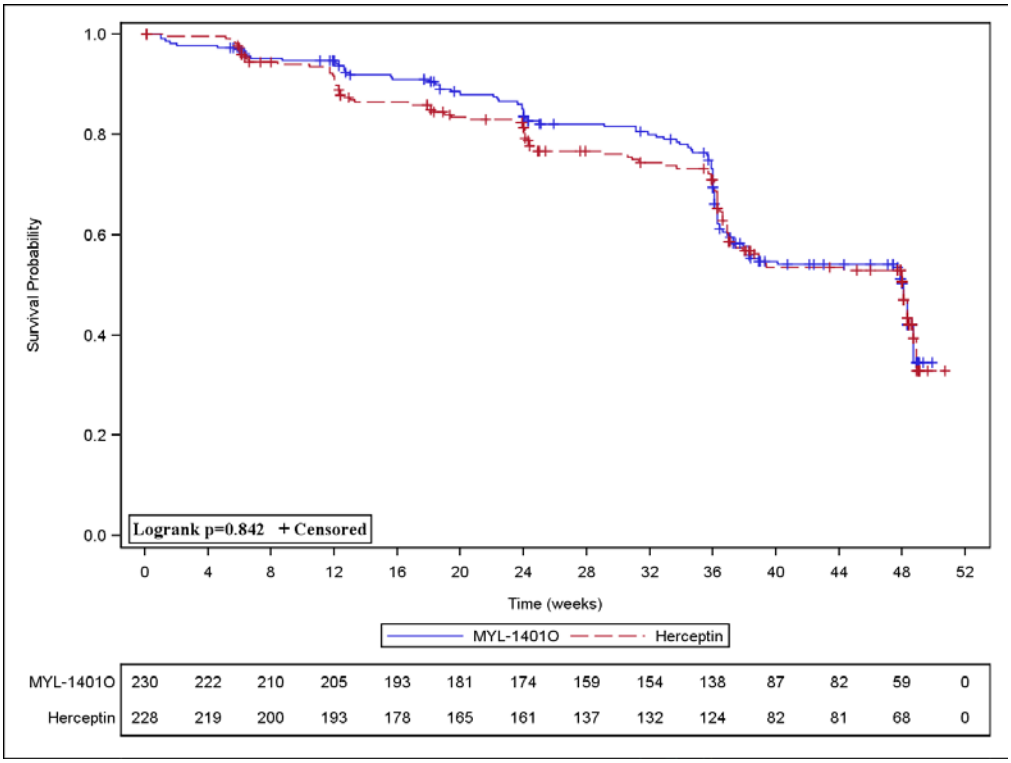
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

[a] *Events occurring after the data cut-off were censored at the date of cut-off.*

[b] *The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average hazard rate and a longer PFS for MYL-1401O relative to Herceptin.*

[c] *Stratified by assigned taxane, tumour progression, and tumour endocrine status.*

Figure 16: Kaplan-Meier Plot of Progression-Free Survival at Week 48, ITT1 Population



ITT: intent-to-treat
Numbers at risk are displayed at the bottom of the figure.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Overall Survival

In the MYL-1401O arm, 223 patients (97.0%) survived until Week 24 compared to 218 patients (95.6%) in the Herceptin arm, and according to the log-rank test, this difference was not statistically significant.

The average hazard rate (= death) from the Cox proportional hazard model was slightly lower and OS was slightly longer for MYL-1401O compared with Herceptin. The difference was however not statistically significant.

Until Week 48 (

Table 26), 89.1% of MYL-1401O subjects survived compared with 85.1% in the Herceptin group. According to the log-rank test, the survival curves for both treatment groups were not statistically significantly different (Figure 19).

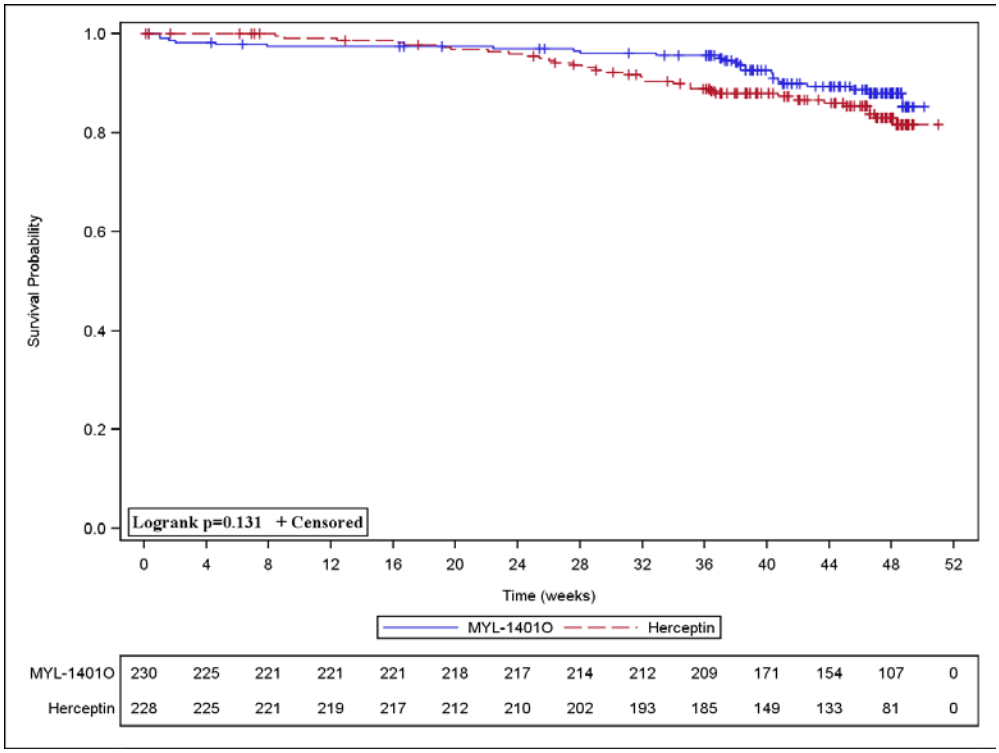
At Week 48 the Cox-proportional hazard ratio was again in favour of MYL-1401O, with the average hazard rate for death being lower for MYL-1401O compared with Herceptin confirm the observation at Week 24. Likewise, the difference was again not statistically significant.

Table 22: Overall Survival (OS) at Week 48, ITT1 Population

	MYL-1401O (N = 230)		Herceptin (N = 228)
Patient status			
Number of patients	230		228
Events, n (%)	25 (10.9)		34 (14.9)
Censored,[a] n (%)	205 (89.1)		194 (85.1)
Log-rank test: p-value		0.131	
Kaplan-Meier estimates [months]			
n	230		228
Mean (95% CI)	10.7 (10.45, 10.94)		10.4 (10.20, 10.69)
SE	0.13		0.12
Median (95% CI)	NE (NE,NE)		NE (NE,NE)
Q1, Q3	NE, NE		NE, NE
Min, Max	0.1, 11.5		0.0, 11.7
Cox proportional hazard[b]			
Unstratified hazard (95% CI)			
n	230		228
Hazard ratio (95% CI)		0.67 (0.402, 1.129)	
p-value		0.134	
Stratified hazard[c] (95% CI)			
n	220		220
Hazard ratio (95% CI)		0.61 (0.360, 1.039)	
p-value		0.069	

CI: confidence interval, ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, OS: overall survival defined as the time from date of randomization to date of death due to any cause, divided by (365.25/12), Q: quartile, SE: standard error
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Events occurring after the data cut-off were censored at the date of cut-off.
[b] The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average hazard rate and a longer OS for MYL-1401O relative to Herceptin.
[c] Stratified by assigned taxane, tumour progression, and tumour endocrine status.

Figure 17: Kaplan-Meier Plot of Overall Survival at Week 48, ITT1 Population



ITT: intent-to-treat
Numbers of patients at risk are displayed at the bottom of the figure.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Duration of Response (DR)

Of the MYL-1401O subjects 42.4% with objective response had tumour progression or died before the 48 week cut-off, versus 44.5% in the Herceptin group as seen in

Table 27. Log-rank testing did not show a statistically significant difference in the time-to-event curves for both treatment groups (Figure 20).

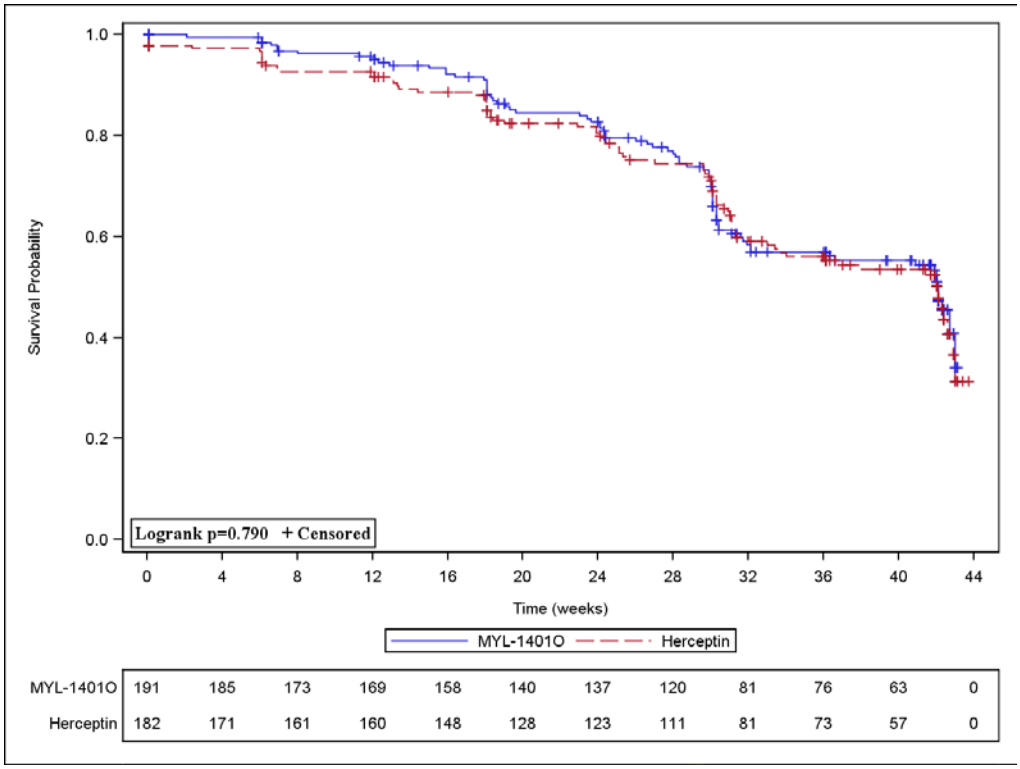
K-M estimate of median time to tumour progression or death after objective tumour response was 9.7 months in both treatment arms.

Table 23: Duration of Response (DR) at Week 48, ITT1 Population

	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	191	182
Events, n (%)	81 (42.4)	81 (44.5)
Censored,[a] n (%)	110 (57.6)	101 (55.5)
Log-rank test: p-value	0.790	
Kaplan-Meier estimates [months]		
n	191	182
Mean (95% CI)	7.9 (7.52, 8.28)	7.7 (7.27, 8.13)
SE	0.19	0.22
Median (95% CI)	9.7 (7.38, 9.89)	9.7 (7.68, 9.87)
Q1, Q3	6.5, NE	6.2, NE
Min, Max	0.0, 9.9	0.0, 10.1
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
n	191	182
Hazard ratio (95% CI)	0.96 (0.705, 1.306)	
p-value	0.795	
Stratified hazard[c] (95% CI)		
n	183	180
Hazard ratio (95% CI)	0.97 (0.706, 1.329)	
p-value	0.846	

CI: confidence interval, DR: duration of response defined as the time from the first documentation of objective tumour response (complete response [CR] or partial response [PR]) to the date of first documentation of objective tumour progression or to death due to any cause, whichever occurred first, divided by (365.25/12).
Only patients with objective response (CR or PR) were included in the analysis. ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, Q: quartile, SE: standard error
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] *Events occurring after the data cut-off were censored at the date of cut-off.*
[b] *The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a better outcome for MYL-1401O relative to Herceptin.*
[c] *Stratified by assigned taxane, tumour progression, and tumour endocrine status.*

Figure 18: Kaplan-Meier Plot of Duration of Response at Week 48, ITT1 Population



ITT: intent-to-treat
Numbers at risk are displayed at the bottom of the figure.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Exploratory analyses results

Disease Control Rate

The analysis revealed no notable differences between the arms for the proportion of patients. The ratio of 1.06 indicated that the patients in both arms showed a similar response and the proportion of patients with disease control at Week 24 was comparable between the 2 treatment arms.

HER2/Extracellular Domain

In exploratory analyses, baseline HER2/extracellular domain (ECD) was assessed as a predictor for ORR, OS, and TTP. HER2/ECD expression decreased from baseline to Week 24 in both treatment arms, with no noteworthy difference between both arms, and remained on a similar level until Week 48.

At Week 24, there was no noteworthy difference in ORR between the subgroups of patients with baseline HER2/ECD values <15 ng/mL and ≥15 ng/mL (66.0% versus 67.8%).

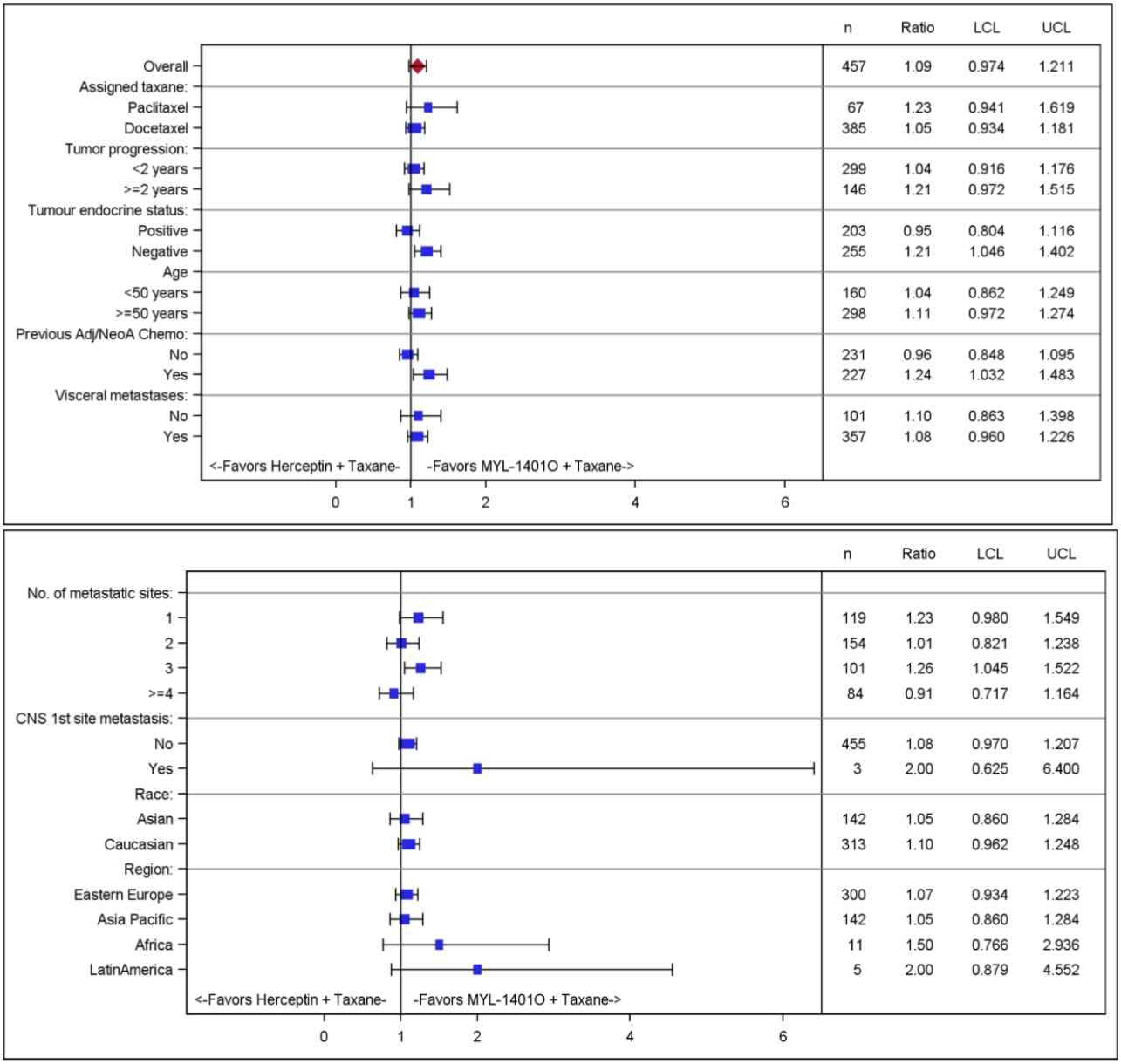
At Week 24 there was a consistent increase in ORR for the subgroups of patients with a significant decrease in HER2/ECD expression compared to patients with a non-significant decrease in HER2/ECD expression. The increase in ORR was higher for the subgroups of patients with a significant decrease in HER2/ECD compared to the patients with a non-significant decrease.

Ancillary analyses

Best ORR

Best overall response rate by subgroup is presented below.

Figure 19: Ratio of Best Overall Response Rate (ORR) at Week 24 Overall and by Subgroup: ITT1 Population



ITT: intent-to-treat, LCL: lower confidence limit, n: number of patients, UCL: upper confidence limit
The hazard ratio is presented with 90% confidence interval.

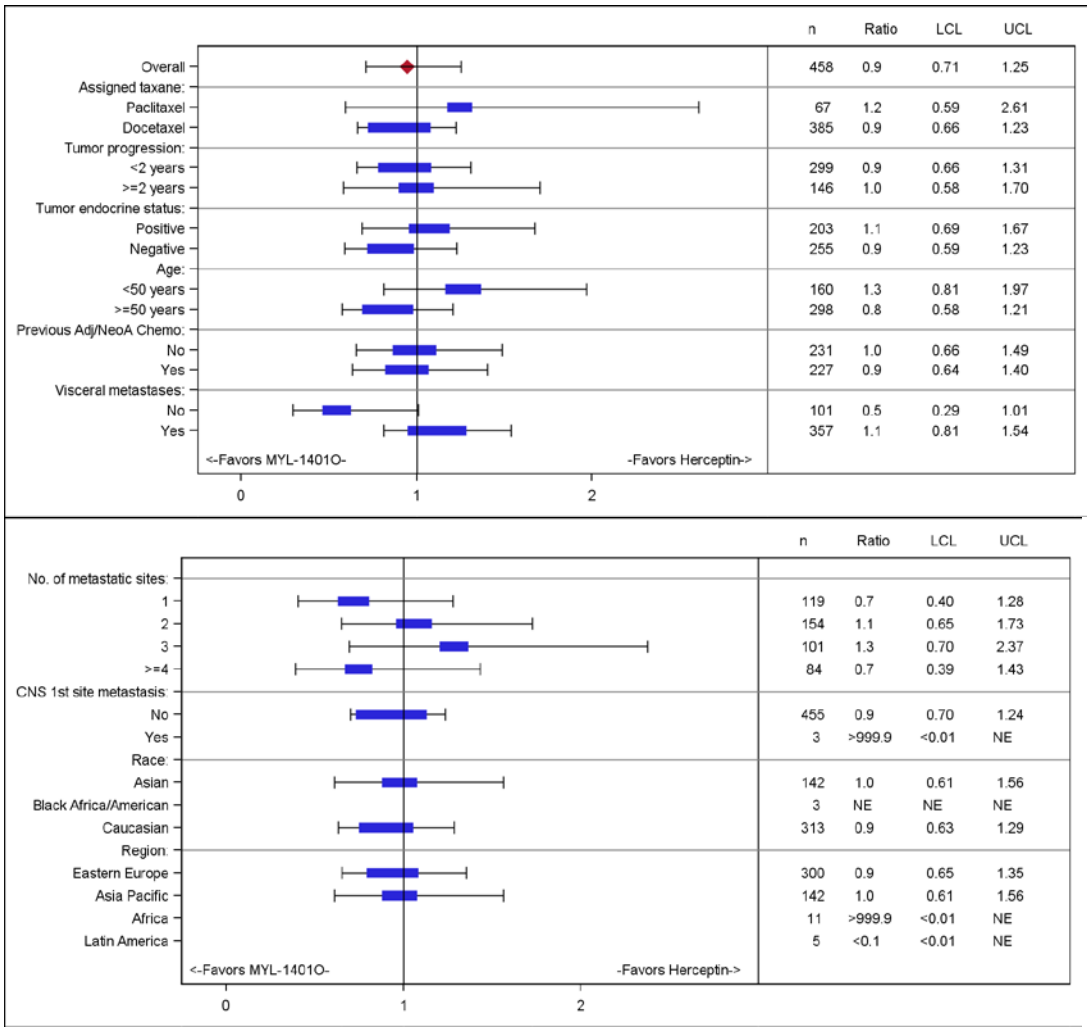
In Study MYL-Her-3001, 385 out of 458 patients (84%) received docetaxel as their taxane in combination with trastuzumab (MYL-1401O or Herceptin). In these patients, the difference of ORRs between the treatment groups and its 95% CI were 3.3% and (-6.05%, 12.55%), respectively, which were consistent with the analysis results for the entire population (ORR difference of 5.5% and 95% CI of (-3.08%, 14.04%), respectively).

Only 67 patients (15%) received paclitaxel as their taxane in combination with trastuzumab. In these patients, the difference of ORRs between the treatment groups and its 95% CI were 14.6 % and (-7.11%, 34.99%), respectively (see discussion on clinical efficacy).

Time to progression

Subgroup analysis did not find any 95% CI of the TTP ratio that did not include '1' and thus no relevant subgroup differences exist.

Figure 20: Time to Tumour Progression at Week 48 Overall and by Subgroup, ITT1 Population



T: intent-to-treat, LCL*: lower confidence limit, n: number of patients, UCL: upper confidence limit The hazard ratio is presented with 95% confidence interval.*
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Sensitivity analyses on TTP using the ITT2 and TP populations confirmed the above findings at week 48.

At 24 Weeks, the final model Cox regression model showed that previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment had a significant influence on TTP (hazard ratio 2.02, p = 0.003).

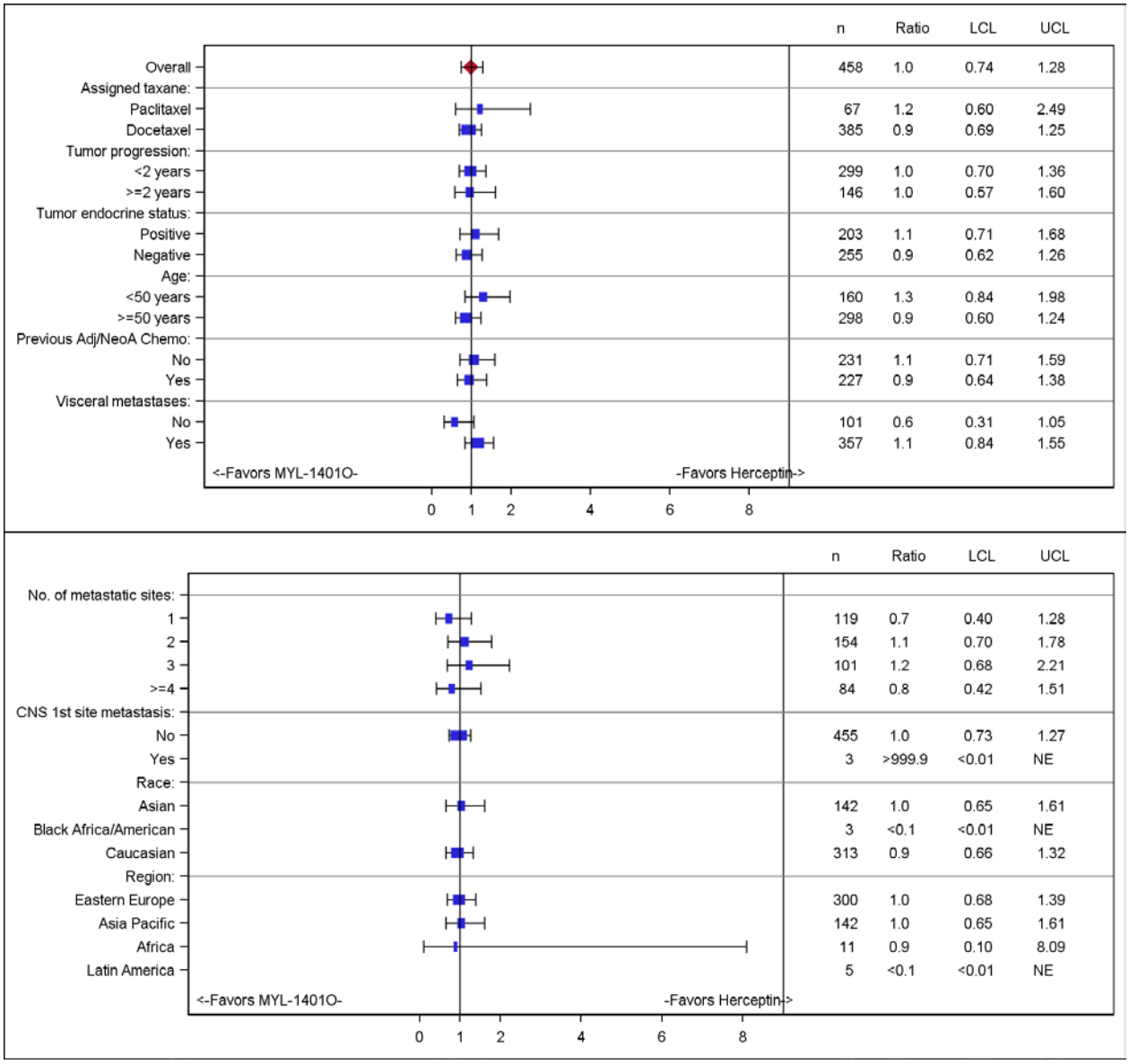
At Week 48, age (p = 0.006), race (p = 0.025), previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment (p = 0.061), and region (p = 0.045) were potential covariates to have an effect on the hazard ratio

for TTP and were included in the final Cox regression model. According to the final model at Week 48, age (≥50 years vs. <50 years) had an influence on TTP (hazard ratio 0.69, p = 0.013).

Progression Free survival

Subgroup analysis did not find any 95% CI of the TTP ratio that did not include '1' and thus no relevant subgroup differences exist.

Figure 21: Progression-Free Survival at Week 48 Overall and by Subgroup, ITT1 Population



T: intent-to-treat, LCL: lower confidence limit, n: number of patients, UCL: upper confidence limit
The hazard ratio is presented with 95% confidence interval.

Sensitivity analyses on PFS using the ITT2 and TP populations confirmed the above findings at Week 48.

According to the Cox regression analysis at Week 24, previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment had an effect on the hazard ratio for PFS and was included in the final model.

At Week 48, age (p = 0.004), race (p = 0.002), previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment (p = 0.039), and region (p = 0.021) were potential covariates to have an effect on the hazard ratio for TTP and were included in the final model. According to said final model at Week 48, age and race had an influence on PFS.

Overall Survival

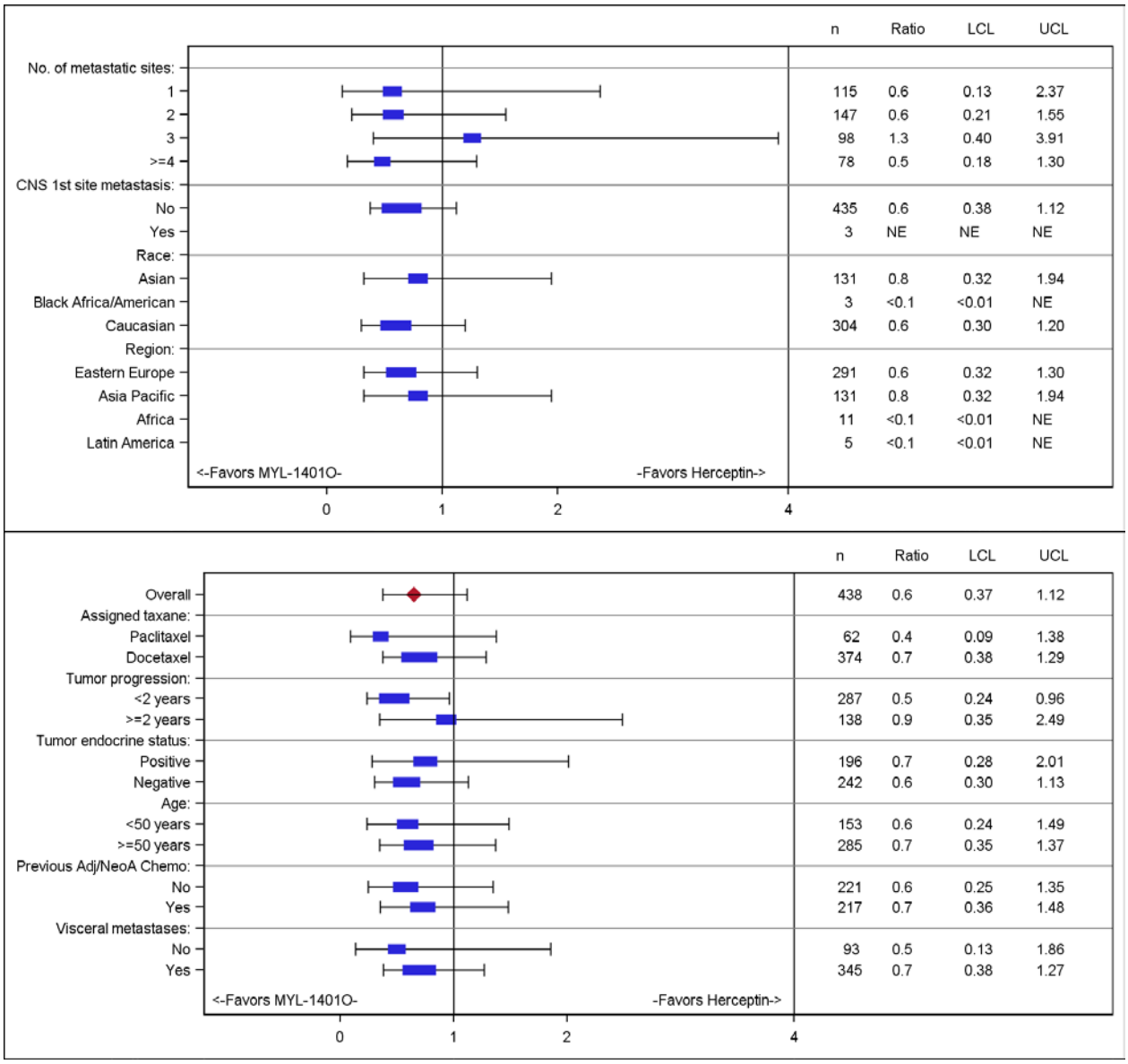
Cox regression analysis at Week 24 indicated that previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment and race had an effect on the hazard ratio for OS and these parameters were thus included in the final model.

At Week 48, tumour endocrine status and number of metastatic sites were also identified as potential covariates with significant impact and were thus also included in the final model.

According to the final Week 48 model, tumour endocrine status and number of metastatic affected OS.

In the analysis of the 95% CI of the OS ratio (Figure 24), the subgroup “tumour progression <2 years” CI at Week 48 did not encompass ‘1’ which indicates a relevant difference in ratio (see discussion on clinical efficacy).

Figure 22: Overall Survival at Week 48 Overall and by Subgroup, ITT1 Population

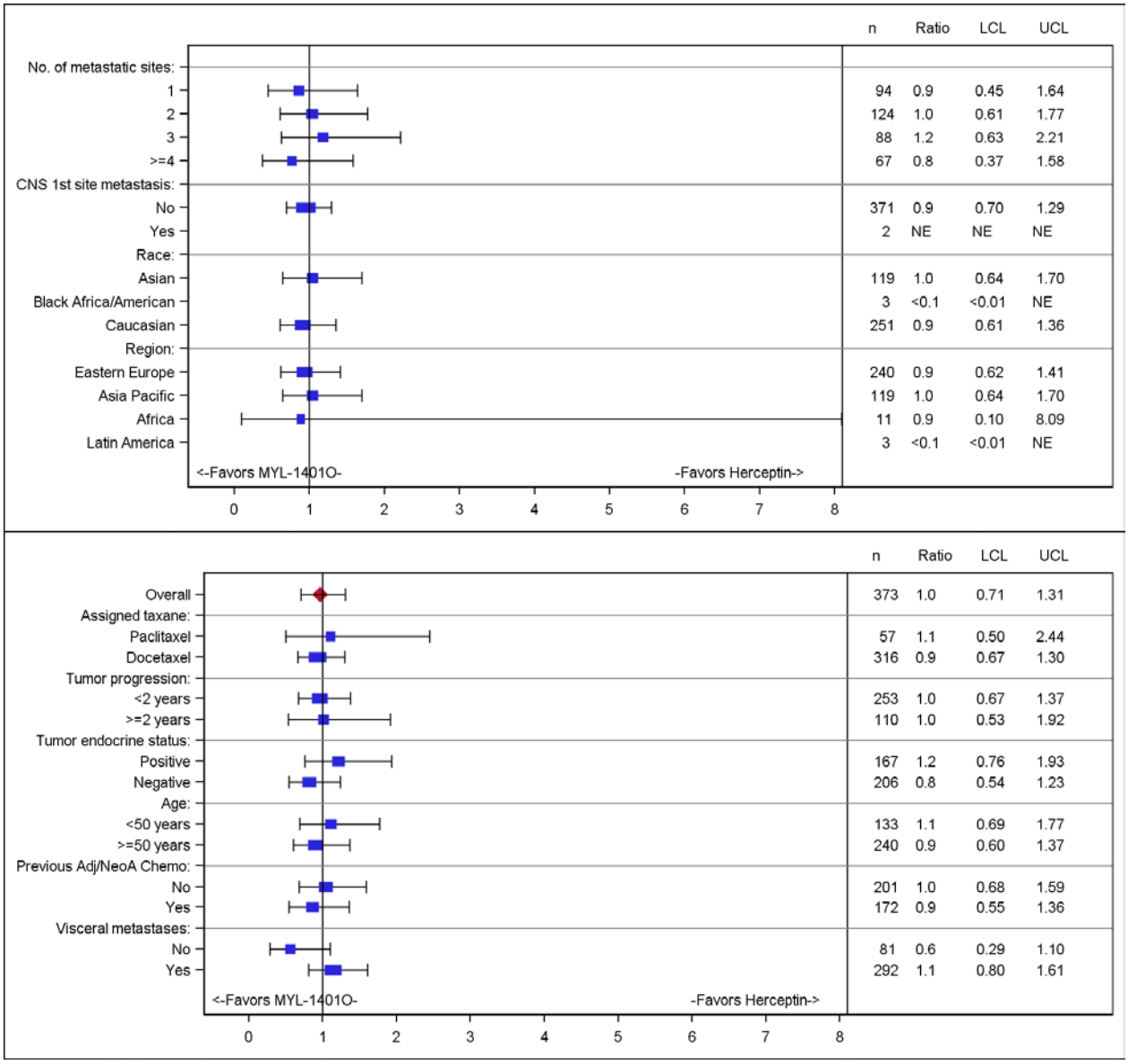


ITT: intent-to-treat, LCL: lower confidence limit, n: number of patients, UCL: upper confidence limit
The hazard ratio is presented with 95% confidence interval.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug
(MYL-1401O or Herceptin) alone.

Duration of response (DR)

As shown in Figure 25, the 95% CI of the DR ratio included '1' for all subgroups at Week 48 and thus no relevant differences between the subgroups exist.

Figure 23: Duration of Response at Week 48 Overall and by Subgroup, ITT1 Population



T: intent-to-treat, LCL: lower confidence limit, n: number of patients, UCL: upper confidence limit
The hazard ratio is presented with 95% confidence interval.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

According to the Cox regression analysis, age, race and region were potential covariates to have an effect on the hazard ratio for DR and were thus included in the final model, according to which race had an influence on duration of response.

Summary of main study

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

Table 24: Summary of Efficacy for trial MYL-Her3001

A Multicentre, Double-blind, Randomized, Parallel-group, Part III Study of the Efficacy and Safety of MYL-1401O Plus Taxane Versus Herceptin Plus Taxane as First Line Therapy in Patients With HER2-Positive Metastatic Breast Cancer			
Study identifier	MYL-Her3001		
Design	A multicentre, double-blind, randomized, parallel-group, study to compare the efficacy and safety of MYL-1401O plus docetaxel or paclitaxel (i.e., taxane) versus Herceptin plus a taxane in patients with HER2+ MBC with continuation of single-agent MYL-1401O versus Herceptin for patients who had at least stable disease (SD) in order to evaluate continued safety and immunogenicity. In Part 1 of the study, MYL-1401O plus a taxane or Herceptin plus a taxane was administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration), and the choice of taxane (docetaxel or paclitaxel) was made by the Investigator at each study site and applied to all patients enrolled by that site. Tumour assessments were conducted every 6 weeks (±3 days). In Part 2 of the study, after completing a minimum of 8 cycles of treatment in Part 1 of the study, all patients with at least SD continued with the trastuzumab product that they were originally allocated to as a single agent until disease progression, unacceptable toxicity, or death, whichever occurred first. Tumour assessments were conducted every 12 weeks (±3 days). The endpoints for the primary and secondary objectives were to be analysed at Week 24 in Part 1 and at Week 48 (only secondary) in Part 2. OS data will continue to be monitored until 240 deaths have been registered or until 36 month have passed, whichever comes first. This data was not yet provided and it is not clear when it can be expected in the context of the current assessment period.		
	Duration of main part: Duration of Run-in part: Duration of Extension part:		24 weeks (Part 1) not applicable 24 weeks (Part 2)
Hypothesis	Equivalence		
Treatments groups	Myl-1401O (Part 1)		Myl-1401O + taxane. 24 weeks, ITT1: 230; ITT2: 249
	Herceptin (Part 1)		Herceptin + taxane. 24 weeks, ITT1: 228, ITT2: 251
	MYL-1401O (Part 2)		Myl-1401O. 24 weeks Safety: 179, ITT1: 169, ITT2: 179
	Herceptin (Part 2)		Herceptin. 24 weeks Safety: 163, ITT1: 151, ITT2: 163
Endpoints and definitions	Primary endpoint	Best ORR ratio	Equivalence defined as the two-sided 90% CI for the ratio of best ORRs at Week 24 being entirely within the equivalence range of (0.81, 1.24). Not analysed in Part 2.

	Primary endpoint	Best ORR difference	Equivalence defined as the two-sided 95% CI for the difference in best ORRs at Week 24 being entirely within the equivalence range of (-15%, 15%). Not analysed in Part 2.
	Secondary endpoint	TTP	Time from randomization to the date of first documentation of objective progression
	Secondary endpoint	PFS	Time from randomization to first documentation of objective progression or to death due to any cause
	Secondary endpoint	OS	Time from randomization to date of death due to any cause.
	Secondary endpoint	Duration of Response (DR)	Time from the first documentation of objective tumor response (CR or PR) to the date of first documentation of objective tumor progression or to death due to any cause, whichever occurs first.
	Exploratory endpoint	Disease control rate	The sum of patients who had CR, PR, and SD according to RECIST 1.1. Not analysed in Part 2.
	Exploratory endpoint	HER2/ECD	Baseline HER2/ECD assessed as a predictor for ORR, OS and TTP.
Database lock	Part 1: final assessment of final patient in Part 1: 25 January 2016 Part 2: final assessment of final patient in Part 2: 13 July 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT1: primary analysis group, all patients randomized under protocol amendment 2, subset of ITT2 ITT2: all patients randomized under protocol amendment 1 (randomization of patients who would receive second-line treatment for MBC) PP: ITT1 subset, meeting following criteria: • Received the treatment to which they were randomized • Absence of any major protocol deviations in Part 1 which precluded evaluation of the patient • At least 1 post-baseline tumour assessment if a progression disease; and at least 2 if CR, PR, or SD • Received at least 2 complete cycles of treatment; however, if a progression, death, or discontinuation occurred before the end of the first 2 cycles, the patient was retained in the PP population. No Changes to ITT1, ITT2 or PP in Part 2. Safety (Part 2): All subjects whom received at least 1 dose of study drug, and whom had reached stable disease at the end of Part 1.		
Effect estimate per comparison	Primary (ORR ratio) – Part 1	Comparison groups	MYL-1401O - Herceptin (ITT1)
		Best ORR ratio	1.09

		90% CI	(0.974, 1.211)
		P-value	N/A
	Primary Sensitivity (ORR difference) – Part 1	Comparison groups	MYL-1401O - Herceptin (ITT1)
		Best ORR Difference (%)	5.5
		95% CI	(-3.08, 14.04)
		P-value	N/A
	Secondary (TTP), Part 1	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Tumour Progression Cox proportional hazard ratio - unstratified - stratified	15.2% versus 19.3% 0.74 0.70
		  95% CI - unstratified - stratified	 (0.477, 1.161) (0.448, 1.106)
		P-value - unstratified - stratified	 0.193 0.128
	Secondary (TTP), Part 2	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Tumour Progression Cox proportional hazard ratio - unstratified - stratified	41.3% versus 43.0% 0.94 0.92
		N/A 95% CI - unstratified - stratified	N/A (0.712, 1.254) (0.692, 1.231)
		P-value - unstratified - stratified	 0.694 0.584
	Secondary (PFS), Part 1	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Tumour Progression/Death Cox proportional hazard ratio - unstratified - stratified	17.8% versus 21.1% 0.80 0.75
		N/A 95% CI - unstratified - stratified	N/A (0.529, 1.218) (0.488, 1.143)

		P-value - unstratified - stratified	 0.302 0.179
	Secondary (PFS), Part 2	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Tumour Progression/Death Cox proportional hazard ratio - unstratified - stratified	44.3% versus 44.7% 0.97 0.95
		N/A 95% CI - unstratified - stratified	N/A (0.740, 1.282) (0.714, 1.251)
		P-value - unstratified - stratified	 0.851 0.694
	Secondary (OS), Part 1	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Death Cox proportional hazard ratio - unstratified - stratified	3.0% versus 4.4% 0.68 0.57
		N/A 95% CI - unstratified - stratified	N/A (0.261, 1.799) (0.208, 1.584)
		P-value - unstratified - stratified	 0.442 0.284
	Secondary (OS), Part 2	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Death Cox proportional hazard ratio - unstratified - stratified	10.9% versus 14.9% 0.67 0.61
		N/A 95% CI - unstratified - stratified	N/A (0.402, 1.129) (0.360, 1.039)
		P-value - unstratified - stratified	 0.134 0.069

	Secondary (DR), Part 2 only	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Tumour progression or Death Cox proportional hazard ratio - unstratified - stratified	42.4% versus 44.5% 0.96 0.97
		N/A 95% CI - unstratified - stratified	N/A (0.705, 1.306) (0.706, 1.329)
		P-value - unstratified - stratified	 0.795 0.846
	Exploratory (Disease Control ratio)	Comparison groups	MYL-1401O – Herceptin (ITT1)
		Disease control ratio	1.06
		95% CI	(0.988,1.132)
		P-Value	N/A
	Exploratory (HER2/ECD)	Comparison groups	MYL-1401O – Herceptin (ITT1)
		ORR at W24 adjusted for baseline HER2/ECD	1.25
		95% CI	(0.836, 1.859)
		P-value	0.2791
Notes	As the primary analysis was for the FDA-approach (i.e. based on a 90%-CI), the overall error type I of the biosimilarity exercise in this study exceeds the requirements for biosimilarity as usually applied in the EU (based on a 95%-CI). Sensitivity analyses were run on all efficacy endpoints by doing the same data analyses on the ITT2 and PP populations. At every endpoint, these outcomes confirmed the initial findings with ITT1.		

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

Comparison between the pivotal study MYL-Her3001 and the supportive study BM200-CT3-001-11 was submitted (data not shown, see discussion on clinical efficacy).

Clinical studies in special populations

No clinical studies in special populations were submitted (see discussion).

Supportive study

BM200-CT3-001-11

This double blind, randomised, active control, parallel assignment part III clinical trial was a comparative study that aimed to investigate the PK, efficacy, safety and immunogenicity of Bmab-200 versus Herceptin, in HER2+ MBC when given in combination with docetaxel.

The primary objective of this study was PK based and any efficacy endpoints were only secondary and exploratory:

- Comparison of the overall response rates (ORR) of Bmab-200 and Herceptin, both in combination with docetaxel over 24 weeks (up to 8 cycles) of combination chemotherapy, based on RECIST 1.1 and imaging performed every twelve weeks. *(Secondary)*
- Correlation of secondary efficacy parameters with shed Her2 extracellular domain (ECD). *(Exploratory)*

Study BM200-CT3-001-11 was not statistically powered to evaluate similarity in efficacy between Bmab-200 and the reference product, and it did not have a provision for confirmation of response. Furthermore, the product Bmab-200 differs in the types of excipients used compared to MYL-1401O. Given all of the above, results of this trial are considered supportive only.

A total of 135 patients were randomized to two arms; the Bmab-200 arm (n=67) and the Herceptin arm (n=68). Of these 135 patients, 103 patients completed all 8 cycles of the study (Bmab-200, n=51; Herceptin, n=52). The study included female patients who had a confirmed histopathological diagnosis of breast cancer and confirmed metastatic disease by biopsy or radiology.

The demographic profile was similar between both study arms and none of the patients had prior exposure to trastuzumab or other anti-Her2 treatments.

The following efficacy data sets were defined:

- Intent to Treat-Full Analysis Set (ITT-FAS) = all patients to whom study treatment has been assigned by randomization. One patient in this population set withdrew consent before the first dosing and was excluded from the efficacy evaluations.
- The Per-Protocol (PP) population = all patients in the ITT-FAS population with exclusions based on pre-specified reasons and consisted of 124 patients.

Efficacy outcomes

ORR

The ORR in the ITT-FAS population was 65.15% in the Bmab-200 arm and 75.00% in the Herceptin arm, similar to the historical ORR i.e. between 61% and 73% with Herceptin in first-line MBC patients. The mean as well as median number of cycles received by the patients in the two groups was similar.

Table 25: Statistical Analysis of Overall Response Rate (ITT-FAS Population)

Overall Response Rate	Bmab-200 N=66[a] [n(%)]	Herceptin® N=68 [n(%)]
No. of Patients with:		
Complete Response (CR)	0(0.00%)	1(1.47 %)
Partial Response (PR)	43(65.15 %)	50(73.53 %)
Stable Disease (SD)	14(21.21 %)	10(14.71 %)
Progressive Disease (PD)	5(7.58 %)	4(5.88 %)
In-evaluable	4(6.06 %)	3(4.41 %)
Responders (CR+PR)	43(65.15 %)	51(75.00 %)
Non-responders	23(34.85 %)	17(25.00 %)
Difference in Response Rate	9.85%	
Odds Ratio (95% CI)	1.60(0.76,3.39)	

Evaluation of the PP subset gave similar results.

Clinical benefit rate (CBR)

The analysis of clinical benefit rate showed an odds ratio of 1.38 (95% CI: 0.48, 3.94), indicating that the arms showed a similar response. The proportion of patients with clinical benefit at week 24 (86.36% vs 89.71%) was comparable between the two treatment arms.

Correlation of Response with Shed HER2 Extracellular Domain

Of all patients who had baseline HER2 ECD data, 47 (75.8%) in Bmab-200 arm and 52 (80.0%) patients in Herceptin arm had baseline ECD levels of at least 15 ng/ml. Those patients with baseline shed Her2 ECD levels of > 15 ng/ml were considered as positive for shed Her2 ECD. Analysis indicated that neither in any of the arms nor in the overall cohort there was any correlation between baseline ECD level and likelihood of response to therapy (p=1).

Progression Free Survival Rate

For the ITT-FAS population, the PFS rate at 12 weeks was 84.85% in Bmab-200 arm compared to 85.29% in Herceptin arm, and 66.67% and 75.00% respectively at week 24.

A similar trend was observed in the PFS rates for PP population showing similarity between Bmab-200 and Herceptin.

Mean Change in Target Lesions Sizes

The mean sum of longest diameter of target lesions over the course of the trial remained similar for Bmab-200 and Herceptin at baseline, week 12 and Week 24; and in both arms the number of target lesions declined to a similar extent from baseline to Week 24 (66.1% for Bmab-200 and 66.0% for Herceptin). Discussion on clinical efficacy

Design and conduct of clinical studies

MYL-1401O (Ogivri) is a proposed biosimilar of Herceptin (trastuzumab) in the indications of metastatic breast cancer, early breast cancer and metastatic gastric cancer. The assessment of comparability in terms of efficacy is based on two clinical trials: one pivotal study, MYL-HER-3001, and one supportive, study BM200-CT3-001-11. The Applicant claims biosimilarity only for IV administration while SC administration is not applied for.

The pivotal trial, MYL-HER-3001, was a multicentre, double-blind, randomized, parallel-group, study to compare the efficacy and safety of MYL-1401O plus docetaxel or paclitaxel (i.e., taxane) versus Herceptin plus a taxane in patients with HER2+ MBC with continuation of single-agent MYL-1401O versus Herceptin for patients who had at least stable disease (SD) in order to evaluate continued safety and immunogenicity.

The use of trastuzumab and a taxane is reflecting the current clinical practice (in those countries where Perjeta is not available) for those patients with a free interval of relapse from adjuvant more than 12 months. In the first version of the protocol only docetaxel was allowed as taxane treatment but in subsequent protocol amendments study sites were given the choice whether to use docetaxel or paclitaxel. Although the inclusion of paclitaxel increased the background noise, it is agreed that the mixed taxane use is a more realistic representation of in practice treatment procedures. The type of taxane received (i.e., paclitaxel or docetaxel) was a stratification factor, along with hormonal status and tumour progression into metastatic phase $\geq$ 2 years OR < 2 years after primary diagnosis. Other stratification factors such as prior adjuvant trastuzumab would have been desirable.

Dosing of the treatments was based on the dosing of the reference product. The chosen dose of 75 mg/m^2 of docetaxel is in line with the current use of this taxane (higher dose of 100 mg, though authorised, are not widely used due to the toxicity). Paclitaxel was given as a Q3W dosing regimen instead of the standard weekly administration schedule based on the results of a phase 3 study showing an improvement in response rate and TTP of weekly administration over of the standard paclitaxel schedule.

Amendments were provided individually for review. After review, changes effected were deemed logical, especially as most important updates were made following requests by regulatory bodies to adapt study elements to be in line with more state-of-the-art knowledge. Unblinding for part 1 of the study was done on 3 March 2016. This in essence means that the last update of the protocol was undertaken post part 1 unblinding, however this last update was done in order to incorporate the additional analysis requested by EMA which was lacking in the original protocol. There is no hint that the protocol changes were related to study data. Thus an impact of these changes on the confirmatory interpretation of study results is considered unlikely.

With regards to inclusion criteria, metastatic population can be heterogeneous in terms of previous therapy and sites of disease. In this regard, the potential pre-treatment with trastuzumab or lapatinib in the adjuvant setting is reflected into the inclusion criteria, albeit they were allowed if metastatic disease was diagnosed at least 1 year after the last dose of treatment. When the baseline characteristics of the patients finally recruited into the trial are observed, only 9.6% vs 7.0% had previously received trastuzumab in the biosimilar arm vs Herceptin group respectively.

Proposed primary endpoint (best ORR) and timing of the efficacy analysis are acceptable for the purpose of comparability exercise. Best ORR was analysed by measuring if the ratio of best ORR fell within a predefined equivalence margin of (0.81, 1.24). The analysis on the difference of best ORR was included as a sensitivity analysis instead of a second primary analysis. An equivalence margin of (-15%, 15%) was chosen for this analysis.

Due to the statistical testing strategy whereby the ORR ratio with the 90% CI was considered as the primary outcome and the ORR difference with a 95% CI as a sensitivity outcome, the overall type I error is larger than usually accepted in a clinical biosimilarity trial. This was considered acceptable given the results of the trial (see discussion under efficacy data and analysis).

The clinical justification of the (-15%, 15%) equivalence range is based on a regression analysis linking TTP (and PFS) to ORR (data not shown). Based on this analysis the applicant claimed that differences in ORR within this interval (15%) will correspond to approximately ± 1.90 months in PFS, which is significantly lower than the margin of 3.5-4 months in PFS considered clinically significant. However, the applicant's approach neglected the

uncertainty inherent to the regression analysis. To address this point, the applicant provided an analysis using 95% confidence bands for the weighted least-squares (WLS) linear regression with time to progression (TTP) as the dependent variable and ln(ORR) as the independent variable (data not shown). This analysis showed that even at the extremes of the 95% CI bands the increase in calculated PFS is around 2.5 months, which is less than what is normally considered clinically meaningful and thus supports the notion that the original equivalence range is sensitive enough to discern equivalence. The Applicant also recalculated the linear regression model using the results of the study itself as an extra variable, and results were still within the previously established ranges. Furthermore, stratification of patients in responders and non-responders showed that the PFS of the former were very much identical over the 48 weeks course of the trail (data not shown).

The validation of use of ORR for margin calculation was done using literature data that was a mix of PFS and TTP weighted outcomes. The interchangeability of PFS and TTP and its impact in the metastatic setting was discussed and it was considered that, in this particular exercise, the mixing of PFS/TTP endpoints will not likely have influenced the robustness of the validation.

Taken together, the chosen equivalence margin was considered acceptable.

Secondary endpoints were TTP, PFS, OS and in Part 2 additionally DR. These secondary endpoints are considered acceptable.

The supportive study, BM200-CT3-001-11, was a double blind, randomised, active control, parallel assignment, comparative phase III clinical trial focused on PK comparison, and was conducted in 23 centres in India. This study was not statistically powered to evaluate similarity in efficacy between Bmab-200 and the reference product, and it did not have a provision for confirmation of response.

Efficacy data and additional analyses

The participant flow did not reveal important concerns in both groups of treatment. Within the ITT1, there appears to be fewer patients with disease progression (17.8% vs 24.2%) and more patients that complete the part 1 of the study (75.2% vs 69.7%) in the biosimilar arm compared to the reference arm. The protocol deviations leading to exclusion from the PP population were evenly balanced, with the highest difference reported in terms of lack of post-baseline tumour assessment. However, absolute numbers were low and the impact on the final results expected to be minor.

Overall, baseline characteristics and disease were generally comparable between arms. Only slight imbalances were observed in terms of ECOG, tumour progression into metastatic phase, presence of visceral disease and number of metastatic sites. Overall these slight imbalances appeared to favour to the biosimilar arm. However the actual weight of these cannot be determined. Additional analyses showed the difference in terms of ECOG and presence of visceral metastasis was non-significant (data not shown). The imbalance in number of metastatic sites was considered to be a randomization effect and no impact on the results was expected. Furthermore, the imbalance in tumour progression into metastatic phase was deemed small and thus was not considered a likely bias factor.

From Part 1 to Part 2 the percentage of patients using concomitant medications remained constant. Note is taken however of the fact that medications previously considered concomitant were reassessed, as they were administered after disease progression, discontinuation of study drug, or as second-line treatment. Therefore, percentages of patients using concomitant medications can be lower across the study compared with Part 1.

The pivotal MYL-HER-3001 study met the primary endpoints, as the 95% CI for the difference in ORR at week 24 [-3.08, 14.04]) fell within the predefined equivalence margins of (-15, 15).

Analysis by subgroup stratification factor was provided. Results generally supported the ORR ratio and difference findings, though three subgroups seemed to indicate a better response with MYL-10401O (tumour endocrine status negative, previous adjuvant/neoadjuvant chemotherapy, subgroup of patients with 3 metastatic sites). However, given the very limited amount of patients per subgroup no clinical or statistical significance can be ascribed to these results.

In the case of the analysis of the difference in ORR for the subgroup of patients that were treated with paclitaxel as concomitant taxane, the upper boundary 95% CI for the difference in ORR rates laid far outside the predefined equivalence margin of [-15%,15%]. The analysis set for each treatment group was relatively small (35 in the MYL-1401O group and 32 in the Herceptin group) and therefore, the percent difference between groups and margins need to be interpreted with caution. Furthermore, the study was not powered for the analyses based on taxane subgroup.

Overall, analysis by subgroup stratification factor confirmed the findings, and sensitivity analyses which consisted of running the same batch of confirmatory analyses on the ITT2 and PP populations, found similar results, thus confirming the validity of the primary outcomes.

Secondary endpoint analyses (ran on ITT1, ITT2 and PP populations for sensitivity analysis reasons) was aimed at TTP, PFS and OS factors. No statistical difference was observed in these endpoints between the two arms in the ITT1 population. Results of the sensitivity analyses using the ITT2 and TP populations confirmed these findings. The results were considered robust as the investigator assessments were in line with the main analysis.

It was noted that TTP and PFS appeared to show a better result for the biosimilar, although the numbers of events were still too low to reach any conclusion (17% in TTP and 19% for PFS). This observation was also reported when looking at the main analysis in terms of ORR (69.6% in the MYL1401O vs 64% in the Herceptin arm) and at the upper bound of the CI for the ORR. More mature data in terms of PFS and TTP (week 48) were provided and supported biosimilarity as discussed further below. Lower upper CIs were also observed at week 48 for the differences in ORR. However, the comparison of the two parts of the study is limited as only patients who had at least SD after the first part of the study were allowed to receive MYL-1401O in monotherapy. Some of the differences observed at baseline, such as number of metastatic sites, presence of visceral disease, ECOG, etc. could have influenced the apparent better efficacy results of MYL-1401O.

Altogether, given the confirmed similarity of secondary endpoints in week 48, the similarity shown in terms of pharmacokinetics, the relatively low numbers involved and the fact that slight baseline differences may have disproportionately affected these relatively small subgroup analyses, the observations are not considered of concern.

The overall observation of no statistical difference in secondary PFS, TTP and OS outcomes were replicated and confirmed through sensitivity analyses in Part 2 of the study. However, as less than 50% of patients presented with tumour progression or death, the values for these parameters can still be expected to change post 48 weeks. For the Kaplan-Meier estimates, the median OS was not reached at Week 24 or at Week 48 due to the relatively small number of patients in the ITT1 population who died prior to those time points. Thus, K-M estimates are of limited value up until the Week 48 data cut-off point. The final CSR including the final OS analysis of the MYL-Her-3001 study is expected to be submitted as soon as available.

According to the final Cox regression models at week 48 some patient and disease characteristics were considered to have an influence on TTP, PFS and OS respectively. Due to the small sample size in these subgroup analyses the data should be considered of limited clinical relevance.

In the analysis of the 95% CI of the OS ratio, the subgroup “tumour progression <2 years” CI at Week 48 did not encompass ‘1’ which indicated a relevant difference in ratio. Upon analysis, no particular clinical explanation could be found. However, given the very small number of patients in this subgroup, as well as the fact that the result was not replicated in the sensitivity analyses on the ITT2 and PP populations, this result is likely an aberrant artefact.

The Week 48 analysis of duration of response likewise indicated that no significant difference exists between MYL-1401O and Herceptin treated subjects.

As for the exploratory endpoints, disease control was defined as the sum of ITT1 patients who had CR, PR, and SD according to RECIST 1.1 (based on central tumour evaluation). The analysis of disease control rate revealed no notable differences in disease control rates between the arms.

HER2/ECD was assessed as a predictor for ORR, OS and TTP and expression decreased from Baseline to Week 24 in both treatment groups with no noteworthy difference between both groups, and this trend continued in Part 2 of the study.

A full analysis of immunogenicity is provided in the safety part of this report, and it was noted that both ADA and Nab titres were low and similar in both arms during the study. Moreover, a summary and analysis of best ORR at Week 48 for patients with at least 1 ADA assessment (PP population) was provided (data not shown). No diminution or suppression of response was observed in relation to ADA positive status. However, the result may not be meaningful due to the small numbers of patients.

In the supportive study BM200-CT3-001-11, the analysis of ORR indicated that a higher number of patients treated with Herceptin had partial response compared to those treated with Bmab-200, but this may be an artefact from the fact that the number of patients with stable disease was higher in the Bmab-200 arm than in the Herceptin arm.

Comparison of the efficacy results between the MYL and BM200 studies is limited in scope due to the differences in the designs, the use of different formulations and the fact that efficacy was a primary endpoint in the former and a secondary in the latter. Based on a very high level comparison both trials are supportive of each other in regards to their respective efficacy findings.

2.5.3. Conclusions on the clinical efficacy

Similarity in terms of ORR at week 24 has been shown with the a priori defined margin of similarity (15%). The results are considered robust enough as different sensitivity analyses support the main analysis, including comparison according to stratification factors and analyses in the ITT2 and PP groups. The results of the primary analysis are further supported by secondary efficacy endpoints. Overall, the clinical efficacy data support biosimilarity.

2.6. Clinical safety

Main safety information for MYL-1401O were generated in the pivotal study MYL-Her-3001 in patients with HER2-positive metastatic breast cancer, provided to date for up to 48 weeks of treatment (Parts 1 & 2). This dataset is further supported by results from two other comparative studies, MYL-Her-1001 and MYL-Her-1002, in healthy male volunteers. The fourth study, supportive Study BM200-CT3-001-11, was conducted in patients with HER2-positive MBC, but with another formulation.

Of the four studies contributing to safety data base, studies MYL-Her-1001 and MYL-Her-1002 were single dose (8 mg/kg) PK studies. In Part 1 of Study MYL-Her-3001, patients received study drug in combination with a taxane (docetaxel or paclitaxel) for a minimum of 8 treatment cycles (1 treatment cycle=3 weeks based on trastuzumab administration; total of 24 weeks) starting with loading dose 8 mg/kg IV, followed by maintenance dose of 6 mg/kg IV, every 3 weeks. In Part 2 of the study, all patients with at least stable disease continued with the trastuzumab product that they were originally allocated to as a single agent until disease progression, unacceptable toxicity, or death, whichever occurred first (maintenance dose for a maximum of 8 treatment cycles; total of 24 weeks). Patients in supportive Study BM200-CT3-001-11 received study drug Bmab-200 or EU-approved Herceptin in combination with docetaxel over 24 weeks (up to 8 cycles) according to the same dosing regimen as in the Study MYL-Her-3001.

A pooled safety analysis was not applicable due to heterogeneity of study populations (patients or healthy subjects) and different duration of treatment exposure (long-term or single-dose).

Analyses of safety included hypersensitivity monitoring via vital sign measurements, electrocardiograms (ECGs), physical examination findings, immunogenicity by measuring the ADA levels. Data also included Adverse Events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs), infections, clinical laboratory analyses and concomitant medications. In addition, AEs of special interest (AESIs), which are potential and identified risks of Herceptin were performed (pulmonary toxicity, cardiotoxicity, hematologic toxicity, infusion reactions, allergic-like reactions and hypersensitivity).

Patient exposure

Overall, 313 patients received at least 1 full or partial infusion of MYL-1401O/Bmab-200 and 314 patients received Herceptin.

In MYL-Her-1001 and MYL-Her-1002, the cumulative dose of MYL-1401O is very close to the cumulative dose of Herceptin (Table 30).

In MYL-Her-3001, the cumulative dose of trastuzumab in Part 1 of the study was similar in both arms, but over a 48 week treatment duration (parts 1 & 2), the cumulative dose of MYL-1401O was slightly higher than Herceptin (Table 30). Across the study through Week 48, patients in the MYL-1401O arm received a median of 2 trastuzumab cycles more than patients in the Herceptin arm.

Table 26: Trastuzumab exposure and cumulative dose per arm (MYL-1401O and Herceptin) per study (MYL-Her-1001, MYL-Her-1002, MYL-Her-3001)

Study	Per subject:	MYL-1401O	Herceptin
MYL-Her-1001*	Range dose	7.8 to 8.6 mg/kg	7.6 to 8.1 mg/kg
	Mean dose (±[SD])	8.06 (±0.41) mg/kg	7.86 (±0.12) mg/kg
	Mean cumulative dose	621.37 mg	611.86 mg
MYL-Her-1002*	Mean dose	7.98 mg/kg	7.91 mg/kg (US Herceptin) 8.00 mg/kg (EU Herceptin)
	Mean cumulative dose	676.2 mg	651.5 mg (US Herceptin) 654.6 mg (EU Herceptin)

MYL-Her-3001 – Part 1	Mean dose	8.0 mg/kg	8.0 mg/kg
	Mean cumulative dose	3380.6 mg	3330.6 mg
MYL-Her-3001 – Part 1 + 2*	Mean cumulative dose	5399.4 mg	5140.3 mg
	Median cumulative dose	5608.0 mg	5597.4 mg

* MYL-Her-1001: Herceptin n=22, MYL-1401O n=19.
MYL-Her-1002: US Herceptin n=44, EU Herceptin n=44, MYL-1401O n=44
MYL-Her-3001 – Part 1 + 2: EU Herceptin n=246, MYL-1401O n=247

In MYL-Her-3001, docetaxel exposure was similar between the 2 treatment groups (Table 31).

Table 27: Docetaxel cumulative dose per arm (MYL-1401O and Herceptin) in study Myl-Her-3001 Part 1 or Parts 1 + 2

Study	Per subject:	MYL-1401O group n = 212	Herceptin group n = 214
MYL-Her-3001 – Part 1	Mean cumulative dose	912.8 mg	910.1 mg
MYL-Her-3001 – Parts 1 + 2**	Mean cumulative dose	929.1 mg	930.3 mg
	Median cumulative dose	991.8 mg	977.5 mg

In MYL-Her-3001, paclitaxel exposure was higher in the MYL-1401O group than in the Herceptin group (Table 32).

Table 28: Paclitaxel cumulative dose per arm (MYL-1401O and Herceptin) in study Myl-Her-3001 Part 1 or Parts 1 + 2

Study	Per subject:	MYL-1401O group n = 35	Herceptin group n = 32
MYL-Her-3001 – Part 1	Mean cumulative dose	2596.5 mg	2142.6 mg
MYL-Her-3001 – Part 1 + 2**	Mean cumulative dose	2807.1 mg	2311.1 mg
	Median cumulative dose	3060.0 mg	2199.1 mg

**For note: A total of 32 patients continued taxane treatment in Part 2 (15 patients in MYL-1401O and 17 in Herceptin)

In MYL-Her-3001, at each cycle (between 1 and 17 cycles), slightly more patients were treated in the MYL-1401O arm than in the Herceptin arm. The difference is globally increasing with the number of cycles (from 50% patients in each arm to around 53% patients in the MYL-1401O arm compared to 47% in the Herceptin arm).

In BM200-CT3-a001-11, the extent of exposure (to trastuzumab and docetaxel) was similar between the 2 treatment groups (Bmab-200 and Herceptin) (Table 33).

Table 29: Overall Exposure to Study Drug by Treatment Group (BM200-CT3-001-11, Safety population)

		BM200-CT3-001-11 (N=135)	
	Safety population	Bmab-200 (+docetaxel)	Herceptin-EU (+docetaxel)
	Total number of exposed MBC patients	66	68
Trastuzumab	Mean subsequent dose intensity in mg/kg/week	2.070	2.039
	Mean duration of exposure in weeks	22.42	22.42
	Mean number of cycles ±SD	7.2 ±1.675	7.12 ±1.889**
	Mean administrated dose in mg/kg ±SD	8.0	8.0
Docetaxel	Mean dose intensity in mg/m2/week	±60-100	±60-100
	Mean duration of exposure in weeks	156.79 ± 37.529	156.66 ± 41.982
	Mean number of cycles	±8	±8

Disposition of patients

Study MYL-Her-3001

A total of 500 patients with HER2-positive MBC were randomized in 1:1 ratio in MYL-1401O plus taxane arm or EU-approved Herceptin plus a taxane arm.

In part 1, the safety population included all patients who received at least 1 dose of study drug and consisted of 493 patients (247 in the MYL-1401O arm and 246 in the Herceptin arm).

In part 2, the safety population included all patients who entered in part 2 and consisted of 342 patients (179 in the MYL-1401O arm and 163 in the Herceptin arm). From them, 32 patients (15 patients in MYL-1401O and 17 in Herceptin, taxane distribution not known: docetaxel or paclitaxel) entered Part 2 and continued using taxane before they switched to trastuzumab monotherapy during Part 2. Continuation of combination therapy and switch to monotherapy, based on potential benefit for the patient, was at the discretion of the Investigator. Data

of these 32 patients are included in the 'Part 2 monotherapy only" subset for the time the patients actually received monotherapy.

As shown in Table 34, 116 (64.8%) patients completed Part 2 in MYL-1401O and 98 (60.1%) patients in the Herceptin arm. The most common reason for discontinuation was disease progression (MYL-1401O 31.3% versus Herceptin 31.9%).

Table 30: Disposition of Patients by Treatment Group during 48 weeks (Parts 1 & 2 of Study) – All Randomized Patients (study MYL-Her-3001)

Part 1	**MYL-1401O + Taxane (N = 249)** n (%)	**Herceptin + Taxane (N = 251)** n (%)	**Overall + Taxane (N = 500)** n (%)
Randomized	249 (100.0)	251 (100.0)	500 (100.0)
Randomized and not treated	2 (0.8)	5 (2.0)	7 (1.4)
Entered Part 1 of study	247 (99.2)	246 (98.0)	493 (98.6)
Completed Part 1 of study (24 weeks)	185 (74.3)	171 (68.1)	356 (71.2)
Discontinued treatment in Part 1 of study	62 (24.9)	75 (29.9)	137 (27.4)
Reasons for treatment discontinuation in Part 1[a]			
Adverse event	4 (1.6)	2 (0.8)	6 (1.2)
Disease progression	47 (18.9)	58 (23.1)	105 (21.0)
Death[b]	6 (2.4)	3 (1.2)	9 (1.8)
Investigator/Sponsor decision	1 (0.4)	3 (1.2)	4 (0.8)
Lost to follow-up	1 (0.4)	0 (0.0)	1 (0.2)
Withdrawal of consent	2 (0.8)	7 (2.8)	9 (1.8)
Other[c]	1 (0.4)	2 (0.8)	3 (0.6)

Part 2	MYL-1401O (N = 179) n (%)	Herceptin (N = 163) n (%)	Overall (N = 342) n (%)
Entered Part 2 of study	179 (100.0)	163 (100.0)	342 (100.0)
Completed 48 weeks in Part 2 of study	116 (64.8)	98 (60.1)	214 (62.6)
Discontinued treatment in Part 2	63 (35.2)	65 (39.9)	128 (37.4)
Continued taxane in Part 2	15 (8.4)	17 (10.4)	32 (9.4)
Reasons for treatment discontinuation between 25 and 48 weeks[a]			
Adverse event	2 (1.1)	4 (2.5)	6 (1.8)
Disease progression	56 (31.3)	52 (31.9)	108 (31.6)
Death[b, d]	1 (0.6)	0 (0.0)	1 (0.3)
Investigator/Sponsor decision	1 (0.6)	1 (0.6)	2 (0.6)
Lost to follow-up	1 (0.6)	2 (1.2)	3 (0.9)
Withdrawal of consent	1 (0.6)	3 (1.8)	4 (1.2)
Other[e]	1 (0.6)	3 (1.8)	4 (1.2)

N: number of patients in a treatment group, n: number of patients with data available
Percentages are based on the number of patients randomized (for Part 1) and on number of patients entering Part 2 (for Part 2).
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

[a] Reasons for treatment discontinuation as documented by the Investigator on the 'End of study treatment' page of the CRF.

[b] Note this is death as reason for treatment discontinuation as entered by the Investigator on the 'End of study treatment' page of the CRF. Numbers here do not indicate patients with fatal TEAEs. Number of patients with fatal TEAEs can be found in Section 12.

[c] MYL-1401O group: alternative treatment of cancer (surgery); Herceptin group: from last investigational product dose more than 42 days lasted that required to discontinue the patient; patient missed more than 2 cycles due to family reason.

[d] Note this patient had a fatal TEAE (Listing 16.2.7.7b). Patient had a fatal TEAE (Listing 16.2.7.7b) but the investigator recorded the reason for treatment discontinuation as 'adverse event' and not 'death' (Listing 16.2.1.1b).

[e] MYL-1401O group: patient completed the study per Protocol Amendment 1 (which did not have survival follow-up); Herceptin group: surgery planned; due to patient's safety according to medical monitor; patient was unable to come to all planned procedures and treatment visits

Source: Table 14.1.1.1a, Table 14.1.1.1b, Listing 16.2.1.1a, Listing 16.2.1.1b

Study MYL-Her-1001

The safety population was the same as the ITT population and consisted of 22 subjects who were randomized and received a single dose of MYL-1401O or Herceptin (N=22) in Period 1 and the alternative in Period 2, except for 3 subjects who were withdrawn (2 due to personal reason, and 1, patient 122, by the Safety Committee as a precaution due to elevated transaminase) before receiving MYL-1401O (N=19).

Study MYL-Her-1002

The safety population included all 132 subjects who received MYL-1401O, Herceptin-EU, or Herceptin-US during the study (44 in each arm).

Study BM200 CT3-001-11

The safety population included all patients randomized in 1:1 ratio who received at least 1 dose of Bmab-200 or Herceptin, and consisted of 134 patients. As shown in Table 35, of the 67 patients randomized to the Bmab-200

arm, 51 completed the study. In the Herceptin arm, of the 68 patients randomized, 52 completed the study. The major reasons for discontinuations were similar in both arms.

Table 31: Disposition of Patients by Treatment Group (ITT-FAS Population, study BM200-CT3-001-11)

Disposition	Bmab-200 N=67 [n(%)]	Herceptin® N=68 [n(%)]
Randomized	67(100.00%)	68(100.00%)
Completed Study	51(76.12%)	52(76.47%)
Discontinued	16(23.88%)	16(23.53%)
Reasons for Discontinuation		
Adverse Event	0(0.00%)	1(1.47%)
Death	2(2.99%)	2(2.94%)
Disease progression	6(8.96%)	6(8.82%)
Lost to follow-up	1(1.49%)	4(5.88%)
Patient was withdrawn at the discretion of the investigator for safety concern.	2(2.99%)	2(2.94%)
Protocol violation	1(1.49%)	0(0.00%)
Withdrawal of Informed Consent	3(4.48%)	1(1.47%)
Other	1[a](1.49%)	0(0.00%)

[a] One Patient was removed from the analyses because the patient was withdrawn from the study before administration of first dose. Then: N = 66 for Bmab-200 and N=68 for Herceptin in safety population.

Adverse events

Study MYL-Her-3001

Overall, at 48 weeks, the safety profiles are comparable in the 2 arms, with as similar number of patients with at least 1 grade 3 or higher TEAE, with serious TEAE, with TEAE leading to interruption of trastuzumab or to discontinuation of the study (Table 36). However, in the Myl-1401O arm compared to in the Herceptin arm, there were slightly more TEAE (2639 and 2376 events, respectively) (but similar number of patients with TEAE: 98% and 97.2%, respectively) (Table 36).

Moreover, in the MYL-1401O arm compared to in the Herceptin arm, there were more treatment-related TEAE (356 and 273 events, respectively) and more patients with treatment-related TEAE; 103 patients (41.7%) and 88 patients (35.8%), respectively.

Table 32: Overview of Treatment-Emergent Adverse Events (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

	MYL-1401O (N = 247)		Herceptin (N = 246)		Overall (N = 493)	
Category	**n (%)**	**Events**	**n (%)**	**Events**	**n (%)**	**Events**
Patients with TEAEs	242 (98.0)	2639	239 (97.2)	2376	481 (97.6)	5015
Patients with Grade 3 or higher TEAE	162 (65.6)	358	162 (65.9)	361	324 (65.7)	719
Patients with serious TEAEs (SAEs)	97 (39.3)	167	91 (37.0)	163	188 (38.1)	330
Patients with treatment-related TEAEs	103 (41.7)	356	88 (35.8)	273	191 (38.7)	629
Patients with TEAEs leading to discontinuation of trastuzumab[a]	10 (4.0)	14	16 (6.5)	27	26 (5.3)	41
Patients with TEAEs leading to interruption of trastuzumab	12 (4.9)	14	11 (4.5)	13	23 (4.7)	27
Patients with TEAEs leading to discontinuation from the study[b]	9 (3.6)	11	9 (3.7)	12	18 (3.7)	23
Patients with fatal TEAEs	6 (2.4)	8	4 (1.6)	6	10 (2.0)	14

n: number of patients with TEAEs, SAE: serious adverse event, TEAE: treatment-emergent adverse event.
Percentages were based on the number of patients in the safety population (N).
TEAE with missing severity grade were considered to be Grade 3.
Treatment-related includes TEAEs possibly, probably, or definitely related to trastuzumab or relationship unknown.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug alone.
[a] Patients with action taken for trastuzumab of "treatment withdrawn" on adverse event case report form page.
[b] Patients with answer "yes" to "withdrawal from study due to adverse event?" on adverse event case report form page.
Source: Table 14.3.2.1.1b

TEAEs that were reported for >5% of patients in either treatment arm are presented by System Organ Class (SOC) and Preferred Term (PT) in Table 37 below.

Table 33: Treatment-Emergent Adverse Events Occurring in >5% of Patients in Either Treatment Arm (Safety Population; Study MYL-Her-3001 –parts 1 & 2)

System Organ Class Preferred Term	MYL-1401O (N = 247) n (%)	Events	Herceptin (N = 246) n (%)	Events	Overall (N = 493) n (%)	Events
Number of patients with at least 1 TEAE	242 (98.0)	2639	239 (97.2)	2376	481 (97.6)	5015
Blood and lymphatic system disorders	168 (68.0)	421	162 (65.9)	396	330 (66.9)	817
Anaemia	41 (16.6)	83	44 (17.9)	85	85 (17.2)	168
Leukopenia	43 (17.4)	68	53 (21.5)	73	96 (19.5)	141
Neutropenia	143 (57.9)	231	133 (54.1)	200	276 (56.0)	431
Gastrointestinal disorders	105 (42.5)	324	93 (37.8)	240	198 (40.2)	564
Diarrhoea	52 (21.1)	91	51 (20.7)	73	103 (20.9)	164
Nausea	52 (21.1)	86	38 (15.4)	64	90 (18.3)	150
Vomiting	27 (10.9)	45	24 (9.8)	29	51 (10.3)	74
General disorders and administration site conditions	131 (53.0)	380	134 (54.5)	311	265 (53.8)	691
Asthenia	57 (23.1)	128	41 (16.7)	83	98 (19.9)	211
Fatigue	30 (12.1)	64	37 (15.0)	68	67 (13.6)	132
Oedema peripheral	38 (15.4)	64	31 (12.6)	42	69 (14.0)	106
Peripheral swelling	11 (4.5)	19	13 (5.3)	15	24 (4.9)	34
Pyrexia	24 (9.7)	31	33 (13.4)	39	57 (11.6)	70
Infections and infestations	82 (33.2)	165	72 (29.3)	131	154 (31.2)	296
Upper respiratory tract infection	18 (7.3)	20	5 (2.0)	8	23 (4.7)	28
Urinary tract infection	24 (9.7)	36	18 (7.3)	32	42 (8.5)	68
Injury, poisoning and procedural complications	22 (8.9)	38	19 (7.7)	28	41 (8.3)	66
Infusion related reaction	17 (6.9)	30	12 (4.9)	20	29 (5.9)	50
Investigations	75 (30.4)	167	69 (28.0)	170	144 (29.2)	337
Alanine aminotransferase increased	22 (8.9)	31	22 (8.9)	41	44 (8.9)	72
Aspartate aminotransferase increased	16 (6.5)	28	24 (9.8)	46	40 (8.1)	74
Metabolism and nutrition disorders	60 (24.3)	131	75 (30.5)	155	135 (27.4)	286
Decreased appetite	23 (9.3)	59	25 (10.2)	47	48 (9.7)	106
Hyperglycaemia	15 (6.1)	18	19 (7.7)	43	34 (6.9)	61
Musculoskeletal and connective tissue disorders	84 (34.0)	176	66 (26.8)	130	150 (30.4)	306
Arthralgia	33 (13.4)	55	14 (5.7)	20	47 (9.5)	75
Bone pain	21 (8.5)	26	14 (5.7)	24	35 (7.1)	50
Myalgia	25 (10.1)	52	23 (9.3)	42	48 (9.7)	94
Nervous system disorders	98 (39.7)	188	108 (43.9)	200	206 (41.8)	388
Headache	24 (9.7)	27	29 (11.8)	36	53 (10.8)	63
Neuropathy peripheral	31 (12.6)	42	30 (12.2)	52	61 (12.4)	94
Peripheral sensory neuropathy	32 (13.0)	44	36 (14.6)	42	68 (13.8)	86
Respiratory, thoracic and mediastinal disorders	72 (29.1)	125	54 (22.0)	103	126 (25.6)	228
Cough	19 (7.7)	27	18 (7.3)	22	37 (7.5)	49
Dyspnoea	17 (6.9)	20	18 (7.3)	24	35 (7.1)	44
Skin and subcutaneous disorders	163 (66.0)	316	162 (65.9)	330	325 (65.9)	646
Alopecia	143 (57.9)	183	135 (54.9)	170	278 (56.4)	353
Nail disorder	17 (6.9)	18	22 (8.9)	23	39 (7.9)	41
Rash	22 (8.9)	31	25 (10.2)	44	47 (9.5)	75

n: number of patients with TEAEs, TEAE: treatment-emergent adverse event.
Percentages were based on the number of patients in the safety population (N).
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0. System organ class and preferred term are ordered alphabetically.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
Source: Table 14.3.2.2.1b

The incidence of TEAEs was similar between the treatment groups. However, there were few noted differences (> 5%) in the incidence of TEAEs between the treatment arms, including nausea (21.1% to 15.4%), asthenia (23.1% to 16.7%), arthralgia (13.4% to 5.7%), and upper respiratory tract infection (7.3% to 2.0%) in the MYL-1401O arm and Herceptin arm respectively. In Part 2 of the study, when patients were on monotherapy, the incidence of these events in MYL-1401O and Herceptin arm were similar and are as follows: nausea 2.2% to 2.5%, asthenia 2.8% to 1.8%, arthralgia 2.8% to 1.2%, upper respiratory tract infection 2.2% to 1.2%.

In terms of causality as reported by investigator, in the MYL-1401O arm compared to in the Herceptin arm, there were more treatment-related TEAE (356 and 273 events, respectively) and more patients with treatment-related TEAE; 103 patients (41.7%) and 88 patients (35.8%), respectively. Overall, the SOCs with the most frequently reported treatment-related TEAEs were General disorders and administrative site conditions (12.8%); Investigations (8.3%); Skin and subcutaneous tissue disorders (7.7%); Respiratory, thoracic and mediastinal disorders (6.5%); Cardiac disorders (6.1%); Gastrointestinal disorders (5.9%); and Musculoskeletal and connective tissue disorders (5.3%). There were more than 5% difference between the MYL-1401O arm compared with the Herceptin arm only for treatment-related Gastrointestinal disorders which was higher in the MYL-1401O arm (8.9%) compared with the Herceptin arm (2.8%). For Part 2 monotherapy patients, the incidence of TEAEs that were considered related to the treatment by the Investigator was similar between the MYL-1401O arm and the Herceptin arm (28 patients; 15.6% and 25 patients; 15.3% respectively).

In terms of severity, the majority of TEAEs were Grade 1 or Grade 2 in severity (Table 38). Overall, 65.7% of patients experienced TEAEs of Grade 3 or greater in severity, and the incidence of these events was similar between treatment groups (Table 39). For Parts 1 and 2, the incidence of Grade 4 neutropenia events was similar between the treatment groups: 70 patients in the MYL-1401O arm and 62 in the Herceptin arm (none in part 2). Most TEAEs resolved by the end of Week 48 and were considered not related to study drug (including Grade 4 neutropenia). Also the majority of these events occurred in Part 1 of the study and the combined Part 1 and Part 2 results are driven by the higher number of events in Part 1 of the study.

Table 34: Number of Patients with Treatment-Emergent Adverse Events by Maximum Severity (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

	MYL-1401O (N = 247)	Herceptin (N = 246)
TEAE CTCAE Grade	**n (%)**	**n (%)**
Grade 1	201 (81)	197 (80)
Grade 2	194 (79)	199 (81)
Grade 3	129 (52)	127 (52)
Grade 4	80 (32)	75 (30)
Grade 5	6 (2)	4 (2)

CTCAE: Common Terminology Criteria for Adverse Events, n: number of patients with TEAEs, TEAE: treatment-emergent adverse event
Percentages were based on the number of patients in the safety population (N).
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0.
Severity CTCAE Grade: 1-Mild, 2-Moderate, 3-Severe, 4-Life-threatening, 5-Death; TEAEs with missing severity grade were considered to be Grade 3.
If a patient had more than 1 occurrence of the same event, the most severe occurrences was reported.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
Source: Table 14.3.2.5.1.1b

Table 35: Treatment-Emergent Adverse Events of Grade 3 or Higher Occurring in ≥2% of Patients in Either Treatment Arm by SOC and PT (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

System Organ Class Preferred Term	MYL-1401O (N = 247)		Herceptin (N = 246)		Overall (N = 493)	
	n (%)	Events	n (%)	Events	n (%)	Events
Number of patients with at least 1 TEAE Grade 3 or greater	162 (65.6)	358	162 (65.9)	361	324 (65.7)	719
Blood and lymphatic system disorders	129 (52.2)	235	121 (49.2)	213	250 (50.7)	448
Anaemia	1 (0.4)	2	6 (2.4)	7	7 (1.4)	9
Febrile neutropenia	12 (4.9)	14	10 (4.1)	11	22 (4.5)	25
Leukopenia	32 (13.0)	43	38 (15.4)	44	70 (14.2)	87
Lymphopenia	3 (1.2)	3	7 (2.8)	8	10 (2.0)	11
Neutropenia	118 (47.8)	171	105 (42.7)	140	223 (45.2)	311
Gastrointestinal disorders	5 (2.0)	6	13 (5.3)	17	18 (3.7)	23
Diarrhoea	2 (0.8)	2	7 (2.8)	8	9 (1.8)	10
Infections and infestations	12 (4.9)	15	16 (6.5)	17	28 (5.7)	32
Pneumonia	3 (1.2)	3	5 (2.0)	5	8 (1.6)	8
Investigations	17 (6.9)	23	15 (6.1)	24	32 (6.5)	47
Alanine aminotransferase increased	7 (2.8)	7	6 (2.4)	6	13 (2.6)	13
Aspartate aminotransferase increased	4 (1.6)	4	7 (2.8)	8	11 (2.2)	12
Metabolism and nutrition disorders	13 (5.3)	16	19 (7.7)	29	32 (6.5)	45
Hyperglycaemia	4 (1.6)	4	6 (2.4)	7	10 (2.0)	11
Hyperuricaemia	6 (2.4)	7	2 (0.8)	2	8 (1.6)	9
Nervous system disorders	10 (4.0)	12	13 (5.3)	17	23 (4.7)	29
Headache	0	0	5 (2.0)	5	5 (1.0)	5

n: number of patients with TEAEs, TEAE: treatment-emergent adverse event
Percentages were based on the number of patients in the safety population (N).
TEAEs were defined as any adverse event that started or deteriorated at or after first dose of study treatment but on or within 28 days following the last dose.
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0. System organ class and preferred term are ordered alphabetically.
TEAEs with missing severity grade were considered to be Grade 3.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
Source: Table 14.3.2.4.1b

No notable differences between treatment groups were observed through Week 48 for vital signs, physical examination findings, or ECOG status.

Study MYL-Her-1001

Slightly less AEs were reported during the study with MYL-1401O compared to Herceptin: 47 AEs in 16 subjects (84.2%) and 73 AEs in 21 subjects (95.5%), respectively.

The SOCs with the most frequently reported TEAEs for MYL-1401O were nervous system disorders (47.4%) and infections and infestations (42.1%), and for Herceptin they was a higher incidence of infections and infestations (81.8%) and a similar incidence of nervous system disorders (45.5%).

The most frequently reported AE preferred terms for MYL-1401O were headache (47.4%), followed by nasopharyngitis (26.3%) and CRP increased (21.2%), while for Herceptin they were nasopharyngitis (54.5%), followed by headache (45.5%), rhinitis (36.4%), and CRP increased (31.8%). Most TEAEs were mild (42 for MYL-1401O, and 68 for Herceptin). There was only a single severe TEAE of streptococcal pharyngitis which was considered to be possibly related to the administration of MYL-1401O. Most of the TEAEs were considered to be

at least possibly related to study drug administration (44 for MYL-1401O and 67 for Herceptin; including all of the most common preferred terms: headache, nasopharyngitis, rhinitis, and CRP increased).

Overall, MYL-1401O and EU approved Herceptin were well tolerated after 8 mg/kg as a single dose administered to healthy male volunteers as an IV infusion over 90 minutes. There were no clinically relevant differences in the incidence, nature, and severity of TEAEs reported.

Study MYL-Her-1002

Over the course of the study, the number (percentage) of patients reporting TEAEs was slightly higher in the MYL-1401O arm compared to the Herceptin-EU arm, which was slightly higher than the Herceptin-US arm: 31 patients (70.5%, 91 TEAEs), 28 patients (63.6%, 80 TEAEs) and 24 (54.5%, 56 TEAEs), respectively.

The most frequently reported adverse event (AE) following administration of MYL-1401O was headache which was reported by 12 patients/44 (27.3%), then back pain (7/44, 15.9%), and influenza like illness (5/44, 11.4%). Following administration of Herceptin-EU, the most frequently reported AE were headache (13/44, 29.5%), chills (11/44, 25%) and upper respiratory tract infection (4/44, 9.1%). Following administration of Herceptin-US, the most frequently reported AE were headache (10/44, 22.7%), then nausea (4/44, 9.1%) and dizziness (3/44, 6.8%).

The investigator considered 54 of the 91 TEAEs to be at least possibly related to MYL-1401O, 52 of the 80 TEAEs at least possibly related to Herceptin-EU, and 32 of the 56 TEAEs at least possibly related to Herceptin-US. All TEAEs were considered resolved by the principal investigator at the end of the study.

The TEAEs were mild to moderate in severity (no severe TEAE).

Overall, MYL-1401O, EU-approved Herceptin, and US-licensed Herceptin were well tolerated after 8 mg/kg as single dose administered to healthy male volunteers as an IV infusion over 90 minutes. There were no clinically relevant differences in the incidence, nature, and severity of TEAEs reported from the 3 treatment groups.

Study BM200 CT3-001-11

In both arms, trastuzumab was only used in combination with docetaxel. The incidence of TEAEs, severe TEAE, treatment-related TEAEs and SAE was observed to be slightly lower in the Bmab-200 arm than in the Herceptin arm (Table 40).

Table 36: Overview of Treatment-Emergent Adverse Events (Safety Population; Study BM200-CT3-001-11)

Description	Bmab-200 N=66 [n(%)]	Herceptin® N=68 [n(%)]	overall N=134 [n(%)]
At least one Treatment Emergent AE	52(78.79%)	61(89.71%)	113(84.33%)
At least one Severe Treatment Emergent AE	10(15.15%)	20(29.41%)	30(22.39%)
At least one Related Treatment Emergent AE	18(27.27%)	26(38.24%)	44(32.84%)
At least one Treatment Emergent SAE	11(16.67%)	20(29.41%)	31(23.13%)

Most common treatment emergent adverse events were pyrexia and diarrhoea (incidence >10% in both arms). The following TEAEs occurred >5% in both the treatment arms: anaemia, abdominal pain, constipation, diarrhoea, vomiting, asthenia, oedema peripheral, pain, pyrexia, hyperglycaemia, back pain, pain in extremity, cough, and alopecia.

In terms of severity, the majority of the TEAEs were mild or moderate. Similar numbers of patients (and % of patients) had Grade 1 (mild) or Grade 5 (death related) TEAE in Bmab-200 arm and the Herceptin arm (Table 41). However, Grade 2 (moderate) and Grade 3 (severe) TEAEs were less frequent in Bmab-200 arm than Herceptin arm. The number of Grade 4 TEAE was not provided.

Table 37: Summary of Treatment-Emergent Adverse Events by Severity (Study BM200- CT3-001-11)

Description	Bmab-200 (N=66) [n(%)]	Herceptin® (N=68) [n(%)]
Grade 1 -Mild	43(65.15%)	45(66.18%)
Grade 2 -Moderate	33(50.00%)	47(69.12%)
Grade 3 -Severe	10(15.15%)	20(29.41%)
Grade 5 -Death Related	2(3.03%)	2(2.94%)

Overall the treatment with Bmab-200 was well tolerated in combination with docetaxel and no new or unexpected safety signals were observed. There were no relevant differences between the 2 arms for any safety parameters.

Serious adverse event / deaths / other significant events

Serious adverse events

No SAEs, no deaths and no other significant AE were reported in the studies MYL-Her-1001 and MYL-Her-1002.

In the Study MYL-Her-3001, over 48 weeks, the incidence of SAEs was similar in the treatment groups: 167 events in 97 patients (39.3%) in the MYL-1401O arm, and 163 events in 91 patients (37.0%) in the Herceptin arm (Table 42). The majority reported SAEs were in the SOC of Blood and lymphatic system disorders (111 events in MYL-1401O, and 103 events in Herceptin).

Table 38: Serious TEAE That Occurred in at Least 5 Patients Overall (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

System Organ Class	MYL-1401O + Taxane (N=247)		Herceptin + Taxane (N=246)	
	n (%)	Events	n (%)	Events
Patients with at least 1 serious TEAE	97 (38.1)	167	91 (37.0)	163
Blood and lymphatic system disorders	79 (32.0)	111	70 (28.5)	103
Gastrointestinal disorders	6 (2.4)	8	9 (3.7)	12
General disorders and administration site conditions	2 (0.8)	2	5 (2.0)	5
Immune system disorders	3 (1.2)	3	2 (0.8)	2
Infections and infestations	13 (5.3)	16	16 (6.5)	17
Metabolism and nutrition disorders	3 (1.2)	3	8 (3.3)	8
Respiratory, thoracic and mediastinal disorders	7 (2.8)	9	6 (2.4)	6

At the PT level, the most frequently reported SAE were:

- Neutropenia with 68 patients (27.5%, 92 events) in the MYL-1401O arm and 62 patients (25.2%, 78 events) in the Herceptin arm; nearly all of them were Grade 4.
- Febrile neutropenia: 11 patients (4.5%, 13 events) in the MYL-1401O arm and 10 patients (4.1%, 11 events) in the Herceptin arm.
- Leukopenia: 5 patients (2%, 5 events) in the MYL-1401O arm and 12 patients (4.9%, 13 events) in the Herceptin arm.
- Pneumonia: 6 patients (2.4%, 6 events) in the MYL-1401O arm and 5 patients (2%, 5 events) in the Herceptin arm.

Generally, the vast majority of SAEs occurred in Part 1 of the study while patients were receiving combination therapy, and, in Part 2, there were no SAEs in the Blood and lymphatic disorder SOC (and thus no neutropenia SAEs). The majority of SAEs were considered unrelated to study drug. Nevertheless, more SAEs (11 SAEs in 9 patients) in the MYL-1401O arm than in the Herceptin arm (6 SAEs in 4 patients) were attributed by the Investigators to the study drug. Most SAEs that began in Part 1 resolved or resolved with sequelae, except for those that were fatal. In general, the number and type of SAEs were those expected for this patient population, and there were no notable differences in SAEs between the treatment arms. Two SUSARs were reported (accelerated hypertension and pneumothorax spontaneous, both in Part 1).

In the supportive study BM200 CT3-001-11, incidence of serious adverse events was observed to be lower in the Bmab-200 arm over the course of the trial: 11 patients with treatment-emergent SAEs in the Bmab-200 arm (16.67%, 16 events) vs 20 in the Herceptin arm (29.41%, 28 events).

In the Bmab-200 arm, the SOC with the most frequent treatment-emergent SAEs was general disorders and administration site conditions (9.09%); the events reported being: disease progression, infusion related reaction, and multi-organ failure (all occurred once in 1 patient each); fatigue (occurred twice in 1 patient); and pyrexia (occurred once in 2 patients). The SOC injury, poisoning and procedural complications was second most prevalent; the events reported being: animal bite and clavicle fracture (once in 1 patient each).

In the Herceptin arm, the SOC with the most frequent treatment-emergent SAEs was infections and infestations (7.35%); the events reported being: lower respiratory tract infection and sepsis (all occurred once in 1 patient each); gastroenteritis (4 events in 3 patients). The SOC general disorders and administration site conditions was the second most prevalent (5.88%); the events reported being: disease progression (occurred once in 1 patient) and pyrexia (occurred once in 3 patients).

The incidence of SAE, severe SAE, and treatment-related SAE was observed to be slightly lower in the Bmab-200 arm than in the Herceptin arm (Table 43). In both arms, the majority of patients with SAE had SAEs deemed unrelated to study drug (Bmab-200, 15.15%; Herceptin, 17.65%).

Table 39: Summary of Patients with Severe and Related Serious TEAEs (Study BM200-CT3-001-11)

Description	Bmab-200 N=66 [n(%)]	Herceptin® N=68 [n(%)]
At least one Treatment Emergent SAE	11(16.67%)	20(29.41%)
At least one Severe Treatment Emergent SAE	5(7.58%)	12(17.65%)
At least one Related Treatment Emergent SAE	2(3.03%)	7(10.29%)

Deaths

In MYL-Her-3001, for Part 1 and 2 through Week 48, 10 patients experienced fatal TEAEs, 6 in the MYL-1401O arm (2.4%, 8 events) and 4 in the Herceptin arm (1.6%, 6 events) .

For the part 2 monotherapy patients, 2 patients in the MYL-1401O arm experienced 1 fatal TEAE each (none in the Herceptin arm); however, neither event was considered related to study drug by the Investigator. Most of the remaining fatal events (part 1: 4 deaths in each arm) were considered related to taxane, concomitant medication, or underlying or progressive disease. Only 1 event of respiratory failure in each arm was considered as possibly related to the study drug.

Adverse events of special interest (AESIs)

Infusion Reactions, Allergic-like Reactions, and Hypersensitivity

In MYL-Her-3001, over 48 weeks, a total of 67 events were documented for infusion related reactions (IRRs), anaphylactic reaction, drug hypersensitivity, and hypersensitivity. In both treatment groups the majority of the events were unrelated to treatment (MYL-1401O 66.7% [26 unrelated events out of 39 events], Herceptin 71.4% [20/28]). For note: Only 1 patient in the Herceptin group experienced an IRR during Part 2.

The incidence of infusion-related reactions was low but slightly higher in MYL-1401O (30 events in 17 patients – 6.9%) compared to Herceptin (20 events in 12 patients – 4.9%). Fifteen patients (3.0%) had IRRs that were considered related to trastuzumab, 9 in the MYL-1401O arm and 6 in the Herceptin arm. The majority of these occurred in the first cycle, and all of the IRRs resolved the same day of onset with interruption of the infusion and/or conservative treatment. The nature and severity of these reactions were consistent with known trastuzumab and taxane infusion reactions and do not yield any new safety concerns.

The other most frequently reported significant TEAE was hypersensitivity in 12 patients (2.4%), where the incidence was similar between treatment arms. Most of these events were Grade 1 or 2 in intensity, and the majority of TEAEs hypersensitivity was considered not related to study drug.

Two anaphylactic reaction events were reported in 2 patients in the MYL-1401O arm (none in the Herceptin arm). Both were reported as SAEs of Grade 3 intensity, and both events resolved; 1 event was considered related to MYL-1401O and resolved on the same day, the other event was unrelated to MYL-1401O but was considered related to concomitant medication (piperacillin/tazobactam). Anaphylactic reactions are known effects associated with trastuzumab.

In the Study BM200 CT3-001-11, infusion reactions, which were adjudged as AEs related to infusion, were comparable in both arms. 8 patients (12.12%) in Bmab-200 arm and 10 patients (14.71%) in Herceptin arm reported at least one AE which is related to the study drug infusion. The most frequently reported event considered related to study drug infusions by investigators was pyrexia for both treatment arms (6.06% in the Bmab-200 arm and 5.88% in the Herceptin arm). The majority of the infusion-related reactions were mild to moderate in severity. No severe anaphylactic reactions were reported in either treatment arm.

Pulmonary toxicity

In MYL-Her-3001, over 48 weeks, the incidence of significant TEAEs of pulmonary toxicity (including dyspnea, dyspnea exertional, pneumonia, pneumonitis, pulmonary fibrosis, and respiratory failure) was low and similar in each arm: 41 events in 32 patients (13%) in MYL-1401O arm, and 43 events in 30 patients (12.2%). Of these significant TEAEs, dyspnea (6.9% in MYL-1401O and 7.3% in Herceptin), pneumonia (2.8%/4.1%), and pneumonitis (1.6%/0.8%) were reported more frequently. Most of the TEAEs were Grade 1 or 2 in intensity. The

incidence of Grade 3 or greater TEAEs, and of SAE was similar between the 2 arms. The majority of TEAEs of potential of pulmonary toxicity were considered not to be related to the study drug and related to the taxane.

Five fatal events were related to pulmonary toxicity: 4 during part 1 (1 fatal pneumonia in Herceptin arm and 3 events of respiratory failure: 2 in MYL-1401O and 1 in Herceptin), and 1 during part 2 monotherapy (dyspnea in MYL-1401O). Two fatal AEs of respiratory failure were considered to be possibly related to the study drug (1 in each arm).

Most events indicating pulmonary toxicity occurred during taxane therapy in Part 1.

In the Study BM200 CT3-001-11, 13 patients (19.70%) in the Bmab-200 arm and 14 patients (20.59%) in the Herceptin arm reported at least 1 TEAE related to the SOC Respiratory, thoracic, and mediastinal disorders. The frequent pulmonary events reported for Bmab-200 were cough (12.12%), exertional dyspnoea (4.55%), and pleural effusion (4.55%); and for Herceptin were cough (13.24%), dyspnoea (2.94%), and pneumonitis (2.94%). No fatal events were related to pulmonary toxicity.

Cardiac toxicity

In MYL-Her-3001, patients with abnormal LVEF and significant cardiac problems at baseline were excluded from the study (inclusion criterion 12 and exclusion criterion 6).

Over 48 weeks, the incidence of significant TEAEs of cardiac toxicity (including cardiac failure, cardiotoxicity, left ventricular dysfunction, and metabolic cardiomyopathy) was low and similar in each arm: 13 events in 12 patients (4.9%) in MYL-1401O, and 10 events in 10 patients (4.1%) in Herceptin. There were more cardiac failure in MYL-1401O (6 events in 6 patients – 2.4%) than in Herceptin (1 event in 1 patient – 0.4%). There were also more Grade 3 or greater TEAE in the MYL-1401O arm (6 events: 3 cardiac failure, 1 carditis, 2 left ventricular dysfunction, including 2 fatal cases) than in the Herceptin arm (1 left ventricular dysfunction). There were 3 SAE in the MYL-1401O arm (2 cardiac failure, and 1 carditis), and none in the Herceptin arm. The majority of cardiac toxicity TEAEs were considered related to study drug in both arms: 8 related TEAE in MYL-1401O (including 4 cardiac failure), and 6 in Herceptin.

In addition, the following results were obtained for the ejection fraction decreased: TEAEs (all unrelated) MYL-1401O 12 patients (4.9%, 16 events), Herceptin 7 patients (2.8%, 8 events); Grade 3 or greater MYL-1401O 1 patient (0.4%, 1 event), Herceptin 1 (0.4 %, 1 event); SAE MYL-1401O 1 patient (0.4 %, 1 event), Herceptin 0).

Around 69% of the cardiac events occurred during Part 1 while patients received combination therapy.

One event of cardiac failure was fatal (Grade 5). This fatal event was considered unlikely related to study drug (unknown cause); the patient also had concurrent fatal respiratory failure. No fatal events due to cardiac toxicity have been reported in the Herceptin arm.

Mean, median, minimum and maximum LVEF values did not change appreciably from Baseline to Week 48 for either treatment group, and were similar between treatment groups. Few patients, 10 (4.0%) in the MYL-1401O group and 8 (3.3%) patients in the Herceptin group, had drops in LVEF below 50% during the study. Most of these patients had previously received anthracyclines, had a previous or concomitant cardiovascular disorder, previous thoracic radiation, diabetes mellitus, or high levels of blood pressure.

Finally, out of the 5 TEAEs resulting in treatment discontinuation for at least 2 patients, 6 TEAEs were related to cardiac toxicity: 3 patients with cardiac failure in MYL-1401O (none in Herceptin) and 3 patients with ejection fraction decreased (2 patients in the MYL-1401O arm and 1 patient in the Herceptin arm).

No notable differences between treatment groups were observed for ECG results.

In the Study BM200 CT3-001-11, a small number of patients in both arms showed abnormal ECG findings during the course of study, but they were not clinically significant (9 patients in the MYL-1401O arm and 9 patients in the Herceptin arm). Although there were no observations of symptomatic congestive heart failure in the trial, 2 (3.03%) patients in Bmab-200 arm and 4 (5.88%) patients in Herceptin arm reported to have clinically significant reduction in ejection fraction (LVEF); these were reported as TEAEs. 1 patient (1.52%) in Bmab-200 arm had a TEAE of palpitations that was considered an infusion-related reaction by the Investigator; the patient's palpitations completely resolved. The incidence of cardiovascular events in the Bmab-200 arm was marginally lower than that in the Herceptin arm.

Laboratory findings

Haematology

In MYL-Her-3001, there were no notable differences in shifts of haematology parameters between treatment arms from baseline through Week 48.

In the MYL-Her-3001 study, of the significant TEAEs of hematologic toxicity through Week 48, including all PTs within the system organ class of Blood and lymphatic system disorders, neutropenia was reported most frequently (56.0%) and occurred in similar frequencies in both treatment arms. Most of these TEAEs were Grade 1 or 2 in intensity. The majority of these blood and lymphatic system disorder events were considered unrelated to study drug. Many of these TEAEs are known side effects of taxanes. Notably, most of these TEAEs were not present during monotherapy with trastuzumab. For Part 1 and 2 overall, the SOC with the most frequently reported SAEs was Blood and lymphatic system disorders: 79 patients (32%) with 111 events in MYL-1401O, and 70 patients (28.5%) with 103 events in Herceptin. At the PT level, the most frequently reported SAE was neutropenia: 68 patients (27.5%) with 92 events in MYL-1401O, and 62 patients (25.2%) with 78 events in Herceptin. In Part 2, there were no SAEs in the Blood and lymphatic disorder SOC (and thus no neutropenia SAEs).

Of these, 167 SAEs of neutropenia were considered Grade 4 in intensity, 91 events in the MYL-1401O arm and 76 events in the Herceptin arm. All of these SAEs resolved or resolved with sequelae and were considered not related to study drug. Most were considered related to taxanes. Of these neutropenia SAE, only 1 event caused discontinuation of taxane treatment in the MYL-1401O arm.

One pancytopenia event was fatal in the MYL-1401O arm.

In the Study MYL-Her-1001, there were no clinically significant changes in the haematology parameters during the course of the study. During the course of the study, 1 subject had clinically significant abnormal haematology values (after administration of Herceptin). This subject experienced abnormally increased white blood cell, neutrophils S, and monocyte counts at 48 hours after Herceptin administration, which was most probably likely due to nasopharyngitis.

In the Study BM200 CT3-001-11, 7 patients (10.61%) in the Bmab-200 arm and 7 patients (10.29%) in the Herceptin arm reported at least 1 TEAE related to the SOC Blood and lymphatic system disorders. In the Bmab-200 arm, the reported TEAEs in this SOC were anaemia (7.58%), thrombocytopenia (3.03%), leukopenia (1.52%), and eosinophilia (1.52%). In the Herceptin arm, the reported haematological TEAEs were anaemia (8.82%) and disseminated intravascular coagulation (1.47%). Of these, disseminated intravascular coagulation reported in the Herceptin arm was fatal.

Biochemistry

In MYL-Her-3001, through 48 weeks, the frequency of abnormal results in biochemistry values was similar in both treatment arms. The means and medians, as well as shifts based on longitudinal review of data from Baseline to Week 48, were reviewed for each parameter. No significant differences in mean, median, or any shifts were observed between the treatment arms for serum biochemistry parameters.

In the Study MYL-Her-1001, of the values considered clinically significant by the investigator 48 hours after treatment, most (9) were increased CRP values (marker of acute reaction). For both study drugs, the CRP response increased with a peak at 24 h, decreasing thereafter to 48 h (but higher value still evident), with full recovery occurred after 8 days.

In the Study MYL-Her-1002, no clinically significant changes in the clinical laboratory measurements which could be reasonably associated with the formulations under investigation. CRP increased in all subjects at 24 hours (usually within normal range) and had returned to each subject's baseline by Day 8. A statistically significant difference in change from baseline at 24 hours and 48 hours was noted between MYL-1401O and US-licensed Herceptin, and between EU-approved Herceptin and US-licensed Herceptin. However, there were no corresponding changes in ECGs or echocardiography.

In the Study BM200 CT3-001-11, none of the biochemistry parameters showed any notable change in the mean values from baseline to week 24 in either treatment arm. The frequency of clinically significant biochemistry abnormalities was similar in both treatment arms. All clinically significant abnormalities were reported as adverse events.

Urinary analysis

In MYL-Her-3001, no notable differences between treatment groups in urinalysis results from Baseline through Week 48 were observed.

Safety in special populations

No cases of pregnancy were reported in MYL-Her-3001 and BM200-CT3-001-11.

In MYL-Her-3001, statistically significant differences between treatment groups in the frequencies of some TEAEs were observed for patients < 65 years of age through 24 and 48 weeks of treatment, for instance for nausea (through 24 weeks - 20.9% of MYL-1401O patients versus 11.1% of Herceptin patients and through 48 weeks - 21.9% of MYL-1401O patients versus 12.1% of Herceptin patients), upper respiratory tract infection (through 24 weeks 6.0% of MYL-1401O patients versus 1.0% of Herceptin patients, through 48 weeks - 7.5% of MYL-1401O patients versus 1.4% of Herceptin patients), arthralgia (through 24 weeks-11.4% of MYL-1401O patients versus 3.9% of Herceptin patients; through 48 weeks-12.9% of MYL-1401O patients versus 5.3% of Herceptin patients).

The incidences of AEs and SAEs by geographical region were analysed by the Applicant. No significant differences have been observed. There is no clear indication from the provided data that potential differences in clinical practice and/or reporting might interfere in the comparability exercise.

Immunological events

Study MYL-Her-3001

Analysis of all patients

As part of the immunogenicity assessment of MYL-1401O, samples were tested for the presence of ADA and NAb through Week 48. Samples for the determination of ADA were taken at Baseline (Cycle 1 Week 0), Cycle 3 Week 6, Cycle 5 Week 12, Cycle 7 Week 18, Cycle 9 Week 24, Cycle 13 Week 36, Cycle 17 Week 48.

Table 44 presents a summary of the ADA results by visit and treatment.

Table 40: Summary of ADA Results by Visit and Treatment (safety population, Study MYL-Her-3001, parts 1 & 2)

		MYL-1401O (N = 247)	Herceptin (N = 246)
Visit	**ADA result**	**n (%)**	**n (%)**
Baseline (Cycle 1 Week 0)	ADA result available	237	240
	ADA positive	14 (5.9)	22 (9.2)
	ADA negative	223 (94.1)	218 (90.8)
	Missing	8	5
Cycle 3 Week 6	ADA result available	201	200
	ADA positive	5 (2.5)	6 (3.0)
	ADA negative	196 (97.5)	194 (97.0)
	Missing	5	5
Cycle 5 Week 12	ADA result available	213	205
	ADA positive	2 (0.9)	2 (1.0)
	ADA negative	211 (99.1)	203 (99.0)
	Missing	5	1
Cycle 7 Week 18	ADA result available	190	174
	ADA positive	2 (1.1)	1 (0.6)
	ADA negative	188 (99.9)	173 (99.4)
	Missing	1	2
Cycle 9 Week 24	ADA result available	179	166
	ADA positive	2 (1.1)	1 (0.6)
	ADA negative	177 (98.9)	165 (99.4)
	Missing	0	1
Cycle 13 Week 36 [a]	ADA result available	140	130
	ADA positive	3 (2.1)	1 (0.8)
	ADA negative	137 (97.9)	129 (99.2)
	Missing	0	0
Cycle 17 Week 48 [a,b]	ADA result available	103	93
	ADA positive	0	0
	ADA negative	103 (100.0)	93 (100.0)
	Missing	3	2
Last non-missing result post-baseline [c]	ADA positive	3 (1.3)	3 (1.3)
	ADA negative	225 (98.7)	224 (98.7)
At least one positive ADA sample post-baseline regardless of baseline result [c,d]		9 (3.9)	10 (4.4)

ADA: antidrug antibody, n: number of patients
Baseline was Cycle 1 Day 1, prior to first dose of study treatment.
Samples were taken before administration of study drug since study drug levels can interfere with the detection of antidrug antibody.
Percentages are based on the number of patients in the safety population (N) with an ADA assessment performed at the respective cycle. Missings are the number of patients who attended the visit but did not have an ADA sample collected.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Five patients at Cycle 13 Week 36 (3 in the MYL-1401O and 2 in the Herceptin arm) and 1 patient at Cycle 17 Week 48 in the Herceptin arm continued to receive taxane, but these patients are included in Cycle 13 Week 36 and Cycle 17 Week 48 of Part 2.
[b] Cycle 17 Week 48 data include results occurring after the Week 48 cut-off.
[c] Post-baseline includes only on treatment samples until Week 48 and excludes EOT/EOS samples.
[d] The denominator for this calculation is the number of non-missing post-baseline samples available in each arm, which include 228 patients in the MYL-1401O arm and 227 patients in the Herceptin arm.
Source: Table 14.3.4.1.4.1.1b

Prior to dosing (baseline), 14 of the 237 patients (14/237, 5.9%) with results available were positive for ADA in MYL-1401O group and 22 (22/240, 9.2%) were positive for ADA in the Herceptin group.

Given the type of patient population and study protocol, the number of patients continuing in the study decreased over time, thus the number of samples available for immunogenicity assessment also decreased over time. The number of ADA-positive samples and proportion at each time point are calculated.

With regard to NAb analysis, confirmed positive ADA samples were further tested using a validated cell based NAb assay. Table 45 presents a summary of the NAb results by visit and treatment.

Table 41: Summary of NAb Results by Visit and Treatment (safety population, Study MYL-Her-3001 – parts 1 & 2)

Visit			MYL-1401O (N = 247)	Herceptin (N = 246)
Baseline (Cycle 1 Week 0)	ADA result available	n	237	240
	ADA positive	n	14	22
	NAb negative	n	13	20
	NAb positive	n (%)	1 (0.4)	2 (0.8)
Cycle 3 Week 6	ADA result available		201	200
	ADA positive	n	5	6
	NAb negative	n	5	3
	NAb positive	n (%)	0	3 (1.5)
Cycle 5 Week 12	ADA result available		213	205
	ADA positive	n	2	2
	NAb negative	n	2	2
	NAb positive	n (%)	0	0
Cycle 7 Week 18	ADA result available		190	174
	ADA positive	n	2	1
	NAb negative	n	2	1
	NAb positive	n (%)	0	0
Cycle 9 Week 24	ADA result available		179	166
	ADA positive	n	2	1
	NAb negative	n	2	1
	NAb positive	n (%)	0	0
Cycle 13 Week 36[a]	ADA result available		140	130
	ADA positive	n	3	1
	NAb negative	n	2	1
	NAb positive	n (%)	1 (0.7)	0
Cycle 17 Week 48 [a,b]	ADA result available		103	93
	ADA positive	n	0	0
At least one positive NAb sample post-baseline regardless of baseline result [c,d]		n (%)	1 (0.4)	3 (1.3)

ADA: antidrug antibody, n: number of patients, NAb: neutralizing antibodies
Baseline was Cycle 1 Day 1, prior to first dose of study treatment.
Samples were taken before administration of study drug since study drug levels can interfere with the detection of antidrug antibody. Confirmed positive ADA samples were further tested using a validated cell based NAb assay.
Percentages are based on the number of patients in the safety population (N) with available ADA results.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Five patients at Cycle 13 Week 36 (3 in the MYL-1401O and 2 in the Herceptin arm) and 1 patient at Cycle 17 Week 48 in the Herceptin arm continued to receive taxane, but these patients are included in Cycle 13 Week 36 and Cycle 17 Week 48 of Part 2.
[b] Cycle 17 Week 48 data include results occurring after the Week 48 cut-off.
[c] Post-baseline includes only on treatment samples until Week 48 and excludes EOT/EOS samples.
[d] The denominator for this calculation is the number of non-missing post-baseline samples available in each arm, which include 228 patients in the MYL-1401O arm and 227 patients in the Herceptin arm.
Source: Table 14.3.4.1.4.1.6b

At baseline, of the patients who were ADA positive, NAbs were detected in 1 patient in the MYL-1401O group and in 2 patients in the Herceptin group. Post-baseline, the only Nab-positive sample were observed at week 6 (3 samples in Herceptin), and week 36 (1 sample in MYL-1401O).

The overall ADA and NAb rate was calculated using a conservative approach, which considers all patients who tested positive for ADA or NAb at least once at any time point post-baseline regardless of the ADA result at baseline (Table 46).

Table 42: Summary of Overall ADA and NAb Rate (Includes Part 1 and 2 Through Week 48): Safety Population

	MYL-1401O (N = 247)	Herceptin (N = 246)
	n (%)	n (%)
Overall ADA rate	9 (3.9)	10 (4.4)
Overall NAb rate	1 (0.4)	3 (1.3)

ADA: antidrug antibody, NAb: neutralizing antibody
Percentages were based on the number of patients in the safety population (N) with non-missing post-baseline samples available in each arm, which include 228 patients in the MYL-1401O arm and 227 patients in the Herceptin arm.
Note, post-baseline includes only on treatment samples until Week 48 and excludes EOT/EOS samples.
Source: Table 14.3.4.1.4.1.1b, Table 14.3.4.1.4.6b

Analysis of patients excluding ADA baseline-positive patients

Given that 6-9% of patients (36/477, Table 45) had pre-existing antibodies against the test and reference product prior to study entry, an additional analysis that excluded these subjects was conducted. Table 47 presents a summary of the treatment-induced ADA-positive samples by visit and treatment.

Table 43: Summary of ADA Results by Visit and Treatment Excluding ADA Baseline-Positive Patients (Includes Part 1 and 2 Through Week 48): Safety Population

Visit			MYL-1401O (N = 223)	Herceptin (N = 224)
Cycle 3 Week 6	ADA results available	n	192	180
	ADA positive	n (%)	3 (1.6)	1 (0.6)
Cycle 5 Week 12	ADA results available	n	206	186
	ADA positive	n (%)	1 (0.5)	1 (0.5)
Cycle 7 Week 18	ADA results available	n	184	158
	ADA positive	n (%)	1 (0.5)	0
Cycle 9 Week 24	ADA results available	n	174	152
	ADA positive	n (%)	2 (1.1)	1 (0.7)
Cycle 13 Week 36 [a]	ADA results available	n	137	119
	ADA positive	n (%)	2 (1.5)	1 (0.8)
Cycle 17 Week 48[a,b]	ADA results available	n	101	83
	ADA positive	n	0	0
At least one positive ADA sample post-baseline[c,d]		n	4 (1.7)	4 (1.8)

ADA: antidrug antibody, n: number of patients
Percentages were based on the number of patients in the safety population (N) with available ADA post-baseline results.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Cycle 17 Week 48 data include results occurring after the Week 48 cut-off.
[a] Five patients at Cycle 13 Week 36 (3 in the MYL-1401O and 2 in the Herceptin arm) and 1 patient at Cycle 17 Week 48 in the Herceptin arm continued to receive taxane, but these patients are included in Cycle 13 Week 36 and Cycle 17 Week 48 of Part 2.
[b] Cycle 17 Week 48 data include results occurring after the Week 48 cut-off.
[c] Post-baseline includes only on treatment samples until Week 48 and excludes EOT/EOS samples.
[d] The denominator for this calculation is the number of non-missing post-baseline samples available in each arm, which include 229 patients in the MYL-1401O arm and 227 patients in the Herceptin arm.
Source: Table 14.3.4.1.4.9b

The treatment-induced ADA rate was calculated based on baseline ADA-negative patients (or patients with no baseline results) who tested positive for ADA at least once at any time point post-baseline. The treatment-induced NAb rate was calculated based on baseline Nab negative patients (or patients with no baseline results) who tested positive for NAb at least once at any time point post-baseline. For the treatment-induced NAb rate also patients were included who were ADA-positive (but NAb-negative) at baseline. These results are presented in Table 48. The Nab positivity was isolated and, in this small group of patients, none of them had positivity at more than one post-baseline time-point.

Table 44: Summary of Treatment-Induced ADA and NAb Rate (Includes Part 1 and 2 Through Week 48): Safety Population

	MYL-1401O (N = 233)	Herceptin (N = 224)
Visit	**n (%)**	**n (%)**
Treatment-induced ADA rate	4 (1.7)	4 (1.8)
Treatment-induced NAb rate	1 (0.4)	2 (0.9)

ADA: antidrug antibody, NAb: neutralizing antibody
Percentages were based on the number of patients in the safety population (N) with available ADA post-baseline results and include 229 patients in the MYL-1401O arm and 227 patients in the Herceptin arm.
Note, post-baseline includes only on treatment samples until Week 48 and excludes EOT/EOS samples.
For the treatment-induced NAb rate also patients were included who were ADA-positive but NAb-negative at baseline.
Source: Table 14.3.4.1.4.9b, Listing 16.2.8.1.11b

ADA titers

ADA titers across the study are presented in Table 49.

Table 45: Summary of ADA Titers by Visit and Treatment (Includes Part 1 and 2 through Week 48): Safety Population

Visit	Statistic	MYL-1401O (N = 247)	Herceptin (N = 246)
Baseline (Cycle 1 Week 0)	N	14	22
	Mean (SD)	2.786 (1.9402)	2.482 (1.5349)
	Median	2.250	2.300
	Min, Max	1.00, 7.10	1.00, 6.90
Cycle 3 Week 6	N	5	6
	Mean (SD)	1.960 (0.6768)	2.800 (1.3609)
	Median	1.900	2.600
	Min, Max	1.40, 3.10	1.70, 5.40
Cycle 5 Week 12	N	2	2
	Mean (SD)	6.955 (0.6435)	1.050 (0.0707)
	Median	6.955	1.050
	Min, Max	6.50, 7.41	1.00, 1.10
Cycle 7 Week 18	N	2	1
	Mean (SD)	3.800 (2.5456)	1.000 (NA)
	Median	3.800	1.000
	Min, Max	2.00, 5.60	1.00, 1.00
Cycle 9 Week 24	N	2	1
	Mean (SD)	4.550 (5.0205)	5.500 (NA)
	Median	4.550	5.500
	Min, Max	1.00, 8.10	5.50, 5.50
Cycle 13 Week 36	N	3	1
	Mean (SD)	7.833 (5.9231)	1.000 (NA)
	Median	11.000	1.000
	Min, Max	1.00, 11.50	1.00, 1.00
Cycle 17 Week 48	N	0	0

Max: maximum, Min: minimum, N: number of patient in treatment group, n: number of patients with available data, SD: standard deviation
Baseline was Cycle 1 Day 1, prior to first dose of study treatment.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
Source: Table 14.3.4.1.4.11b

Overall, ADA titers were low in both arms across all time points. The highest pre-dose ADA titers obtained were 7.1 and 6.9, respectively, in the MYL-1401O and Herceptin arms. The highest post-dose ADA titers obtained were 11.5 and 5.5, respectively, in the MYL-1401O and Herceptin arms.

During the treatment with MYL-14010, 6 patients had ADA-positive samples. From them, only 2 were positive at baseline. Three were still positive at week 36 (with 1 Nab-positive sample), but none at week 48 presented an increase of ADA titer during the treatment.

During the treatment with Herceptin, more patients had ADA-positive samples (9) than with MYL-1401O. From them, 6 were positive at baseline. Only 1 was still positive at week 36 (Nab-negative sample), and none at week 48. No sample with continued increase of ADA-titer is seen.

Administration-related reactions by ADA status

A summary of administration-related reactions (ARRs) by ADA status is presented in Table 50.

Table 46: Summary of Administration-related Reactions by ADA Status: Safety Population

	MYL-1401O (N = 247)	Herceptin (N = 246)	Overall (N = 493)
Visit	**n (%)**	**n (%)**	**n (%)**
ADA-negative post-baseline, n[a]	219	217	436
Patients with 1 or more ARR	20 (9.1)	13 (6.0)	33 (7.6)
ADA-positive post-baseline, n[b]	9	10	19
Patients with 1 or more ARR	1 (11.1)	1 (10.0)	2 (10.5)

ADA: antidrug antibody, ARR: administration-related reactions
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
Post-baseline includes only treatment samples until Week 48 and excludes EOT/EOS samples.
[a] ADA-negative post-baseline group included only patients who were ADA-negative at all time points post-baseline, irrespective of their ADA status at baseline or with no baseline ADA result..
[b] ADA-positive post-baseline group included patients having at least 1 positive ADA result at any time point post-baseline irrespective of their ADA results at baseline or with no baseline ADA result.
Source: Table 14.3.4.1.4.4.1b

Of the 19 patients who were ADA-positive post-baseline (irrespectively of ADA results at baseline: 9 in MYL-1401O and 10 in Herceptin), only 1 patient each in the MYL-1401O and Herceptin arm experienced 1 or more ARRs. Furthermore, of the patients experiencing ARR, only 4.8% (1/21) in the MYL-1401O and 7.1% (1/14) in Herceptin arm were ADA-positive indicating that most patients experiencing ARR were ADA negative.

Study MYL-Her-1001

The immunogenicity of MYL-1401O and Herceptin was assessed by evaluating the incidence and the ADA levels in blood samples collected at baseline (preinfusion, at 0 hours) and at 2 weeks and 10 weeks during each treatment period. All post-baseline sera collected for ADA in this study were negative, and there was no indication of immunogenicity in this population of healthy volunteers after administration of MYL-1401O or Herceptin.

Study MYL-Her-1002

The occurrence of ADA-positive samples was low for each of the drug products administered and, based on the titer, they were then re-classified as ADA-negative subjects. There were no instances of either treatment-induced or treatment-boosted ADA-positive subjects in the study.

Study BM200 CT3-001-11

Immunogenicity to trastuzumab was assessed in both arms using assays to detect anti-drug antibodies (ADA). The presence of antibody, as well as antibody titre, was measured. Blood samples were collected at baseline, at 12 weeks and at the end of the trial (24 weeks) (Table 51 below).

Table 47: Immunogenicity Incidence of Positive Anti-Drug Antibody by treatment group in safety population (Confirmatory Assay; Study BM200-CT3-001-11)

	Bmab-200 N=66 [n(%)]	Herceptin® N=68 [n(%)]
Baseline	4(6.06%)	4(5.88 %)
Week 12	2(3.03%)	0(0.00%)
Week 24	1(1.52%)	0(0.00%)

At baseline, 4 patients were seropositive in each arm. However, in the Herceptin arm, all these patients became sero-negative while on treatment. Since all patients were treatment-naïve for Herceptin, it is likely that the baseline results represent false positives resulting from assay interference.

Two patients (3.03%) in the Bmab-200 arm tested positive for ADA at 12 weeks and only 1 (1.52%) at week 24. For this patient, the titres dropped from week 12 to week 24 (4 fold to 1 fold) and can be considered weakly positive for ADA; hence these data are of limited clinical significance. In corroboration, these two ADA-positive patients did not experience any infusion reactions over the duration of the trial.

The clinical trial was not powered to detect differences in comparative immunogenicity between Herceptin and Bmab-200. Overall the ADA positivity rate (3.03%, 2/66 subjects) observed for the Bmab-200 arm was similar to the rate reported for Herceptin (3.4%, 10/295 subjects) (Ismael et al, 2012).

No autoimmune adverse events (lupus, demyelinating disorders) were reported in the clinical program.

Discontinuation due to adverse events

Study MYL-Her-3001

Overall, in MYL-Her-3001 (trough week 48), the incidence of TEAEs leading to study drug discontinuation was slightly higher in the Herceptin arm (27 events in 16 patients, 6.5%) than in the MYL-1401O arm (14 events in 10 patients, 4%) . From them, there were 4 treatment-related TEAE in 4 patients (1.6%) in MYL-1501O and 4 events in 3 patients (1.2%) in Herceptin.

Table 48: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Safety Population; Study MYL-Her-3001– parts 1 & 2, data from CSR MYL-Her-3001 Table 14.3.2.6.1b)

System Organ Class	MYL-1401O + Taxane (N=247)		Herceptin + Taxane (N=246)	
	n (%)	Events	n (%)	Events
Patients with ≥1 TEAE leading to discontinuation	10 (4.0)	14	16 (6.5)	27
Blood and lymphatic system disorders	2 (0.8)	2	1 (0.4)	3
Cardiac disorders	3 (1.2)	3	1 (0.4)	1
Gastrointestinal disorders	0	0	1 (0.4)	1
General disorders and administration site conditions	1 (0.4)	1	0	0
Hepatobiliary disorders	0	0	1 (0.4)	1
Infections and infestations	2 (0.8)	3	2 (0.8)	3
Injury, poisoning and procedural complications	0	0	1 (0.4)	1
Investigations (ejection fraction decreased)	2 (0.8)	2	2 (0.8)	2
Metabolism and nutrition disorders	1 (1.4)	1	1 (0.4)	2
Nervous system disorders	0	0	6 (2.4)	6
Respiratory, thoracic and mediastinal disorders	2 (0.8)	2	6 (2.4)	7

Only 5 TEAEs resulted in treatment discontinuation for at least 2 patients each: cardiac failure (3 patients in the MYL-1401O arm), ejection fraction decreased (2 patients in the MYL-1401O arm and 1 patient in the Herceptin arm), dizziness, pneumonitis and pneumonia (2 patients each in the Herceptin arm), dyspnea (1 patient in the MYL-1401O arm and 2 patients in the Herceptin arm), and respiratory failure (1 patient in each arm).

In the studies MYL-Her-1001 and MYL-Her-1002, no serious TEAEs were reported, and no subjects were withdrawn from the study due to TEAEs.

In the Study BM200 CT3-001-11, excluding AEs related to disease progression, 1 TEAE led to withdrawal from the study in the Herceptin arm: a moderate TEAE of ejection fraction decreased, which was considered to be definitely related to the drug.

Interruption

In MYL-Her-3001, over 48 weeks, 27 events leading to interruption of study drug were reported in 23 patients. The incidence of these TEAEs was similar between treatment arms, 12 patients (4.9%) in the MYL-1401O arm and 11 patients (4.5%) in the Herceptin arm. Of these, 21 events in 19 patients were considered treatment related, 11 patients (4.5%) in the MYL-1401O arm and 8 patients (3.3%) in the Herceptin arm. The only related TEAEs occurring in more than 1 patient were hypersensitivity (2 patients in the MYL-1401O arm and 1 patient in the Herceptin arm) and infusion related reaction (5 patients in the MYL-1401O arm and 4 patients in the Herceptin arm).

Post marketing experience

Biocon Limited (co-development partner of Mylan) received marketing authorisation for another formulation in India. This formulation has been available on the Indian market since January 2014. Sales data indicate a patient exposure of more than 5000-patient treatment courses since launch of the product.

Safety information received from the post approval exposure is being continuously evaluated and analysed for inclusion in the Periodic Safety Update Reports as per local regulations. Periodic review of this safety data does not indicate any new safety signals from the post-approval experience of more than 2 years. None of the articles screened during the worldwide literature review contained safety information indicating a newly identified or potential risk with trastuzumab.

2.6.1. Discussion on clinical safety

The main comparative data in terms of safety were generated in the pivotal study MYL-Her-3001 in patients with HER2-positive metastatic breast cancer involving 247 patients exposed to MYL-1401O, out of whom 185 patients completed Part 1 of the study (MYL-1401O + taxanes, docetaxel or paclitaxel, for 24 weeks), and 116 patients completed Part 2 (MYL-1401O monotherapy: 24 to 48 weeks). A comparable number of patients was exposed to EU Herceptin.

Additionally, 63 healthy volunteers received one dose of MYL-1401O in 2 PK studies (MYL-Her-1001 and MYL-Her-1002) which can only contribute to evaluation of short term safety. Moreover, a fourth supportive clinical study (BM200-CT3-001-11) was conducted with another formulation. 66 patients were exposed to Bmab-200 and 68 to EU Herceptin.

The size of the safety database is considered appropriate to evaluate the general safety profile of MYL-Her-3001. Nevertheless, there are inherent limitations with size of the biosimilar product safety database for the purpose of characterisation and evaluation of rare events of special interest.

In terms of treatment duration, safety data through 48 weeks (Parts 1 & 2) of Study MYL-Her-3001 were provided. It is considered that the current safety database is sufficient to allow for adequate assessment of the safety of MYL-1401O compared to that of the reference product.

In part 1, given concomitant administration with chemotherapy, the sensitivity for detecting potential differences in safety profiles may be diminished, but this setting is nevertheless suitable for initial comparability exercise provided that the most homogeneous population of patients is enrolled. In Part 2 of the study (24 to 48 weeks), after completing a minimum of 8 cycles of treatment in Part 1 of the study, all patients with at least stable disease continue with the trastuzumab product that they were originally allocated to as a single agent until disease progression or unacceptable toxicity. Since Herceptin and Ogivri will be used as monotherapy, part 2 comparative analysis without concomitant chemotherapy backbone is informative.

In summary, as expected for comparative studies, in MYL-Her-1001 and MYL-Her-1002, the cumulative dose of MYL-1401O is very close to the cumulative dose of Herceptin. In BM200 CT3-001-11, the extent of exposure (to trastuzumab and docetaxel) was similar between the 2 treatment groups (Bmab-200 and Herceptin).

In MYL-Her-3001, the cumulative dose of trastuzumab in Part 1 of the study (24 weeks) was similar in both arms, but over a 48 week treatment duration (parts 1 & 2), the cumulative dose of MYL-1401O was slightly higher than Herceptin (median of 2 trastuzumab cycles more), and it can be deduced that the difference of exposure occurred during part 2 (monotherapy). As discussed below, the safety profile during Part 2 of the study

was similar in both treatment arms, therefore, the difference in the cumulative dose does not seem to have a specific effect on the safety profile.

In part 2, the safety population included all patients who entered in part 2 and consisted of 342 patients (179 in the MYL-1401O arm and 163 in the Herceptin arm). From them, 32 patients (15 patients in MYL-1401O and 17 in Herceptin) entered Part 2 and continued using taxane before they switched to trastuzumab monotherapy during Part 2. Continuation of combination therapy and switch to monotherapy, based on potential benefit for the patient, was at the discretion of the Investigator.

With regards to taxane use through 48 weeks, majority of the patients (~88%) received docetaxel and the cumulative dose of docetaxel was similar in both arms. In the paclitaxel group (~12% patients), the overall exposure to paclitaxel was higher in the MYL-1401O arm compared to Herceptin arm. As discussed below, similarity has been shown in terms of safety between the biosimilar and the originator through 48 weeks, with some observed differences. As these differences, have not been seen in part 2 (monotherapy), this higher exposure to paclitaxel in MYL-1401O compared to Herceptin might play a role.

At each cycle (between 1 and 17 cycles), slightly more patients were treated in the MYL-1401O arm than in the Herceptin arm. The difference is globally increasing with the number of cycles (to around 53% patients in the MYL-1401O arm compared to 47% in the Herceptin arm at cycle 17). As the safety profile is similar during part 2 (monotherapy) between the 2 arms with a low number of TEAE, this difference should not impact the comparability exercise.

Similarity has been observed in terms of safety between the biosimilar and the originator at longer term (MYL-Her-3001 48 weeks). Overall, MYL-1401O and Herceptin safety profiles, when administered with a taxane as first-line therapy to patients with HER2+ MBC, and when given as monotherapy, were similar without any new safety concerns observed with MYL-1401O. Nevertheless, some differences have been observed. In the Myl-1401O arm compared to in the Herceptin arm, there were slightly more TEAE (2639 and 2376 events, respectively) but similar number of patients with TEAE: 98% and 97.2%, respectively. There were few noted differences (> 5%) in the incidence of TEAEs between the treatment arms, including nausea, asthenia, arthralgia, and upper respiratory tract infection in the MYL-1401O arm compared to the Herceptin arm. Moreover, in the MYL-1401O arm compared to in the Herceptin arm, there were more treatment-related TEAE (356 and 273 events, respectively) and more patients with treatment-related TEAE; 103 patients (41.7%) and 88 patients (35.8%), respectively. The reason of these slight differences is unclear, whether these should be attributed to differences in underlying properties of the biologics being evaluated or to chance finding, especially in studies that are not powered to evaluate statistically meaningful differences in AEs. It could be related to a different excipient used or the slight difference in exposure of paclitaxel (higher in MYL-1401O than in Herceptin). However, as the safety profile is similar during part 2 (monotherapy) between the 2 arms with a low number of TEAE, the comparability is globally established between MYL-1401O and Herceptin.

In part 1, the incidence of TEAEs leading to study drug discontinuation was the same in the MYL-1401O arm and the Herceptin arm: 7 patients (2.8%, 10 events) and 7 patients (2.8%, 17 events), respectively. From them, there were 3 treatment-related TEAE in 3 patients (1.2%) in MYL-1401O and 2 treatment-related TEAE in 1 patient (0.4%) in Herceptin. In Part 2, 3 patients (1.7%, 4 events) in the MYL-1401O arm and 8 patients (4.9%, 9 events) in the Herceptin arm experienced TEAEs leading to study drug discontinuation. None of the TEAEs leading to discontinuation occurred in more than 1 patient each. Three patients experienced related TEAEs leading to study drug discontinuation as follows: 1 patient discontinued because of cardiac failure (MYL-1401O arm) and 2 patients discontinued in Herceptin (cardiomyopathy and pneumonitis).

During monotherapy treatment (part 2), the incidence of TEAEs was overall similar between treatment arms (MYL-1401O and Herceptin). Of the total 5015 TEAEs through Week 48, only 513 TEAEs had on onset while patients were receiving trastuzumab monotherapy (part 2: 257 in MYL-1401O arm and 256 in Herceptin arm), clearly suggesting that most of the TEAE seen over 48 weeks, were driven by data until Week 24 (part 1), and most likely attributable to the background taxane therapy.

Although the incidence of significant TEAEs of cardiac toxicity was low and similar in each arm (13 events in MYL-1401O, and 10 events in Herceptin), there were more cardiac failure in MYL-1401O (6 events in 6 patients – 2.4%, 3 events were Grade 1 or 2 and 3 events were Grade 3 or greater) than in Herceptin (1 event in 1 patient – 0.4%), and more Grade 3 or greater TEAE in the MYL-1401O arm (6 events: 3 cardiac failure, 1 carditis, 2 left ventricular dysfunction; including 2 fatal cases, one of them in the monotherapy part) than in the Herceptin arm (1 left ventricular dysfunction). Moreover, there were 3 SAE in the MYL-1401O arm (2 cardiac failure, and 1 carditis), and none in the Herceptin arm. And there were 3 patients in MYL-1401O who discontinued treatment because of cardiac failure (none in Herceptin). The majority of cardiac toxicity TEAEs were considered related to study drug in both arms: 8 (out of 12 patients) related TEAE in MYL-1401O (including 4 cardiac failure), and 6 (out of 10 patients) in Herceptin. In addition, there were 12 patients (4.9%, 16 events) with ejection fraction decreased in MYL-1401O, compared to 7 patients (2.8%, 8 events) in Herceptin. However, the incidence of new onset myocardial dysfunction was similar in both treatment arms with 10 patients (4.0%) in the MYL-1401O arm and 8 patients (3.3%) in the Herceptin arm having at least 1 post-treatment value of <50%. Of these 18 patients, 16 had LVEF of <50% and at least 10 percentage point reduction compared to baseline with a similar incidence (9 patients (3.6%) in the MYL-1401O arm and 7 patients (2.8%) in the Herceptin arm). These data are consistent with historical data from prior studies with Herceptin.

For the comparability exercise trough 48 weeks, in patients with previous exposure to anthracyclines, or in patients without previous exposure to anthracyclines, although some isolated statistically significant differences of frequencies have been noticed at PT level between treatment groups, the TEAE frequencies were mostly similar (no SOC with statistically significant differences for the common TEAE) between arms (MYL-1401O and Herceptin).

Over 24 weeks (part 1), in patients co-treated with paclitaxel, or in patients co-treated with docetaxel, although some isolated statistically significant differences of frequencies have been noticed at PT level between treatment groups, the TEAE frequencies were mostly similar (no SOC with statistically significant differences for the common TEAE) between arms (MYL-1401O and Herceptin).

Over 48 weeks (parts 1 & 2), in patients co-treated with paclitaxel, or in patients co-treated with docetaxel, the TEAE frequencies were very closed to the frequencies observed over 24 weeks (with a similar distribution between arms with some isolated statistically significant differences). As seen for the overall population (treated with paclitaxel or docetaxel), it can be conclude that the majority of the observed TEAE over 48 weeks (with paclitaxel or docetaxel) were already observed during the first 24 weeks (part 1).

In MYL-Her-3001, statistically significant differences between treatment groups in the frequencies of some TEAEs were observed for patients < 65 years of age through 24 and 48 weeks of treatment. These differences were considered attributable to co-treatment with chemotherapy, concomitant medications, and comorbidities, which is a plausible explanation. Such differences were not observed in the older age group or in the monotherapy setting.

As part of the immunogenicity assessment of MYL-1401O, samples were tested for the presence of ADA and NAb through Week 48 in MYL-Her-3001. The number of ADA-positive patients, which was 14 samples in MYL-1401O and 22 samples in Herceptin at baseline, declined over time. A similar baseline ADA-positive rate was observed

in previous clinical studies with the originator product. Baseline positivity may be due to presence of pre-existing antibodies or ADA assay interference with high levels of extracellular domain of HER2 receptor (HER2 ECD).

The maximum proportion of ADA-positive patients post-baseline was seen at Week 6 and was 5 samples in MYL-1401O and 6 samples in Herceptin. At the Week 48 time-point, none of the patients in either arms were ADA-positive.

At baseline, of the patients who were ADA positive, NAbs were detected in 1 patient in the MYL-1401O group and in 2 patients in the Herceptin group. Post-baseline, the only Nab-positive sample were observed at week 3 (3 samples in Herceptin), and week 38 (1 sample in MYL-1401O).

Using a conservative approach, which considers all patients who tested positive for ADA or NAb at least once at any time point post-baseline regardless of the ADA result at baseline, the overall ADA rate was 9 patients (3.9%) in the MYL-1401O arm (out of 228 patients with non-missing post-baseline samples available) and 10 patients (4.4%) in the Herceptin arm (out of 227 patients with non-missing post-baseline samples available). The overall NAb rate was very low with 1 patient (0.4%) and 3 patients (1.3%) in MYL-1401O and Herceptin arms respectively.

The treatment-induced ADA rate, excluding patients who were ADA-positive at baseline, in the MYL-1401O arm was 1.7% (4 patients) and 1.8% (4 patients) in the Herceptin arm. The treatment-induced NAb rate, excluding patients who were NAb-positive at baseline, was 0.4% (1 patient) and 0.9 % (2 patients) in the MYL-1401O and Herceptin arms respectively.

Overall, ADA titers were low in both arms across all time points. The highest pre-dose ADA titers obtained were 7.1 and 6.9, respectively, in the MYL-1401O and Herceptin arms. The highest post-dose ADA titers obtained were 11.5 and 5.5, respectively, in the MYL-1401O and Herceptin arms.

Because of the low number of ADA-positive samples, there are no consistent trends that would be of relevance by comparing immunogenicity in monotherapy (part 2) to immunogenicity in treatment combined with taxanes (part 1), or by comparing the evolution of the immunogenicity (ADA- and Nab-positive samples and ADA titers) between arms (MYL-1401O and Herceptin).

Finally, the analysis of administration-related reactions (ARRs) by ADA status indicates that there is no specific correlation between the 2 parameters.

According to the HannaH study (Ismael et al. 2012, Hegg et al., 2012), the percentage of ADA was 3.4% (10/295 patients) after intravenous use regardless of baseline ADA status in patients with early breast cancer when trastuzumab was used in combination of docetaxel. Of the patients who had confirmed positive ADA responses to trastuzumab at baseline, NAbs were detected in one patient. Therefore, it is not unexpected to have NAb-positive results at baseline. Of note, in the neoadjuvant-adjuvant EBC treatment setting, 8.1 % (24/296) of patients treated with trastuzumab intravenous developed antibodies against trastuzumab (regardless of antibody presence at baseline). NAb were detected in post-baseline samples in 2 of 24 trastuzumab intravenous patients.

In summary, through 48 weeks, the incidence of antidrug antibodies against MYL-1401O and Herceptin was very low and consistent with literature. These antibodies were transient and the titers were low. Also the incidence of neutralizing antibodies was very low and similar in both arms. Overall, the treatment-emergent immune response was similar between the 2 treatment arms. No association was observed between the presence of ADAs and ARRs.

The immunoassays to measure ADA and Nab, their validation, and the relation between ADA and the trastuzumab clearance are discussed in the section on pharmacokinetics.

The applicant discussed the current knowledge on the safety profile of the excipient used in the final formulation, Macrogol 3350, when included in IV formulations at clinical relevant doses and the observed hypersensitivity reactions. While initially considered as immunologically safe, macrogols, have been increasingly associated with cases of mild to life-threatening immediate-type hypersensitivity (Wenande and Garvey, 2016). Due to a lack of suspicion towards excipients, awareness of PEGs allergenic potential is minimal leading to unrecognised potential risk of life-threatening reactions and misdiagnosis. In recent years more report appeared in literature, including immediate type reactions to macrogol 3350 (Wylon et al, 2016). Two cases of a reaction after receiving IM injections of medroxyprogesterone (Depo-Provera), containing as excipients macrogol 3350 and polysorbate have been related to previous treatment with a drug conjugated with PEG. These two subjects reported serious AEs (SAEs) that were assessed as moderate in severity (Longo et al, 2014). Both SAEs were categorized as immune system disorders of anaphylactic reaction: urticaria for one subject and hypersensitivity (an allergic reaction) for another subject. Concerning the mechanisms of reactions mediated by PEGs, Ig-E/M/G mediated mechanisms and complement activation have been proposed (Schellekens e al, 2013; Wylon et al, 2016; Hamad et al, 2008). Results of the study Hamad et al (2008) provides a plausible explanation to the previously reported unexplained anaphylaxis or the referred cardiovascular collapse in sensitive animals that have received medicines containing high levels of PEG as solubilizer/carrier. The Applicant presented preclinical, clinical, toxicity and safety data with Macrogol as well as infusion-related data from MYL-1401O. These data revealed no major difference in hypersensitivity events or infusion related reactions between MYL-1401O and Herceptin in the clinical program. The CHMP concludes that the information in sections 4.3, 4.4 and 4.8 of the Herceptin SmPC are sufficient to address the potential risks associated with the administration of MYL-1401O.

The dose of sorbitol used as an excipient will be less than 0.5 g and thus limiting the potential risk of toxicity. The intended use of Ogivri only in adult patients suggests that most of the patients will be aware of their medical history of hereditary fructose intolerance. The applicant also included a warning in the SmPC for patients with the rare genetic disorder of hereditary fructose intolerance (HFI), in accordance with the guideline for excipients labelling.

The applicant claimed the same therapeutic indications for the biosimilar as granted for Herceptin for intravenous administration in the EU. Considering Herceptin is also marketed for subcutaneous administration, adequate risk minimisation measures to avoid the potential route of administration error have been included in the SmPC section 4.2.

From the safety database of trastuzumab all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics of Ogivri which follows the one of Herceptin. Furthermore, the RMP of Ogivri adequately addresses the safety concerns of trastuzumab, in line with Herceptin.

2.6.2. Conclusions on the clinical safety

The data up to 48 weeks in the pivotal trial MYL-Her-3001 indicate a similar safety profile between biosimilar candidate MYL-1401O and reference product Herceptin despite a slightly higher number of patients with treatment-related TEAE in the MYL-1401O arm (103 patients [41.7%] vs 88 patients [35.8%]). Most of the TEAE seen over 48 weeks, were driven by data until Week 24 (part 1), and most likely attributable to the background taxane therapy. The observed AE and SAE were as expected for trastuzumab and chemotherapy combination.

The results indicated that there was no clinically meaningful difference between MYL-1401O and Herceptin in terms of immunogenicity and that these data are consistent with the literature (low immunogenic potential of the innovator product).

In conclusion, the treatment of MBC patients with MYL-1401O is well tolerated (in combination with taxanes or in monotherapy), with a low immunogenicity, and no new or unexpected safety signals were observed compared to Herceptin-EU. Therefore, the long term one-year safety, immunogenicity, and tolerability of MYL-1401O and Herceptin are comparable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Administration-related reactions • Oligohydramnios
Important potential risks	None
Missing information	• Safety of docetaxel 75 mg/m^2 versus 100 mg/m^2

Pharmacovigilance plan

There is no planned or ongoing additional study in the pharmacovigilance plan.

Routine pharmacovigilance activities are sufficient to address the safety concerns of this medicinal product.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac dysfunction	Routine risk minimization measures: SmPC Sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities (including guided questionnaire). The Applicant of Ogivri® will closely follow the conclusions of ongoing PSUSA assessment for Herceptin and will implement additional measures for this safety concern (cardiac toxicity) as needed.
Administration-related reactions	Routine risk minimization measures: SmPC Sections: 4.2, 4.3, 4.4 and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities (including guided questionnaire).
Oligohydramnios	Routine risk minimization measures: SmPC Sections: 4.2 and 4.6. Additional risk minimisation measures: None.	Routine pharmacovigilance activities (including guided questionnaire). The Applicant commits to perform follow-up activities of all pregnancy cases with its product globally to collect additional information on women exposed to Ogivri® during pregnancy. With regards to performing follow-up activities of all pregnancy cases exposed to Ogivri® within seven months prior to conception, the MAH foresees difficulties in identifying the patients but has introduced this time frame in the guided questionnaire and will address it where possible.
Safety of docetaxel 75 mg/m^2 versus 100 mg/m^2	Routine risk minimization measures: SmPC Section: 4.2.	Routine pharmacovigilance, including comparative presentation of safety data captured in the global safety database in Periodic Benefit-Risk Evaluation Reports.
	Additional risk minimisation measures: None.	

Routine risk minimisation measures are considered sufficient to minimise the safety concerns of this medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ogivri (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

Ogivri is developed as a biosimilar to Herceptin. The approval is sought for intravenous use in all approved indications of the reference product: metastatic breast cancer, early breast cancer and metastatic gastric cancer (see SmPC).

In support of the application, the applicant provided results from an extensive comparability analysis to demonstrate biosimilarity to the reference product Herceptin. Comprehensive analyses of the proposed biosimilar and reference medicinal product were carried out using sensitive and orthogonal methods covering biological activity, primary structure, higher order structure, product-related substances and purity/impurities.

Data were evaluated against pre-defined similarity assessment criteria. The biological activity was evaluated by a comprehensive set of functional assays and binding studies addressing both Fab and Fc-functions of the molecule.

The non-clinical studies submitted consisted of *in vitro* pharmacodynamic studies, a single-dose pharmacokinetic (PK) study in cynomolgus monkeys, and a combined 28-day repeat-dose toxicokinetic study in cynomolgus monkeys.

To support similarity from the clinical perspective, the Applicant submitted three pivotal studies.

- Study MYL-Her-1001 was a single-centre, single-dose, 2-period, randomized, double-blind, crossover study in healthy male volunteers. The subjects either received the MYL-1401O or EU-approved Herceptin in Period I and an alternative treatment in Period II. The primary objective of Study MYL-Her-1001 was to confirm bioequivalence between MYL-1401O and Herceptin administered at a dose of 8 mg/kg, administered as a single intravenous (IV) infusion over 90 minutes in healthy male volunteers.
- Study MYL-Her-1002 was a single-centre, single-dose, randomized, double-blind, 3- arm parallel-group study investigating the bioequivalence of MYL-1401O versus EU- approved Herceptin and US-licensed Herceptin as well as EU-approved Herceptin versus US-licensed Herceptin after 8 mg/kg as single dose administered as IV infusion over 90 minutes in healthy male subjects under fasting conditions.
- Study MYL-Her-3001 is a multicenter, double-blind, randomized, parallel-group, pivotal confirmatory study to compare the efficacy and safety of MYL-1401O plus docetaxel or paclitaxel (i.e., taxane) versus EU-approved Herceptin plus a taxane in patients with HER2-positive metastatic breast cancer (MBC; documented by central laboratory results) with continuation (part 2 of the study) of single-agent MYL-1401O versus Herceptin for patients who had at least stable disease in order to evaluate continued safety and immunogenicity.

3.2. Results supporting biosimilarity

From the quality perspective, the data provided indicate that Ogivri can be considered as biosimilar to EU-approved Herceptin at the quality level. The minor differences observed have been appropriately justified.

From a non-clinical perspective, the *in vitro* assays performed on an appropriate number of batches have shown similarity between MYL-1401O and the EU Herceptin reference product in terms of HER 2 binding, inhibition of proliferation, ADCC, C1q binding, Fc receptor binding.

As for pharmacokinetic aspects, the submitted primary PK analysis showed PK comparability of the test and reference products at the dose of 8 mg/kg body weight given that the 90% confidence intervals for the ratios of both primary parameters (Cmax and AUC0-t/AUC0-∞) were well contained within the standard bioequivalence interval of 0.80–1.25 in studies Myl-Her-1001 and Myl-Her-1002. In addition, the terminal half-life, Vz and CL parameters were also similar across the groups.

Pharmacodynamic findings support the available data for the overall comparability exercise.

From the clinical efficacy perspective, the analysis of ORR at 24 weeks in the phase III study MYL-Her-3001 in metastatic breast cancer patients, showed that the differences in the response rates according to RECIST 1.1 criteria (69.6% and 64.0% MYL-1401O and Herceptin respectively) were within the pre-defined equivalence margin [-15; +15] (5.5% with a 95% CI of -3.08%, 14.04%) based on central tumour evaluation.

The results are considered robust, as the investigator assessments were in line with the main analysis. Various sensitivity analyses (subgroup ORR analyses by stratification factor, replication of analysis in ITT2 and PP populations) confirmed the results of the primary analyses.

Secondary endpoints TTP, PFS, OS and DR were assessed in the Part 1 and Part 2. Analyses of these endpoints in Part 2 (after 48 weeks of treatment in total) confirmed the similarity outcomes observed at the Week 24 endpoint. Tumour progression occurred in 41.3% and 43.0% of patients treated with Ogivri and Herceptin, respectively (p=0.684), 55.7% and 55.3% did not experience tumour progression or death (PFS, p=0.842) whereas 89.1% and 85.1% survived until 48 weeks (OS, p=0.439), respectively. Additionally, 42.4% of MYL-1401O subjects compared to 44.5% of Herceptin subjects (p = 0.790) with objective response had tumour progression or died before the 48 week cut-off (DR). These findings were also confirmed through sensitivity analyses.

Safety and immunogenicity data were provided from the clinical studies in patients with metastatic breast cancer and healthy volunteers. Due to the vast experience gained from the reference medicinal product Herceptin, the safety profile is well known. Overall, treatment with MYL-1401O was well tolerated during 48 weeks and no new or unexpected safety signals were observed (mostly in line with Herceptin safety profile + taxanes).

In MYL-Her-3001, at 48 weeks, the safety profiles were comparable between the 2 arms (MYL-1401O and Herceptin), with as similar number of patients with at least 1 grade 3 or higher TEAE, with serious TEAE, with TEAE leading to interruption of trastuzumab or to discontinuation of the study.

The incidence of SAEs was similar in the treatment groups. The majority reported SAEs were in the SOC of Blood and lymphatic system disorders, and the most frequently reported PT overall was neutropenia. The majority of SAEs were considered unrelated to study drug. Nevertheless, more SAEs in the MYL-1401O arm than in the Herceptin arm were attributed by the investigators to the study drug. Most SAEs that began in Part 1 resolved or resolved with sequelae, except for those that were fatal. Two SUSARs were reported in Part 1.

Through Week 48, 10 patients experienced fatal TEAEs, 6 in the MYL-1401O arm (2.4%, 8 events, 6 deaths during part 1 and 2 deaths during monotherapy: 1 dyspnea not related to study drug and 1 carditis unlikely related to drug) and 4 in the Herceptin arm (1.6%, 6 events during part 1). Most of the TEAE and SAE seen over 48 weeks, were driven by data until Week 24 (part 1), and most likely attributable to the background taxane therapy.

The immunogenicity of MYL-1401O and Herceptin was assessed during 48 weeks by measuring the ADA levels in blood samples. The incidence of antidrug antibodies against MYL-1401O and Herceptin was very low and consistent with literature. These antibodies were transient and the titers were low. Also, the incidence of neutralizing antibodies was very low and similar in both arms. Overall, the treatment-emergent immune response was similar between the 2 treatment arms. No association was observed between the presence of ADAs and efficacy (as measured by ORR), nor to ARRs. These results indicate that there was no clinically meaningful difference between MYL-1401O and Herceptin in terms of immunogenicity and that these data are consistent with the literature (low immunogenic potential of the innovator product).

Overall, the treatment of MBC patients with MYL-1401O is well tolerated (in combination with taxanes and in monotherapy), with a low immunogenicity, and no new or unexpected safety signals were observed compared to Herceptin-EU. Therefore, although some slight differences have been reported between two arms, the long term (48 weeks) safety, immunogenicity, and tolerability of MYL-1401O and Herceptin are overall comparable.

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties regarding the comparability of Ogivri with Herceptin.

3.4. Discussion on biosimilarity

The analytical biosimilarity of Ogivri to EU-approved Herceptin has been satisfactorily demonstrated.

From a non-clinical perspective, biological function parameters such as HER 2 binding, inhibition of proliferation, ADCC, C1q binding and Fc receptor binding were found to be similar between MYL-1401O and Herceptin. In addition, the assays have been adequately qualified.

With regards to clinical efficacy, similarity in terms of ORR at week 24 has been shown with the a priori defined equivalence margin (15%). The results are considered robust enough as different sensitivity analyses support the main analysis, including comparison according to stratification factors and analyses in the ITT2 and PP groups. The results of the primary analysis are further supported by secondary efficacy endpoints. Overall, the clinical efficacy data support biosimilarity.

A comparable safety and immunogenicity profile has been shown between the biosimilar candidate MYL-1401O and the originator product, establishing biosimilarity (in combination with taxanes and in monotherapy).

Biosimilarity is supported from a quality, non-clinical, pharmacokinetic, pharmacodynamics, as well as from a clinical efficacy and safety point of view.

3.5. Extrapolation of safety and efficacy

Herceptin is authorised in the treatment of HER2-positive MBC, early breast cancer (EBC), and metastatic gastric cancer (MGC). The mechanism of action of trastuzumab is the same in all three indications (i.e., to inhibit the proliferation of human tumour cells that overexpress HER2). The target receptor involved in the mechanism of action in EBC and MGC is same as in MBC (i.e., HER2). Trastuzumab is indicated in EBC and MGC only if HER2 positivity is demonstrated. The dosage is also similar for all the indications. Trastuzumab is administered by the same route in all indications.

The available safety data of the reference product does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population. There are no toxicities that are related to off-target activities in MBC compared with EBC or MGC.

Research performed on the active substance of the reference product shows that it does not interact with several receptors that may have a different impact in the tested and non-tested therapeutic indications, and molecular typing has indicated that it does not have more than one active site other than the HER2 targeting area.

Overall, results of the physico-chemical, structural, and biological characterisation studies together with the evidence from non-clinical and clinical studies support extrapolation to the other oncology indications.

3.6. Additional considerations

The applicant claimed the same therapeutic indications for the biosimilar as granted for Herceptin for intravenous administration in the EU. Considering Herceptin is also marketed for subcutaneous administration, adequate risk minimisation measures to avoid the potential route of administration error have been included in the SmPC section 4.2.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ogivri is considered biosimilar to Herceptin. Therefore, 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 Ogivri is favourable in the following indication:

Breast cancer

Metastatic breast cancer

Ogivri 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

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

Ogivri 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 SmPC sections 4.4 and 5.1).

Metastatic gastric cancer

Ogivri in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Ogivri should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see SmPC 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 MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.