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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ogivri

International non-proprietary name: Trastuzumab

Procedure No. EMEA/H/C/004346/0000

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
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
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
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
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. Recommendation

Based on the CHMP review of the data on quality, safety, efficacy and risk management plan, the CHMP considers that the application for Ogivri, in the treatment of Metastatic breast cancer, Early breast cancer and Metastatic gastric cancer,

is not approvable since a major objection has been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objection precluding a recommendation of marketing authorisation, pertains to the following principal deficiencies:

- Quality: the lack of a valid GMP certificate for the Drug Product manufacturing site Biocon Ltd (India).

Questions to be posed to additional experts

n/a

Inspection issues

GMP inspection(s)

A request for GMP inspection has been adopted for the following site in order to verify the GMP compliance status: Biocon Ltd, Bangalore, India (DS and DP manufacture, QC testing).

The outcome of this inspection is required for the Committee to complete its examination of the application and will be needed by Day 181.

GCP inspection(s)

MYL-Her-3001

For the time being, there is no proposal for GCP inspection.

MYL-Her-1001

For the time being, no GCP inspection is judged necessary for this study.

MYL_Her_1002

This study was conducted in accordance with the guidelines set forth by the European Medicines Agency (EMA), International Conference on Harmonisation (ICH) of Guidelines for Good Clinical Practice (ICH Guideline E6), and the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice (21 CFR Parts 50 and 56) regarding the treatment of human subjects in a study.

For the time being, no GCP inspection is judged necessary at the clinical site.

Study BM200-CT3-001-11

This study was conducted in compliance with ICH E6 R1 'Guidance on Good Clinical Practice', Indian Good Clinical Practices Guideline, Schedule Y, ICMR guidelines, the Declaration of Helsinki and relevant SOPs of Biocon Limited, identified for specific activities. This study is only a supportive study and no GCP inspection is judged necessary.

New active Substance status

Not applicable.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed clinical use of Ogivri is identical to that of the reference medicinal product, Herceptin. Ogivri is proposed for the treatment of adult patients with HER2-positive metastatic breast cancer (MBC) and early breast cancer (EBC). It is also proposed for the treatment of adult patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Breast cancer poses an enormous burden in the global health care sector, as by far, it is the most frequently diagnosed and second most leading cause of death in women worldwide.

Around 1.67 million new cancer cases have been diagnosed as per the breast cancer incidence statistics by WHO in 2012. Per this report in 2012, less developed countries have a higher prevalence of breast cancer cases compared with developed countries (883,000 vs 794,000 cases, respectively). There seems to be a 4-fold variation in the incidence rates of breast cancer across the world population ranging from 27 per 100,000 as reported in Middle Africa and Eastern Asia to 92 per 100,000 cases as reported in North America. In the year 2012, around 44 deaths were observed out of 233 cases per 100,000 in the US. Similarly, based on a 2012 survey, 92 deaths were observed out of 362 cases per 100,000 in the EU (Ferlay et al. 2015).

Gastric cancer accounts for around 723,000 estimated deaths globally every year. The mortality rates in Eastern Asia seem to be the highest with an estimate of 24 deaths in 100,000 men and 9.8 deaths in 100,000 women and lowest in Northern America with an estimate of 2.8 deaths in 100,000 men and 1.5 deaths in 1000,000 women due to gastric carcinomas. Also, higher number of deaths have been recorded in Central and Eastern Europe due to gastric cancer. The incidence rates of gastric cancers are about twice as high in men than women in Western Africa when compared to developed countries (Ferlay et al. 2015).

2.1.3. Biologic features, aetiology and pathogenesis

Advances in understanding the biology of breast cancer have led to the classification of breast cancer based upon the molecular features, and to the advent of targeted therapies for the treatment of EBC,

MBC and MGC (Gravalos 2008; Bullock and Blackwell 2008). One such breakthrough is the understanding of the role of HER2 protein in breast cancer as well as gastric cancer. HER2 is a transmembrane receptor with tyrosine kinase activity but without a known ligand. It belongs to a family of 4 receptors (EGFR/HER1, HER2, HER3, and HER4) that are involved in regulating cell growth, survival and differentiation through interlinked signal transduction involving activation of the PI3K/Akt and the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) pathways. Overexpression of HER2 has been observed in up to 20% to 30% of primary breast cancers. Patients with HER2/neu gene amplification and HER2 protein overexpression have a more aggressive phenotype with an associated poorer prognosis. HER2 is overexpressed in 10–25% of gastric cancers (Krishna et al. 2013). In HER2-amplified advanced gastric cancer patients the median survival was observed to be 5.5 months compared with 12.6 months in nonamplified patients (Song et al. 2010).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam; the performance of a CBC, LFTs, chest diagnostic CT, bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan; consideration of diagnostic CT of the abdomen (with or without diagnostic CT of the pelvis) or MRI scan of the abdomen; and biopsy documentation if possible.

Determination of hormone receptor status (ER and PR) and HER2 status should be repeated in all cases when diagnostic tissue is obtained. ER and PR assays may be falsely negative or falsely positive, and there may be discordance between the primary and metastatic tumours due to change in biology of disease, differential effect of prior treatment on clonal subsets, tumour heterogeneity, or imperfect accuracy and reproducibility of assays.

Patients with recurrence of breast cancer or metastatic breast cancer at diagnosis are initially stratified according to whether bone metastasis is present and are then further stratified further by tumour hormone receptor and HER2 status.

2.1.5. Management

One of several breakthroughs in the elucidation of the molecular pathways of carcinoma formation and lifecycle was the understanding of the role of HER2 protein, which is found in the majority of breast and gastric cancers.

As for the relevance of a HER2 targeting therapy, it is known that about 30% of breast cancers have an overexpression of HER2 that is associated with highly aggressive tumour phenotypes and associated poor survival prognosis. In gastric carcinoma about 25% of cases present with HER2 overexpression and these phenotypes have a 50% reduced median survival time.

Trastuzumab was developed as a humanized recombinant IgG monoclonal antibody specifically directed against the HER2 receptor, and binding of the latter's extracellular domain leads to tumour cell growth inhibition.

Since approval and marketing of Herceptin trastuzumab has been convincingly demonstrated to be efficacious and safe in the treatment of HER2-positive MBC, and is part of the recommended, in

combination with chemotherapy, 1st line treatment options for eligible cancer types in the ESMO and NCCN guidelines.

2.2. About the product

Trastuzumab is a humanized recombinant IgG monoclonal antibody specifically directed against the HER2 receptor. The binding of trastuzumab to the extracellular domain (ECD) of HER2 receptor leads to inhibition of tumour cell growth. It is indicated for the treatment of HER2 positive EBC as well as MBC and MGC, alone or in combination with chemotherapy and has demonstrated therapeutic benefits (Bang, et al. 2010). Trastuzumab is the recommended treatment, in both adjuvant and neo-adjuvant setting for EBC (Excellence NIfHaC 2015).

Trastuzumab is demonstrated to be efficacious and safe in the treatment of HER2-positive MBC. In various clinical studies of patients with operable breast cancer, trastuzumab was also found to have a better efficacy and safety profile than lapatinib in the neoadjuvant setting (Network NCC 2015; Ahn et al. 2012). In a meta-analysis assessing the comparative effectiveness of neoadjuvant therapy for HER2 positive breast cancer, it was found that trastuzumab plus chemotherapy has a well-balanced profile for efficacy, completion, and safety (Nagayama et al. 2014). Trastuzumab has been found to be effective in combination with capecitabine or 5-fluorouracil and cisplatin in the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

The mechanism of action of trastuzumab is the same in all the 3 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. Trastuzumab has been demonstrated to be safe and effective in the additional indications of EBC and MGC (Ismael et al. 2012; Goldhirsch 2013; Krishna et al. 2013). 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. Thus, it can be concluded that the active substance of the reference product does not interact with several receptors that may have a different impact in the tested and non-tested therapeutic indications.

The applicant's proposed biosimilar product is for intravenous infusion and contains 150 mg of trastuzumab as a lyophilized powder for concentrate for solution for infusion. The clinical programme was initiated with the aim to prove biosimilarity between both products in the setting of metastatic breast cancer, and extrapolating similarity in the other indications if biosimilarity in MBC in regards to quality, non-clinical, PK, pharmacodynamic and clinical aspects was confirmed.

Breast cancer is the most frequently diagnosed and second most leading cause of death in women worldwide, while gastric cancer has an especially high burden in Eastern Asia, Central and Eastern Europe.

2.3. The development programme/compliance with CHMP guidance/scientific advice

This application is submitted under Article 10 (4) of Directive 2001/83/EC with Herceptin (150 mg powder for concentrate for solution for infusion; Roche Registration Limited) representing the reference medicinal product.

Ogivri development program was designed to meet the recommendations in the following European Medicines Agency and US Food and Drug Administration's regulatory guidelines on biosimilars:

- Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1; 2014)
- Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010; 2012)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005; 2006)
- ICH guideline S6 (RI) – Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals Step 5" (EMA/CHMP/ICH/731268/1998; 2011).
- Guidance for industry: Scientific considerations in demonstrating biosimilarity to a reference product (FDA), 2015.
- Guidance for industry: Clinical pharmacology data to support a demonstration of biosimilarity to a reference product (draft guidance; FDA), 2014.
- Guidance for industry: Quality considerations in demonstrating biosimilarity (FDA), 2015.

The applicant has obtained endorsement on critical aspects of the development program of Ogivri from the Paul-Ehrlich-Institute, Germany.

2.4. General comments on compliance with GMP, GLP, GCP

The nonclinical studies performed to support this application 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 facilities were GLP-compliant during the study period (27/10/2010 to 11/07/2012).

The *in vitro* pharmacodynamic studies (presented in Module 2.6.2 Pharmacology Written Summary, section 2.6.2.2 'Primary Pharmacodynamics' and in Module 3.2.R 'Regional Information') performed to establish the biosimilarity have been validated.

The applicant states that all clinical studies with Ogivri were conducted in accordance with International Council for Harmonization Good Clinical Practice, the principles of the Declaration of Helsinki, the US Code of Federal Regulations, and the EU Clinical Trials Directive, as well as any other applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

According to the Eudra GMP database, the last GMP inspection of the manufacturing site (Biocon Ltd, Bangalore, India; DS and DP manufacture, QC testing), has been performed in December 2010. A new inspection should be performed.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

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

  Ogivri falls under the "mandatory scope" criterion (the Art. 3(1) of the (EC) No. 726/2004 Annex (1) Biotech medicinal product)

- Accelerated procedure

  N/A

- Conditional approval

  N/A

- Exceptional circumstances

  N/A

- Biosimilar application

  Mylan's trastuzumab (Ogivri) clinical program consists of 3 pivotal studies and 1 supportive study. The reference products used in these studies are EU-approved Herceptin and/or US-licensed Herceptin.

  The following company codes differentiate the formulation types used during the development program:

  MYL-1401O: This is the formulation intended to be marketed in the European Union (EU) and used for the global development program, which is slightly different from the EU approved and United States (US)-licensed Herceptin formulations.

  Bmab-200: This is the initially developed product used in clinical study BM200-CT3-001-11 to obtain marketing authorization in the country of origin.

  Pivotal Studies

The applicant has submitted three different pivotal studies.

- Study MYL-Her-1001 was a single-center, 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-center, 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.

Supportive Study

Mylan is in a co-development partnership with Biocon, Limited (Bangalore, India). This collaboration partner conducted a supportive clinical study in patients with MBC in India with another formulation (Bmab 200). This study is described briefly as follows:

Study BM200-CT3-001-11 was a comparative PK, efficacy, safety, and immunogenicity study in which patients received, in combination with docetaxel, MYL-1401O (a proposed biosimilar to trastuzumab) either Bmab-200 or the reference product, EU-approved Herceptin according to a double-blind, randomized, parallel design. Both Bmab-200 and the reference product were administered as an IV infusion of 8 mg/kg IV loading, followed by 6 mg/kg IV maintenance, every 3 weeks for 8 cycles. Overall treatment duration for each subject was up to 24 weeks. Study objectives included demonstration of bioequivalence, comparative efficacy (overall response rate at 24 weeks), safety, and immunogenicity. Single-dose comparative PK was the primary endpoint of this study. The efficacy and safety of Bmab-200 compared with EU-approved Herceptin was evaluated as secondary endpoints. The study was completed (last patient's last visit) on 21 July 2013.

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

  N/A (biosimilar application)

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Ogivri (also referred to as MYL-1401O), a proposed biosimilar to Herceptin (trastuzumab, Roche Registration Limited), is a humanized immunoglobulin G1 monoclonal antibody (mAb) produced in mammalian CHO cells and purified by chromatography steps and viral inactivation and removal steps.

MYL-1401O binds with high affinity and specificity to the extracellular sub-domain IV of HER-2. Its binding inhibits ligand-independent HER-2 signalling resulting in inhibition of proliferation of human tumour cells that overexpress HER-2. Additionally, it is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC).

3.1.2. Active Substance

General Information

The recommended International Non-proprietary Name (rINN) is trastuzumab.

MYL-1401O, a proposed biosimilar product 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 a total of 1328 amino acids and is comprised of two identical HCs and two identical LCs. Each HC is comprised of 450 amino acid residues and each LC is comprised of 214 amino acids. MYL-1401O's HCs are fully glycosylated at Asn300.

MYL-1401O formulated bulk drug substance (DS) is a clear to slightly opalescent non-turbid liquid.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

MYL-1401O is expressed in Chinese Hamster Ovary (CHO) cells and is manufactured by a fed-batch process at Biocon Limited (Bangalore, India) in a production bioreactor. Following cell culture and harvest, MYL-1401O is purified from the harvest culture fluid through a series of filtration and chromatography steps. Excipients are added to generate the formulated DS.

No reprocessing is foreseen for the manufacturing process of MYL-1401O.

Control of materials

The raw materials and reagents used in the manufacture of MYL-1401O DS are either commercially available or prepared from commercially available materials. The raw materials used during the production of MYL-1401O DS are either of compendial or non-compendial quality. The compendial raw materials are tested as per the compendial methods. The non-compendial raw materials used during

the manufacturing process of MYL-1401O DS are tested according to internal specification to ensure that their quality meets the requirements of the process.

A CHO-derived cell line expressing high levels of MYL-1401O DS was established. Initially, a two-tiered cell banking system of MCB and WCB had been established and qualified according to ICH Q5A and ICH Q5D.

Control of Critical Steps and Intermediates

Based on process experience throughout development, risk assessment, and process characterization at small scale, process and performance parameters are classified as critical and non-critical controls prior to process validation at the proposed commercial scale. Critical Process Parameters (CPPs) are those that impact resultant product quality and Non-Critical Process Parameters (NCPPs) are those that do not impact product quality. The CPPs were validated using three batches and the results are provided in the appropriate section. The critical In-Process Controls (IPCs) for cell culture, purification and formulation steps along with the justifications for their limits are also presented.

Process validation and/or evaluation

Three full scale batches manufactured using the final commercial manufacturing process were used in the validation studies of the DS manufacturing process. Several other aspects have also been validated or evaluated, including impurity clearance (by spiking study with a scaled-down process confirmed at commercial scale), microbial control (bioburden and bacterial endotoxin tests), virus clearance (section 3.2.A.2.2), chromatography resins lifetime (first with a scaled-down process to be confirmed at commercial scale) and membranes lifetime. In-process hold studies and extractable/leachable studies were also carried out.

A continued process verification (CPV) is in place to monitor the manufacturing process of MYL-1401O by evaluating CPP, Critical Quality Attributes (CQAs), Non-CQAs and performance parameters, and by establishing control limits for the manufacturing process based on statistical evaluation of variability estimates.

Manufacturing process development

The development of MYL-1401O has encompassed several manufacturing changes. Comparability studies were provided.

In addition, a Process Characterization for MYL-1401O DS was performed in order to establish the functional relationship between input and output parameters and to provide the acceptance range for the input parameters so that within this range, the process is expected to perform in a way that the output quality attributes are within the desired range. To achieve these two goals, a scale down model qualification of the manufacturing process, a risk assessment using FMEA for categorization of process parameters and the identification of CPPs and corresponding acceptance ranges were performed.

Characterization

In order to examine the structural, physicochemical and biological attributes of MYL-1401O drug substance (DS) process validation (PV) batches using the final commercial process manufactured at Biocon Limited (Bangalore, India), state-of-the-art techniques were used and comparison with European Reference Medicinal Product (EURP) and United States Reference Listed Drug (USRLD) was performed. Some of the attributes have been analyzed with orthogonal techniques.

MYL-1401O is structurally composed of two identical heavy chains (HC) and two identical light chains (LC), which are cross-linked through four inter-chain disulphide bonds; two cystine bridges connect the

HC at their hinge region and each heavy chain is disulphide bonded to the carboxy terminal cysteine of the respective LC. In addition to this, each LC and HC contains two and four intra-chain disulphide bonds, respectively. N-glycosylation of MYL-1401O occurs at the consensus asparagine found at amino acid 300 in the heavy chain sequence. However, both the heavy chains in the intact antibody do not have a C terminal lysine, as lysine removal occurs due to expression in CHO cells and digestion with carboxypeptidase B (CpB).

The intact mass, reduced mass, N- and C-terminal analysis as well as > 95 % coverage of the protein sequence by peptide mass fingerprinting were performed, concluding that the primary structure of MYL-1401O is identical to the theoretical/published sequence of Herceptin.

The secondary and tertiary structure of MYL-1401O were analyzed using near- and far-CD concluding that the protein is a predominant β sheet structure, and UV profile of disulphide and peptide map analysis confirmed the correct tertiary structure of the molecule.

Heterogeneity and product related variants were analyzed using various techniques concluding that the major structural form was the intact monoclonal antibody with the appropriate molecular weight, surface and net charge.

The glycoforms as well as the sialic acids associated with the protein were also analyzed showing two major forms (G0f and G1f) and less predominant forms (G2f, Man5, G0, G0f-GN, etc.). Also, the sialic acid was of the NANA (N-Acetylneuraminic acid) type with no evidence of the N-glycolylneuraminic acid (NGNA) type being present.

Functional analysis of the protein was performed by means of SKBr3 proliferation, SKBr3 binding kinetics, ADCC and CDC analysis. In all the biological assays, MYL-1401O's activity was found to be comparable to the reference medicinal product Herceptin indicating that the molecule is structurally intact and in the required conformation.

Product related variants (HMWP (High Molecular Weight Proteins)/aggregates, LMWP (Low Molecular Weight Proteins)/fragments and charge variants) are isolated, analyzed and appropriately characterized using different state-of-the-art analytical techniques. Product variant characterization is carried out using variants purified from process intermediates or DS for MYL-1401O. Commercially available EU approved Herceptin drug product (DP) batch is used to purify variants of Herceptin.

Process related impurities of MYL-1401O DS are originated either from the raw materials or CHO cell line including HCP, HCDNA, Leached protein A and Carboxypeptidase B. The clearance of the process related impurities was successfully demonstrated at large scale during the PV studies and at small scale in spiking studies performed using qualified scaled down. In addition, consistent clearance of process related impurities has been shown in all the development batches and clinical batches analyzed.

Specification

The release specification for MYL-1401O drug substance includes tests for appearance, identity, purity and impurities, content, potency, determination of pH, microbiological attributes, selected process related substances, HCP, host cell DNA and Leached Protein A.

Batch analysis

Batch data provided include all batches used for the purpose of non-clinical and clinical testing, as well as those batches utilized for validation of the drug substance manufacturing process. Batches from

different versions of the manufacturing processes were analyzed and they all met the release acceptance criteria.

Reference standards

The history of reference standards used during development has been presented. Four different reference standards were used during product development. Preparation and testing for three of them are provided.

The strategy for qualification of new IRS is described and included both release testing and extensive characterization current IRS and/or EU sourced. The new IRS will be prepared from MYL-1401O DS batch derived from the final commercial process.

Additional in-house standards used in analytical methods are also briefly described.

Stability

Based on the available data, the proposed shelf life at the intended storage condition for MYL-1401O DS is acceptable

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

MYL-1401O 150 mg powder for concentrate for solution for infusion is supplied as a single use vial containing 150 mg of trastuzumab as drug substance, intended for reconstitution with 7.2 mL of sterile WFI (not supplied with the pack) to yield a solution containing approximately 21 mg/mL trastuzumab.

The container closure system was described and adequately qualified; leachables and extractables studies were performed.

The pharmaceutical development for MYL-1401O DP was focused on developing a formulation that was highly similar to the reference product, Herceptin from a quality and stability perspective.

The reference product (Herceptin) contains trehalose dihydrate (which functions as a lyoprotectant, cryoprotectant, and bulking agent) and polysorbate 20 (which functions as a surfactant).

Manufacture of the product and process controls

The DP manufacturing process involves thawing of formulated drug substance (DS), pooling of individual DS bags followed by mixing, pre-filtration, sterile filtration, aseptic filling of the formulated DS, lyophilization, and sealing of vials containing the lyophilized product.

Three batches of MYL-1410O 150 mg DP were used for process validation. These batches were manufactured at full batch size.

In addition to validation of each individual manufacturing step, the results of filter validation, hold time validation, tunnel validation, aseptic process simulation (media fill runs) and cleaning validation have also been presented.

The MYL-1401O DP manufacturing process is continually monitored by evaluating the process for CPP, NCPP, CQAs, Non-CQAs and performance parameters at the level established during the PC, and by

establishing control limits for the manufacturing process based on statistical evaluation of variability estimates. Continued process verification (CPV) is a passive process carried out for CQAs and other performance attributes to verify that a given process is performing as per expectation.

Product specification

The release specification for MYL-1401O drug product includes tests for appearance, identity, purity and impurities, content, excipient, potency, determination of pH, general pharmacopeial tests, and safety testing.

The applicant has provided batch data for several DP lots. Also, justifications were provided for the specifications.

Stability of the product

Real time (2-8°C) and accelerated (25°C) and stressed (40°C) stability studies have been performed. No decrease or trends were observed for potency or purity at 2-8°C or 25°C. The current available stability data for up to six months for 3 PV DP batches and up to 48 months' stability data for 3 representative commercial scale DP batches support the proposed shelf life.

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

Comparability exercise for Finished Medicinal Drug Product

To support the claim that MYL-1401O DP can be considered as a biosimilar to EU Herceptin, the applicant has performed an extensive comparability analysis which included batches of EU Herceptin, batches of US Herceptin and batches of MYL-1401O DP.

An extensive exercise has been conducted to demonstrate analytical similarity of MYL-1401O with the EU-approved Herceptin and, as part of a global development program, the US-licensed Herceptin has also been compared using state-of-the-art, sensitive and orthogonal methods. These methods were validated or qualified at the time of testing and demonstrated to be suitable for the intended use. The methods were selected to evaluate primary, secondary and tertiary structures, content, impurities, charge variants, glycan profiles and other post translational modifications. In addition, extensive evaluation of binding and resulting biological effects was performed, either as a system suitability check or as a reference for relative activity calculations. This standard was derived from a representative clinical batch and has been extensively characterized. Quantitative ranges have been established for the analytical similarity exercise, which are primarily based on the measured quality attribute ranges derived from analysis of multiple lots of the reference product.

Most of the quality attributes proved to be highly similar between MYL-1401O DP and EU Herceptin. For a few structural parameters slight differences were observed. However, these differences were very small and are unlikely to have any impact on safety and/or efficacy. Importantly, the biological function parameters (HER 2 binding, inhibition of proliferation, ADCC, C1q binding, Fc receptor binding) of MYL-1401O DP were all very similar to those of EU Herceptin. Therefore, it can be concluded that from a quality point of view MYL-1401O DP can be considered as biosimilar to EU Herceptin.

Comparative forced degradation studies were performed on 3 batches of MYL-1401O DP and 3 batches of EU Herceptin (Table 3.2.P.8.1/8):

1) Forced degradation study on lyophilized state of DP: One batch of each MYL-1401O and EU Herceptin were subjected to forced conditions
2) Forced degradation study on liquid state of DP: Two batches of each MYL-1401O and EU Herceptin were subjected to stress conditions

Adventitious agents

Raw materials are sufficiently controlled for possible contaminating viruses. In-process testing is performed on the DS 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 DS manufacturing process contains validated virus removal/inactivation steps.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

The DS and DP manufacturing process and process controls are described in detail. The main manufacturing site for production and QC testing of MYL-1401O DP (Biocon Ltd, Bangalore, India) has no valid GMP certificate. Therefore, the major objection raised at D120 is maintained.

Raw materials are sufficiently described and controlled. A cell bank system was established and tested and qualified in line with ICH Q5A and Q5D.

Critical process parameters were identified and the process was appropriately validated.

The DS and DP specifications proposed by the applicant are deemed suitable to control the quality of DS and DP. However, the applicant is requested to revise the lower specification limit for afucosylated species in the DS specifications.

The proposed shelf lives for DS and DP are supported by the performed stability studies.

As regards the biosimilarity analysis, the applicant has performed an extensive testing on batches of MYL-1401O DP, batches of EU reference product Herceptin and batches of US Herceptin. Most of the quality attributes proved to be highly similar between MYL-1401O DP and EU Herceptin. For a few structural parameters slight differences were observed. However, these differences were very small and are unlikely to have any impact on safety and/or efficacy. Importantly, the biological function parameters (HER 2 binding, inhibition of proliferation, ADCC, C1q binding, Fc receptor binding) of MYL-1401O DP were all very similar to those of EU Herceptin. Therefore, it can be concluded that from a quality point of view MYL-1401O DP can be considered as biosimilar to EU Herceptin.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The manufacturing process for MYL-1401O DS and DP are adequately described, sufficiently controlled and properly validated. DS and DP are sufficiently controlled. Analytical methods were adequately validated. Container closure systems of DS and DP were qualified. The proposed shelf lives for DS and DP are supported by the performed stability studies. The biosimilarity analysis revealed that from a quality point of view MYL-1401O DP can be considered as biosimilar to EU Herceptin.

The applicant has adequately addressed most of the questions raised in the D120 LoQ. There are, however, still a few points that need further follow-up and/or clarification. In addition, the main

manufacturing site for production and QC testing of MYL-1401O DP (Biocon Ltd, Bangalore, India) has no valid GMP certificate. Therefore, the major objection raised at D120 is maintained.

3.2. Non-clinical aspects

This application is based on the comparison of biological activities between MYL-1401O (Ogivri) 150mg/vial powder for concentrate for solution for infusion and the reference product Herceptin which is authorised in Europe since 2000-08-28 (EU/1/00/145/001 Roche Registration Limited, United Kingdom). The active substance is trastuzumab (ATC code L01XC03, antineoplastic agents, monoclonal antibodies) a recombinant DNA-derived humanized monoclonal antibody targeted against human epidermal growth factor receptor type 2 (HER2). All the comparison assays described in the primary pharmacodynamic section below were performed with MYL-1401O - which is the formulation corresponding to that intended for marketing; except the complement dependent cytotoxicity assay, which was performed with a previous formulation (Bmab200). The applicant submitted additional results on the CDC activity confirming similar activity between MYL-1401O lot and Herceptin.

Additional clarification on the composition of the lots manufactured according to a previous version of the manufacturing process used during the in vitro biosimilarity exercise is however still needed (See "List of Outstanding issues").

Finally, the applicant provided adequate validation reports for the ADCC, cell growth inhibition, HER2 binding, Fc receptor binding assays.

The claimed indications are the same as those of the reference product, i.e.: the treatment of adult patients with HER2 positive metastatic breast cancer (MBC), HER2 positive early breast cancer (EBC), and in combination with capecitabine, 5-fluorouracil, or cisplatin for HER2 positive gastric cancer (Herceptin SmPC 2015).

The nonclinical studies performed to support this application 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.

3.2.1. Pharmacology

Trastuzumab is an immunoglobulin G1 (IgG1) kappa isotype antibody specific for human epidermal growth factor receptor-2 (HER2) which contains a framework of human amino acid regions and complementarity-determining regions from the murine 4D5 antibody (muMAb 4D5). HER2 (also referred to as c-erbB2) is a proto-oncogene that encodes a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally-related to the epidermal growth factor receptor. The extracellular domain of HER2 assumes a fixed conformation resembling a ligand-activated state thereby permitting it to dimerize and activate in the absence of a ligand. Receptor over-expression or mutation can also induce dimerization and activation. Once activated, the signal-transduction cascades of these receptors promote cellular proliferation and spread. Moreover, when overexpressed, HER2 undergoes proteolytic cleavage, which releases the extracellular signalling fragment (p95) at the cell membrane resulting in increased activation and cell proliferation. Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxtamembrane region of HER2's extracellular domain. 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 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 preferentially exert its effect on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

The biosimilarity assessment proposed by the applicant has been based on in vitro pharmacological studies conducted on a sufficient number of batches of MYL-1401O against the reference medicinal product, Herceptin (European Union [EU]-approved [EU-Herceptin], and United States [US]-licensed [US-Herceptin]). The assays are: target (HER2) binding assay, ADCC assay, 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, Complement-Dependent Cytotoxicity Assay (CDC assay), and MYL-1401O inhibition of proliferation (IOP) assay. Those in vitro functionality tests have been classified as highly critical, critical or less critical. Highly critical are the HER2 binding, inhibition of proliferation, ADCC and FCγRIIIa since they are directly linked to the efficacy of trastuzumab. From the results obtained it is concluded that MYL-1401O does not differ from the reference product Herceptin. The applicant has however omitted to perform one important functionality test comparison with regards to functional properties of trastuzumab. Indeed, no functional data with respect to Antibody-Dependent Cell Phagocytosis (ADCP) have been provided. Also, FcγRIIA and FcγIIIA receptors are subject to polymorphism: two forms indeed are described for FcγRIIA depending on histidine or arginine at position 131 (131H and H131R) and 2 forms for FcγRIIIA: 158V and 158 F depending on valine or a phenylalanine at amino-acid position 158. The binding of IgG depends on the isoform of the receptor used in the assays and this could have clinical implications. Therefore, to ascertain that biosimilarity applies for polymorphic forms of both FcγRIIA and FcγIIIA receptors, comparative binding data for isoforms 131H / H131R and 158V / 158F were further requested. The applicant provided additional in vitro studies performed with the FCγRIIA131H and FcγRIIIa158F isoforms. No data were available for the other isoforms FCγRIIA131R and FcγRIIIa158V.

While it is reassuring that binding to FCγRIIA131H and FcγRIIIa158F isoforms were comparable, this was only part of the question and the issue whether biosimilarity also applies for the other isoforms FCγRIIA131R and FcγRIIIa158V. Moreover, no justification is provided why binding data to a single isoform would be sufficient. Elimination of uncertainty on biosimilarity should be achieved by submission of convincing experimental data. The applicant is requested to provide this additional data, on an adequate number of batches of each product, in order to ensure that all relevant modes of action have been investigated and that it is demonstrated that both products have comparative activity (See “List of Outstanding issues”).

The applicant performed in vitro studies to elucidate and compare the relative cardiotoxicities of MYL-1401O and Herceptin using rat and human cardiomyocytes. The results showed a similar and reversible impact on respiration complex I and II (inhibition) and by mobilization of energy over adenosine diphosphate in mitochondrias.

In line with ICH guideline S6 (R1) ‘Preclinical safety evaluation of biotechnology-derived pharmaceuticals’, the applicant included a cardiac safety-pharmacology endpoint in the 5-week repeat-dose study of MYL-1401O and Herceptin in cynomolgus monkeys. The results did not show any abnormalities in electrocardiograms.

The Applicant has not performed any in vivo PD studies, secondary pharmacodynamic studies, or pharmacodynamic drug interaction studies. This is accepted as the product evaluation is regarding biosimilarity.

3.2.2. 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. The results show 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 'bioequivalence' between Herceptin and MYL-1401O and refers to bioequivalence studies provided in human (healthy volunteers and patients).

Anti-drug antibodies (ADA) were assessed 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. No ADA were detected. Of note, ADA was additionally measured during the clinical trials where results generated for all 2130 samples showed a total of 294 positive samples and 62 of these were confirmed positive.

The plasma levels of trastuzumab were determined using a validated enzyme linked immunosorbent assay.

Information on distribution, metabolisation, excretion and pharmacokinetic interactions were not provided but those studies are not considered essential for a similar biological medicinal product.

3.2.3. Toxicology

The toxicity and TK profile of MYL-1401O was compared with EU sourced Herceptin following 5 weekly intravenous (IV) infusions in cynomolgus monkeys, a species known as relevant for this product. The aim of that study was to compare the toxicity profiles of the MYL-1401O final formulation to that of the reference product Herceptin. A comparison of the toxicokinetics profiles was also made after single and repeated doses. No recovery groups were included in this study.

The animals were allocated in groups of 3M/3F receiving respectively 0 (control, group1); 25mg/kg Herceptin (group 2); 25mg/kg MYL-1401O (Group 3); 50mg/kg Herceptin (Group 4); 50 mg/kg MYL-1401O (group 5). The doses administered are based on the public information for the reference product Herceptin.

ECG and blood pressures were also monitored.

There were no drug-related effects on body weight, food consumption (visual appraisal), electrocardiography (ECG), blood pressure, haematology, clinical chemistry, urinalysis or organ weights.

There were no macroscopic or microscopic findings suggestive of effects of MYL-1401O or Herceptin and no notable differences between MYL-1401O and Herceptin treated animals. Based on the results from this study a No-Observed-Effect-Level (NOEL) of 50 mg/kg/day was assigned for both Herceptin and MYL-1401O.

The toxicokinetics results also show accumulation of MYL-1401O and Herceptin in male and female animals, with mean accumulation ratios on Day 22 ranging from 2.0 to 2.4 and 2.0 to 2.5 for both formulations.

Local tolerance toxicity showed a slight trend for phlebitis/periphlebitis animals treated with the high dose of MYL-1401O. Given that the control group did not contain the final formulation excipients and that the clinical safety data provided with MYL-1401O show a trend for increased allergic reactions, reactogenicity, and infusion-related reactions.

No genotoxicity, carcinogenicity or reproductive and developmental toxicity studies were conducted for MYL-1401O, as such studies are not essential for a similar biological product medicinal product (EMA 2006 Guidance [EMEA/CHMP/BMWP/42832/2005]). Impurities are not addressed by the applicant, however information provided in Module 3 is considered sufficient to exclude concerns regarding the level of impurities at release and throughout the claimed shelf-life of the product.

3.2.4. Ecotoxicity/environmental risk assessment

Trastuzumab is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Even though there is no information on how the formulation containing trastuzumab is rapidly degraded in the environment, it can be accepted that this biosimilar product may not lead to an increase of the treated European population, since its introduction on the European market will lead to an authorisation valid in the same countries as the reference product and targeting the same population.

3.2.5. Discussion on non-clinical aspects

The biological and functional similarity of Bmab 200/ 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. These include measurement of primary mechanism of action involving Fab, i.e., binding to Her-2 receptor and inhibition of proliferation of cells that overexpress Her-2. Mediation of the effector functions of immune cells through the constant region (Fc) of the antibody, i.e., ADCC was measured in vitro using SK-BR3 cells with human PBMCs. The binding affinity to the FcγRIIIa receptor, that can directly impact the effector function, has been monitored and compared using a Surface Plasma Resonance (SPR) based assay in kinetic mode. Binding of the antibody to the neonatal receptor, FcRn, that can impact the antibody half-life; and antibody binding to C1q that can affect the complement activation have been measured using an SPR and ELISA based assay respectively. Binding affinity to the other Fc receptors, FcγRIa, FcγRIIa, FcγRIIb, and FcγRIIIb has also been measured using SPR based assays.

Those in vitro functionality tests have been classified as highly critical, critical or less critical. Highly critical are the HER2 binding, inhibition of proliferation, ADCC and FCγRIIIa since they are directly linked to the efficacy of trastuzumab. This classification and its justification are provided in section 3-2-R-5 “Biosimilar Comparability Exercise”. The results showed similarity to the reference product with standard deviations not larger than those of both US/EU Herceptin. Since Antibody-Dependent Cell Phagocytosis (ADCP) is a major mechanism of action for the mAb trastuzumab, the applicant is also asked to provide additional comparison through functional ADCP data, to make sure that all relevant modes of action are investigated and that it is demonstrated that both products have comparative activity. The applicant provided comparative binding results for FCγRIIA131H and FcγRIIIa158F isoforms. However, biosimilarity also applies for the other isoforms FCγRIIA131R and FcγRIIIa158V. Moreover, no justification is provided why binding data to a single isoform would be sufficient. The applicant is therefore requested to provide this additional data.

The applicant has not performed any in vivo PD studies, secondary pharmacodynamic studies nor pharmacodynamic drug interactions studies with MYL-1401O. This is deemed acceptable.

In line with ICH guideline S6 (R1) 'Preclinical safety evaluation of biotechnology-derived pharmaceuticals', functional indices related to safety pharmacology have been 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 have shown that the toxicity originated from reversible impact on inhibition of respiration complex I and II and by mobilization of energy over adenosine diphosphate in mitochondrias. 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 show 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 'bioequivalence' between Herceptin and MYL-1401O and refers to bioequivalence studies provided in human (healthy volunteers and patients).

ADA was assessed 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. No anti-drug antibodies (ADA) were detected. Complementary information related to the validation of the method of analysis has also been requested.

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 indicate there were no notable differences in MYL-1401O and EU-approved Herceptin exposure or bioavailability to monkeys. However, the number of animals is limited. Anti-drug antibody (ADA) studies were not conducted because the applicant did not observe any differences in toxicity profiles, TK, or injection site reactions.

Single dose toxicity study, reproductive and developmental, carcinogenicity, genotoxicity studies were not performed. This is considered acceptable.

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 in the MYL-1401O drug product are said to be commonly used in injectable dosage forms and to comply with applicable European Pharmacopoeial standards. However, given the absence of animal data to justify the safe use of the excipients by the intravenous route the limited human data and the trend for increased allergic reactions, reactogenicity, and infusion-related reactions seen in the

pivotal study MYL-Her-3001, the safety of the proposed excipients should be elaborated further (see clinical safety assessment).

No Environmental Risk Assessment is provided based on the justification that this product is a biosimilar to Herceptin intended for the same population and the same market, therefore the exposure of the environment is not thought to increase significantly.

3.2.6. Conclusion on non-clinical aspects

Overall, the nonclinical biosimilarity and safety data demonstrate that MYL-1401O has a similar activity to the reference product Herceptin with an acceptable safety profile and there are no major objections prevailing this product to be granted a Marketing Authorisation, from a non-clinical point of view. However, the Applicant is requested to answer a list of outstanding issues listed in section 6.2.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 1: Summary of the 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 bioequivalence, PD, safety, immunogenicity	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, immunogenicity	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 similarity of PK among MYL-1401O, EU-Herceptin, and US-Herceptin • To assess comparative safety	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

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	24 weeks (Part 1)
Confirmatory efficacy and safety, immuno-genicity	MYL-Her-3001	• To compare independently assessed clinical activity at Week 48 (TTP, PFS, OS) • To descriptively compare safety, tolerability, and immunogenicity	Multicenter, double-blind, randomized, parallel-group study	MYL-1401O, EU-Herceptin Maintenance dose as allocated in Part 1, according to Herceptin EU dose recommendation IV	342 entered, 214 completed Part **2** / Patients with HER2+ MBC	48 weeks (Part **2**)
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

3.3.1. Pharmacokinetics

Ogivri is developing as a proposed biosimilar medicinal product to Herceptin as the reference medicinal product. Like the reference product, Ogivri will be supplied as a single-use vial containing 150 mg of trastuzumab as drug substance intended for reconstitution with 7.2 mL of sterile WFI (not supplied with the pack) to yield a solution containing approximately 21 mg/mL trastuzumab. This is a lyophilized material reconstituted in two steps for administration as a slow intravenous infusion, as done for Herceptin.

The name Hercules used in the dossier corresponds to the drug product MYL-1401O or Ogivri. MYL-1401O was referred to as Hercules before the company code was generated. During the development program of MYL-1401O, another formulation of drug product was used, described as Bmab-200.

The clinical comparability exercise was performed in a stepwise procedure. In general, the Applicant´s development program to demonstrate the similarity between Ogivri 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 Advices.

The two single dose PK studies (MYL-Her-1001 and 1002) are judged appropriate. The study performed in patients (BM200-CT3-001-11) with another formulation supports the conclusion of similarity.

The applicant has informed the assessors on the GCP inspections that have been carried out by the authorities at the different sites involved in the PK study MYL-Her-1001 in the last years. It should be noted that the CHUV site has been inspected by Swissmedic only and never by EMA inspectors. As no doubts on the compliance can be raised based on the data provided in the dossier, as the quality of the trial performed at CHUV site is sufficient and in accordance with the current requirements, GCP compliance seems to be guaranteed and no further discussion with the GCP inspectors is judged needed. For study MYL-Her-1002, WCCT was audited by the US FDA and PMDA with no critical or major non-conformance observations.

Bioanalytical methods

Quantitative determination of trastuzumab in human serum

Several ELISA analytical methods to quantify the concentration of Hercules 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 Hercules 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.

The ELISA method is suitable for the quantification of Hercules and Herceptin in human plasma and in patients with Her2+ Metastatic Breast Cancer.

All assays were selective in human plasma and in patients with Her2+ Metastatic Breast Cancer.

Dilutional linearity samples gave a response > the ULOQ suggesting no presence of a hook effect for all analytical methods.

The data exhibited no evidence of marked drift across the plate.

Specificity of the bioanalytical methods used for trastuzumab quantitation has been well demonstrated. Because of its methodology, ELISA assays are not affected by carry-over effect. Parallelism is normally assessed with multiple dilutions of actual study samples or with a sample representing the same matrix and analyte combination. Dilutional testing of QCs prepared in both simulated and MBC sera during validation, which generated acceptable accuracy and precision in both cases, support the parallelism of trastuzumab quantitation in MBC study samples.

Quantitative determination of HER2-Neu Oncogene in human serum

The quantitative assay for the determination of HER-2/neu in human serum samples is successfully qualified. The different validation characteristics (accuracy, precision, sensitivity, dilutional linearity, stability, Hook effect) are correctly investigated in the report related to the qualification of the method.

Determination of anti-drug antibodies (ADA) in human serum

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

As recommended by the EMA guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev. 1), 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. Samples that were confirmed as ADA-positive were further analyzed 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. The report describing the neutralization assay should still be provided with the full validation data.

Clinical PK Study Myl-Her 1001

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 is to assess comparative systemic safety and tolerability including local tolerance, and to evaluate immunogenicity with anti-drug antibody (ADA) formation.

This study was a Phase I, single center, single dose, 2-period, randomized, double-blind, cross-over study performed at the Centre Hospitalier Universitaire Vaudois (CHUV), Clinical Pharmacology and Toxicology (Lausanne, Switzerland) with Professor Thierry Buclin as Principal Investigator. A cross-over design is acceptable because it allows reducing the variability and allowing a higher sensitivity to detect differences between both products and the protocol adopted appears to be adequate from a safety point of view.

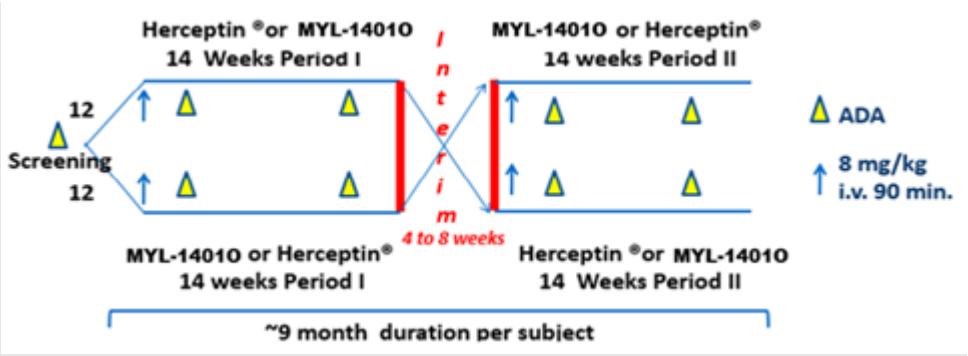


Figure 1: MYL-Her-1001 study design

The subjects either received the test drug (Hercules) or the reference drug (Herceptin) in Period I and the alternate treatment in Period II. The study drugs (Hercules 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). 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 bio-similarity and is 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.

In the context of a cross-over design, based on a terminal T1/2 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 sensitive 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 Subject 103) and before Hercules (99.4 ng/mL for Subject 117) administration. These concentrations were <0.1% of Cmax and no further analysis is 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 is based on need for flexibility and not on pharmacokinetics (PK) considerations, and this extension has no impact on study quality. This is considered acceptable.

In conclusion, the design chosen is considered as satisfactory for the purpose of the study.

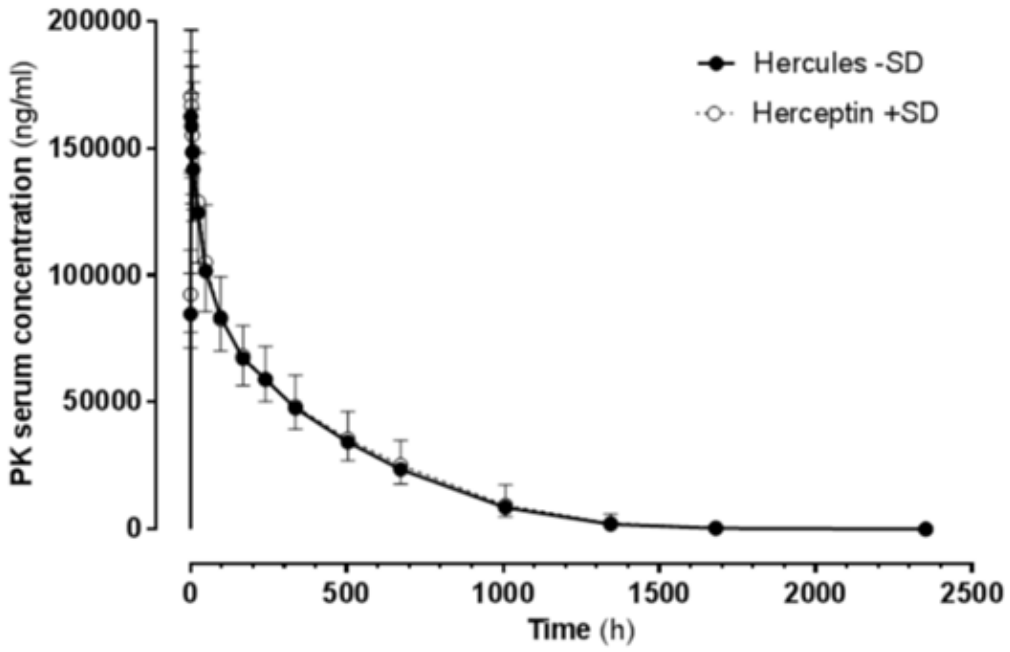
The study was conducted in healthy Caucasian males with a very small group of subjects with other ethnicity. This difference between ethnic groups would not be expected to cause systemic bias in the bio-similar comparison exercise. In addition, healthy subjects represent a homogeneous population and reduce the inherent variability.

In total, 22 subjects were randomized to either Hercules (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 (Subject 112 after end of Period I and Subject 119 on Week 8 of Period I) and 1 by the Safety Committee (Subject 122 after Period I) as a precaution due to raised values for liver function tests (transaminases) in Period I.

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 analyzed by enzyme-linked immunosorbent assay (ELISA).

The PK sampling time points were selected based on the mean trastuzumab elimination half-life (t1/2) ranging from 18 to 27 days (approx. 22 days in healthy subjects). The choice of an interval of 14 weeks corresponds to approximately 4.5 half-lives and allows covering at least 80% of the AUC.



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

Pharmacokinetic results

Table 2: 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. Proposed PK and statistical methods are the standard methods recommended in the guideline on the Investigation of bioequivalence. PK similarity and bioequivalence can be considered to be adequately demonstrated between Ogivri and the reference product with respect to rate and extent of absorption following administration of a 8 mg/kg dose to healthy subjects in study MYL-Her_1001.

The immunogenicity of MYL-1401O and Herceptin was assessed by checking the incidence and the ADA levels in blood samples collected at baseline (pre-infusion, at 0 hours) and at 2 weeks and 10 weeks during each treatment period. There were no detectable ADAs, thus indicating no immunogenicity. This absence of ADA was expected given the known low immunogenicity profile of trastuzumab and given the administration of single doses in healthy subjects.

Clinical PK study Myl-Her 1002

The primary objective of study Myl-Her-1002 was to demonstrate pharmacokinetic similarity of Ogivri (Hercules) versus EU-approved Herceptin and US-licensed Herceptin and pharmacokinetic similarity of EU-approved Herceptin versus US-licensed Herceptin after 8 mg/kg as single dose administered as

intravenous infusion over 90 minutes in healthy male subjects. The study was conducted in the US and was completed (last subject's visit) on 27 February 2014.

GCP inspections have been carried out by the FDA or other regulatory agency at the clinical site WCCT global, Cypress, USA where the study was carried out.

This study is a single-center, 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.

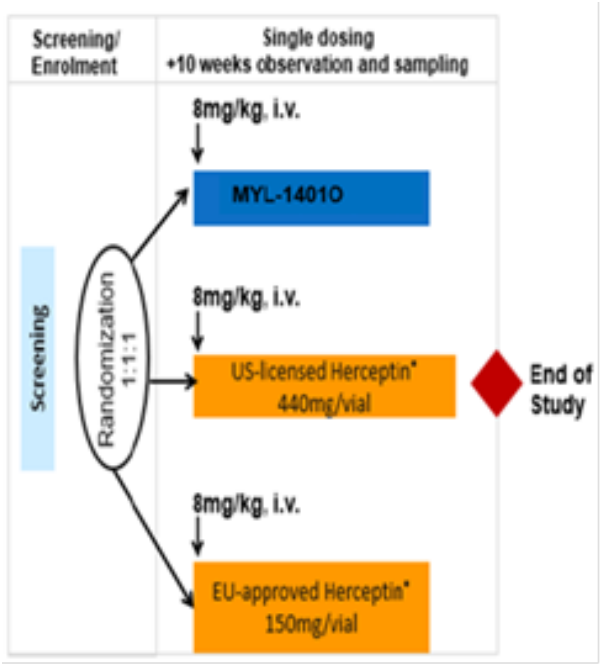


Figure 3: MYL-Her-1002: study design

In the case of a monoclonal antibody with per definition a long half-life and a potential of immunogenicity, a parallel design is accepted by EMA and commonly used.

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. As stated in the EMA scientific advice in 2012, given that the clearance is independent of dose in the therapeutic dose range, any dose in this range is suitable for the study. The single dose of 8mg/kg in intravenous infusion (over 90 minutes) is judged adequate based on the posology of the reference product. This corresponds to a widely used treatment schedule in patients who receive an initial 8 mg/kg loading dose followed by a maintenance dose of 6 mg/kg every 3rd week. Furthermore, this is the intended regimen selected by the applicant for the Phase III study.

Biobatches of US-Herceptin and Ogivri have a protein concentration of 21.8 mg/ml and 21.1 mg/ml respectively, which do not differ more than 5%. However, for EU-Herceptin (batch n° H4078b02), the content of protein is mentioned as 158mg/vial in the certificate of analysis which corresponds to 10.5 mg/ml, the vial volume being 15 ml. As such, the protein concentration is half the content of the two other products. This point should be clarified.

A sufficient number of samples to adequately characterise the whole profile are 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.

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. The subjects were allowed to leave the clinical facility after the 48-hour blood sample collection. 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).

The method developed for the quantitation of trastuzumab in human serum was performed using enzyme-linked immunosorbant assays (ELISA) (see bioanalytical methods).

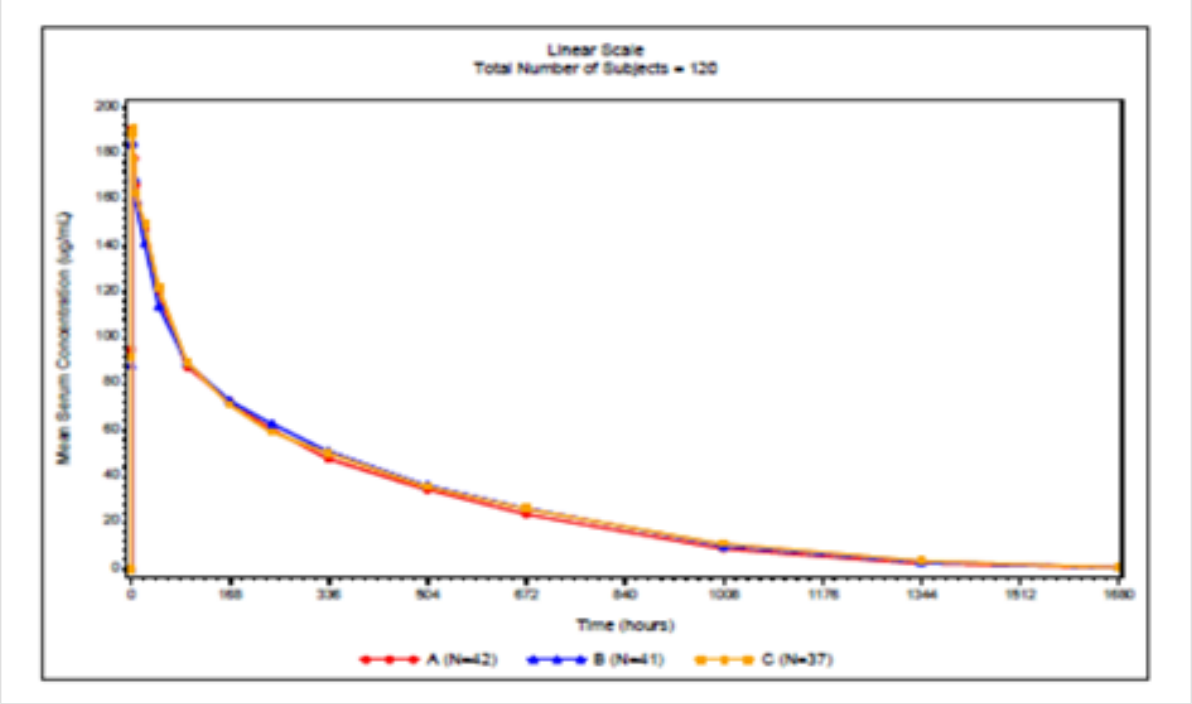


Figure 4: Geometric Mean Serum Concentrations of MYL-1401O, EU-approved Herceptin 150 mg in vial and US-licensed Herceptin 440 mg in vial (dose-normalised analysis, Study MYL-Her-1002)

Pharmacokinetic results

Table 3: 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) = $e^{[\text{LSMEANS of (LNA - LNB)}]}$
**Used Natural Log Transformed Parameter

Bioequivalence for Ogivri and Herceptin was demonstrated since the ratios (90% CI) of geometric means for both primary PK endpoints AUC0-last, AUC0-inf and Cmax are within the acceptability range of 80-125%. In addition, the mean secondary PK endpoints show to be similar for the Ogivri and Herceptin treatment groups.

Table 4: 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

In Study MYL-Her-1002, the immunogenicity of MYL-1401O (Ogivri) and Herceptin was measured at pre-dose (Day 1) and Day 71 (or at early termination). There were no instances of either treatment-induced or treatment-boosted ADA-positive subjects in the study (see safety assessment).

Clinical Study BM200-CT3-001-11

This study is a supportive study. The objective is 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.

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 5: Bioequivalence Analysis of Bmab-200 vs. Herceptin for Single Dose PK Parameters (PK-Population)

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 are 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% which indicate bioequivalence of Bmab-200 to Herceptin.

Population PK

The proposed POP PK model is judged acceptable for the purpose and the derived PK parameters showed good concordance between the 2 products.

In Study MYL-Her-3001, 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. If the Cycle 6 end-of-infusion sample was not feasible, a sample was collected at the end of infusion from any of Cycles 7 to 9. Additional samples were taken from patients enrolled in the PopPK subset of Part 1.

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.

The results showed that the population PK profiles of MYL-1401O versus EU-approved Herceptin were not different in patients with HER2-positive MBC.

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 nor at Cycle 6.

It was also demonstrated 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 modelled 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.

Special populations

Analyses in the special populations are not relevant in the Ogivri MAA as the biosimilar relies on the information already known of the reference product. Renal and hepatic impairment are not expected to influence the PK of an antibody and dedicated PK studies in patients with renal or hepatic impairment have not been carried out. Based on a population pharmacokinetic analysis, the influence of gender and race were rather small for Herceptin (Assessment Report for Herceptin, EMA/842364/2009). Body weight did not appear to significantly influence trastuzumab clearance. Age had no clinically significant effect on the pharmacokinetics of trastuzumab in patients treated (Herceptin SmPC 2015). Dose adjustments on the grounds of advanced age are therefore not required for trastuzumab. No clinical studies have been conducted with Ogivri in the paediatric patient population.

Drug-drug interactions

No formal interaction studies have been performed with Ogivri. Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed. By analogy to endogenous IgG, trastuzumab clearance did not appear to occur by excretion and liver metabolism as conventional drugs. It seems that trastuzumab levels are regulated in the vascular compartment by endothelial cells via the FcRn receptor knowing to possess the function of

transport of IgG and control of IgG catabolism, rendering classical mechanisms for pharmacokinetic interactions unlikely.

3.3.2. Pharmacodynamics

MYL-1401O is a proposed biosimilar to Herceptin (trastuzumab, Roche Registration Lt, UK) indicated for the treatment of human epidermal growth factor receptor2 (HER2) overexpressing cancers. It is a humanized immunoglobulin G1 monoclonal antibody produced by mammalian Chinese hamster ovary cell suspension culture and purified by affinity and ion exchange chromatography, including specific viral inactivation and removal procedures. Trastuzumab is directed against an epitope of the external domain of the HER2 protein, sub-domain IV. It was the first targeted therapy against HER2 to show clinical efficacy in breast cancer.

Overexpression of HER2 is observed in 20 %-30 % of primary breast cancers. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8 % to 34.0 % for IHC and 7.1 % to 42.6 % for FISH. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

HER2 is the only member of the ErbB family that has no known ligand, and it is thought to be primarily the preferential heterodimerization partner for other ErbB receptors (see Figure below). In 2003, analysis of the crystal structure of HER2 revealed that the extracellular region of the receptor is in a fixed dimerization state, making it available to interact with any other ErbB RTK. This key observation led to a better understanding of the transforming capabilities of HER2 overexpression, with increasing availability to form hetero- or homodimers that lead to enhanced signalling in both the presence and absence of ligands.

Mechanism of action

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.

Primary 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.

Pharmacodynamics for MYL-1401O were evaluated in Study MYL-Her-1001, encompassing 22 healthy subjects of which 19 completed the study, though it should be noted that currently no validated PD markers exist. Therefore, the parameters studied in this PD investigation included:

- *Ex vivo* serum antiproliferative activity (PI) in HER2 overexpressing breast tumour cells

- Immunomodulation by way of cytokine production in serum, mononuclear cell subset immunomodulation, and stimulation of peripheral blood mononuclear cells to measure cytokine production.
- Cytotoxicity using markers of apoptosis in PBMCs and Akt phosphorylation

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

- Proliferation inhibition (antiproliferative activity)
  - Ex vivo serum anti-proliferative activity on breast tumour 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, tumour 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 6: Exploratory pharmacodynamic investigations

Table 3: Exploratory pharmacodynamic investigations

Variable	Treatment Difference	Time Effect comparison	Time Effect 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

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.

Secondary pharmacology

For immunogenicity evaluation of MYL-1401O and Herceptin please refer to relevant sections in the PK and safety parts.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

In general, 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 Advices. The comparability exercise was performed between EU sourced reference product (German Market) and the formulation intended to be marketed in the European Union (EU). In addition, comparability with US licensed Herceptin formulations were used as supportive data.

The Ogivri (MYL-1401O) PK program consists of 2 pivotal studies carried out in healthy subjects (Clinical Study Reports MYL-Her-1001 and MYL-Her-1002) and 1 supportive study in combination with docetaxel in patients with Her2+ metastatic breast cancer (Clinical Study Report BM200-CT3-001-11).

The submitted primary PK analysis shows 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.

Based on these data both products can be considered as similar.

A population pharmacokinetic (PopPK) analyses has been carried out for protocol MYL-HER 3001 and the derived parameters showed good concordance between the 2 products.

Analyses in the special populations 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 judged needed.

In conclusion, from a PK perspective, the data provided support the biosimilarity of Ogivri (MYL-1401O) and Herceptin.

Pharmacodynamics

Regarding pharmacodynamics, a wide range of exploratory PD markers were analyzed in study MYL-Her-1001. Results showed no significant difference between Hercules and Herceptin for any of the PD parameters analyzed although many showed marked changes over time for both groups.

PD investigation for this procedure 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.

Trastuzumab can also recruit cytotoxic effector cells due to the Fcγ-fragment, which in turn may contribute to the anti-tumour effect. Thus, the PD investigation was ideally placed for following the immunomodulation effects of MYL-1401O.

Generally, the primary pharmacodynamics comparisons between MYL-1401O and Herceptin indicate that both products have for all intents and purposes a similar PD profile. Curiously though there was a significant difference in the immunomodulatory CD8+ T-cell marker between treatment groups, but given that other makers were well within bounds and the small study population it is not possible to find clinical relevance in this observation. Likewise, independent ANCOVA analysis found that there was a difference in the IgG biomarker expression between treatments, but again the small numbers and the fact that other immunoglobulins were well within similarity bounds makes it hard to make any definite conclusions on this observation.

One apoptosis marker, cleaved caspase-3, had a noticeable increase at 48 hours and showed a marginally non-significant difference between treatment groups ($p = 0.0498$). Nonetheless, no other apoptosis markers mirrored this edge case significance and as such this finding is likely also spurious without any clinical impact.

Based on the lack of a clear dose-response relationship and based on the fact that for the time being, there is no accepted surrogate marker that can be related to patient benefit, the proposed PD endpoints cannot be considered as proof of comparability. Having said that, PD findings does not contradict the available data for the overall comparability exercise.

3.3.4. Conclusions on clinical pharmacology

From a PK perspective, the data currently provided seem to support the biosimilarity of MYL-1401O and Herceptin, although some minor some issues still need to be clarified. Some PK-related other concerns are raised in relation to GCP compliance, bioanalytical methods and assay content (see LOQ). The submitted studies Myl-Her-1001 and Myl-Her-1002 show bioequivalence 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 interval of 0.80-1.25. Results from the population PK analysis showed that the population PK profiles of Ogivri (MYL-1401O) versus EU-approved Herceptin were not different in patients with HER2-positive MBC.

In general, the pharmacodynamics investigation results lend significant support to the claim of equivalence to Herceptin. Some PK-related other concerns are raised in relation to GCP compliance, analytical methods and assay content. PD findings do not contradict the available data for the overall comparability exercise.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

Introduction

MYL-1401O, containing trastuzumab as its active moiety, is intended to be brought to market as a biosimilar product with Herceptin acting as the innovator.

Trastuzumab, an G1 immunoglobulin monoclonal antibody, is currently seen as the standard proscribed care for patients suffering from oncological malignancies that express the human epidermal growth factor 2 (HER2+) expressed in early and advanced breast cancer as well as metastatic gastric cancer. Compared to HER2- cancer patients those burdened with the HER2+ phenotype have an inferior prognosis manifested by shorter disease-free and overall survival.

In support of the efficacy comparison between Ogivri and Herceptin the Applicant provided results of two trials: MYL-Her-3001 and BM200-CT3-001-11.

The MYL-Her-3001 trial was conducted with the formulation meant for marketing, which is slightly different from the Herceptin one due to difference in excipients. The BM200 trial used Bmab-200, which was a product using a formulation that used the same excipients as in the EU-approved and US-licensed Herceptin formulations.

As agreed on during pre-submission meetings the results of the BM200 trial will only be regarded as supportive in this application.

For the overview of studies please see the Table at the beginning of the clinical part.

Main Study

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

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 5. 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. In total 15 patients on MYL-1401O and 17 on Herceptin treatment also received taxanes in Part 2.

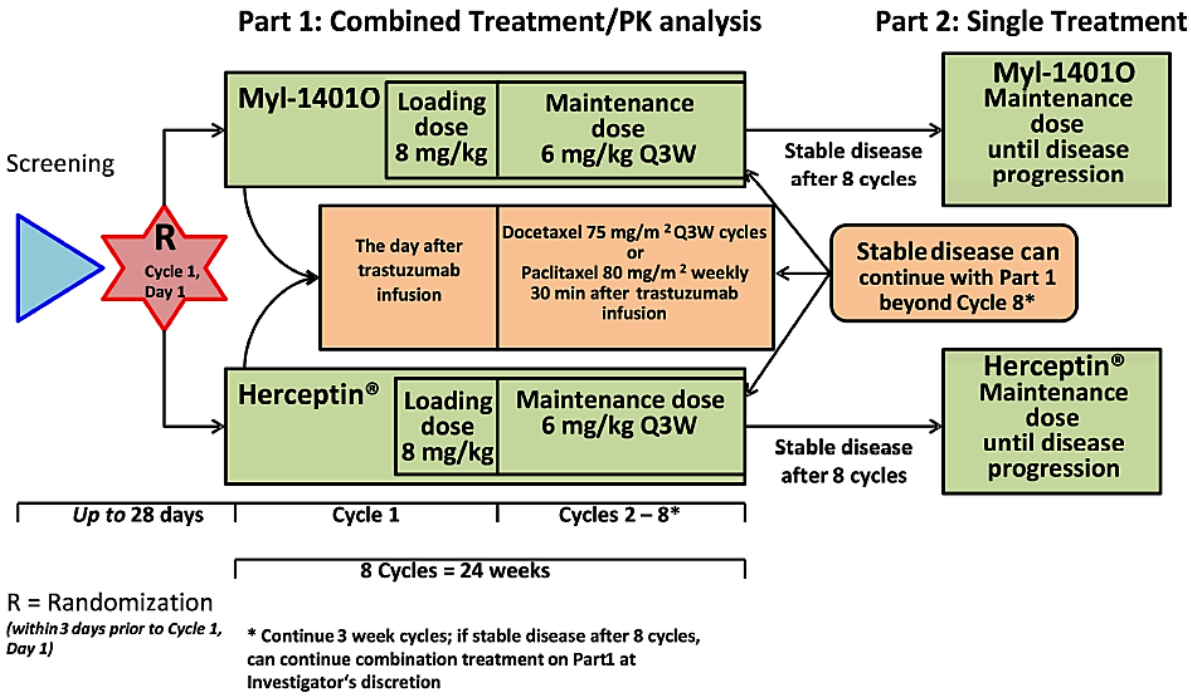


Figure 5: Schematic of the Design of Study MYL-Her-3001

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.

The study included female patients with histologically confirmed diagnosis of breast cancer, and who had not received prior systemic therapy in the metastatic disease setting, and who had HER2 gene amplification as confirmed by fluorescent in situ hybridization (FISH), or HER2-overexpression by immunohistochemistry (defined as IHC3+, or IHC2+ with FISH confirmation). Enrolled patients should have had at least 1 metastatic target lesion. Before randomization, HER2 detection and tumour assessment were conducted independently at a central laboratory.

The demographic profile was similar in the MYL-1401O arm versus the Herceptin arm with respect to height, weight, race, and body surface area. With regards to age, the mean age was slightly lower in the Herceptin arm compared with the MYL-1401O arm (52.9 years vs. 54.3 years) and a slightly higher percentage of patients were <50 years of age in the Herceptin arm compared with the MYL-1401O arm (37.7% vs. 32.2%).

Statistical methods

The primary efficacy endpoint was the best ORR, where objective response was defined as a CR or PR according to Response Evaluation Criteria in Solid Tumour (RECIST) Version 1.1, with central tumour evaluation.

Equivalence of MYL-1401O and Herceptin was analysed using pre-specified equivalence intervals, based on the ratio of ORRs as per advice from the US Food and Drug Administration (FDA). 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 CI was within the equivalence range of (0.81, 1.24).

It was noted that said equivalence margin had been calculated based on combination treatment with various taxanes, and that clinical significance of ORR use was validated based on a method that aimed to link ORR to TTP or PFS (two measures that are not always easily translatable to each other), and this raised doubts whether the calculated margin was indeed the most relevant possible. In their response, the Applicant correctly pointed out that since different taxanes were allowed as concomitant treatment in the pivotal study it would make sense to have this fact represented in the EM calculation. Furthermore, they correctly argued that in studies using trastuzumab in MBC the mortality rate is quite low, which does in fact allow TP and PFS to be considered as practically equivalent. Also, only one study in the study-pool employed to assess clinical relevancy of ORR as an equivalence measure used a different primary endpoint compared to the others. As such it is agreed that the EM calculation based on ORR is both clinically validated and acceptable.

Based on scientific advice from the CHMP, an additional equivalence analysis was conducted using the difference in best ORRs. 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 with/following the EMA Scientific Advice received March 15, 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.

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.

This sample size assumed that both treatment groups would exhibit an ORR of 69% at Week 24 and that the ratio of MYL-1401O to Herceptin was analyzed with a 2-sided 90% CI. If the ratio of MYL-1401O to Herceptin was analyzed with a 2-sided 90% CI, and this CI fell wholly within an equivalence region defined as (0.81, 1.24), then equivalence was to be declared. This sample size of 410 would provide a power of 90% to demonstrate equivalence for the difference in ORR given the margins (-15%, + 15%) using a 95% CI. To arrive at the planned number of patients, the required sample size of 410 was increased to 456 to reflect an approximate 10% attrition rate.

Study participants

Study participants had to be at least 18 years of age, with recurrent or metastatic BC that was not amenable to curative surgery/radiation, have HER2 gene-amplification or over expression, and not having been treated with trastuzumab or lapatinib at least 1 year before study participation.

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 Part 3 study comparing weekly paclitaxel to every-3-week paclitaxel, which demonstrated 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.

In part 2 all patients with at least SD from 1st- line combination therapy continued on their maintenance dose of Part 1, and this until disease progression, discontinuation or death. 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
- Nonstudy drug therapy for MBC, with the exception of hormonal therapy (permitted in Part 2 of the study for ER/PgR-positive patients).

Objectives & Endpoints

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.

The corresponding 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).

Secondary objectives encompassed comparison of independently assessed clinical activity at Week 24 between treatment arms by measuring TTP, PFS, OS and DR, as well 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.

Sample size & randomization

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 as requested by FDA and EMA. Given an estimated 10% attrition rate the required sample size of 410 was then adjusted to the final needed number of 456 persons.

It was noted that during protocol development the number of patients expected to be enrolled was drastically increased without clear reason, despite the originally planned 470 patients being seemingly sufficient to reach 80% power. In their reponse the Applicant carified that these changes were in response to concerns of regulatory agencies (FDA) and updates to the meta-analysis used for population size alculation with more state-of-the-art data.

Randomization was done in a 1:1 proportion to 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).

Choice of concomitant taxane was an Investigator decision at the site level before the start of screening, and subsequently all trial subjects in that centre had to be given the chosen taxane only.

Statistical analysis sets & methods

The statistical analysis sets consisted of the primary ITT1 population (all patients who were randomized under Protocol Amendment 2), used for the primary endpoint analysis, and secondary ITT2 (all randomized patients, including those randomized under protocol amendment 1) and PPP populations used for sensitivity analyses. Further statistical analysis sets were the SP and the PKP, used for safety and PopPK analyses respectively.

The primary efficacy analysis was based on FDA requested ratio of ORR with equivalence margin (0.81, 1.24), and EMA recommended difference in best ORRs with and equivalence margin of (-15%, +15%). For the latter, the following hypotheses were used:

H0: (RT - RC $\leq$ -15%) or (RT - RC $\geq$ 15%)

H1: -15% < (RT - RC) < 15%,

whereby RT was the best ORR of test (MYL-1401O) and RC the best ORR of control (Herceptin). A two-sided 95% CI for the difference of the best ORRs at Week 24 was calculated, and equivalence was declared if said CI was wholly within the pre-specified equivalence margin.

Secondary analyses presented Kaplan-Meier plots by treatment and the log-rank test of the 2 treatment groups unadjusted for any covariates was performed. Forest plots were produced for subgroups according to the stratification factors.

Finally, various sensitivity analyses using the ITT2 and PP populations were executed, including replication of the primary analyses in said sensitivity analysis sets.

Patient Disposition

In total 826 patients were screened, of which 39.5% (n = 326) failed the screening (the majority by lack of HER2+ confirmation). Of the 249 patients that were assigned to the MYL-1401O arm 185 completed Part 1 of the study (74.3%) while the Herceptin2 arm 171 (68.1%) did. The main reason for discontinuation was disease progression (18.9% versus 22.7% in the parallel Herceptin group).

Of the above 356 subjects that completed part 1 of the pivotal study, 342 moved on to participate in part 2 (179 MYL-1401O and 163 Herceptin patients). Of these 342 subjects 62.6% (n = 214, MYl-401O = 116, Herceptin = 98) completed the foreseen 48 week total study time. Of the 128 subjects that discontinued participation in part 2 the vast majority (n = 108) did so due to disease progression. Of note is the fact here that equal rates of MYL-1401O and Herceptin subjects experienced DP (31.3% vs 31.9%), and that about a twice higher rate of Herceptin patients did so due to AEs (1.1% versus 2.5%).

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

Figure 7 provides the patient flow in Part 2. Note that the former is based on the ITT1, whereas the latter is based on the complete safety population. Of the 230 randomized MYL-1401O patients that were part of the primary ITT1 analysis set 75.2%, or n = 173, completed Part 1 of the study, while of the 228 randomized Herceptin ITT1 patients 69.7%, or n = 159, did the same. In this subpopulation, the biggest reason for discontinuation was also disease progression (MYL-1401O = 17.8% versus Herceptin 22.4%). Kaplan-Meier analyses did not reveal any difference in time to discontinuation between both groups.

Demographics for the ITT1 set are provided in Table 7 below. 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.

The demographic profile of the 342 patients in the safety population entering Part 2 was consistent with the Part 1 population. The mean age of patients was slightly lower in the Herceptin arm: the mean age (± SD) of patients in the MYL-1401O arm was 55.1 ± 10.40 years with a range of 31 years to 79 years, and the mean age (± SD) of patients in the Herceptin arm was 53.1 ± 11.60 years with a range of 26 years to 81 years.

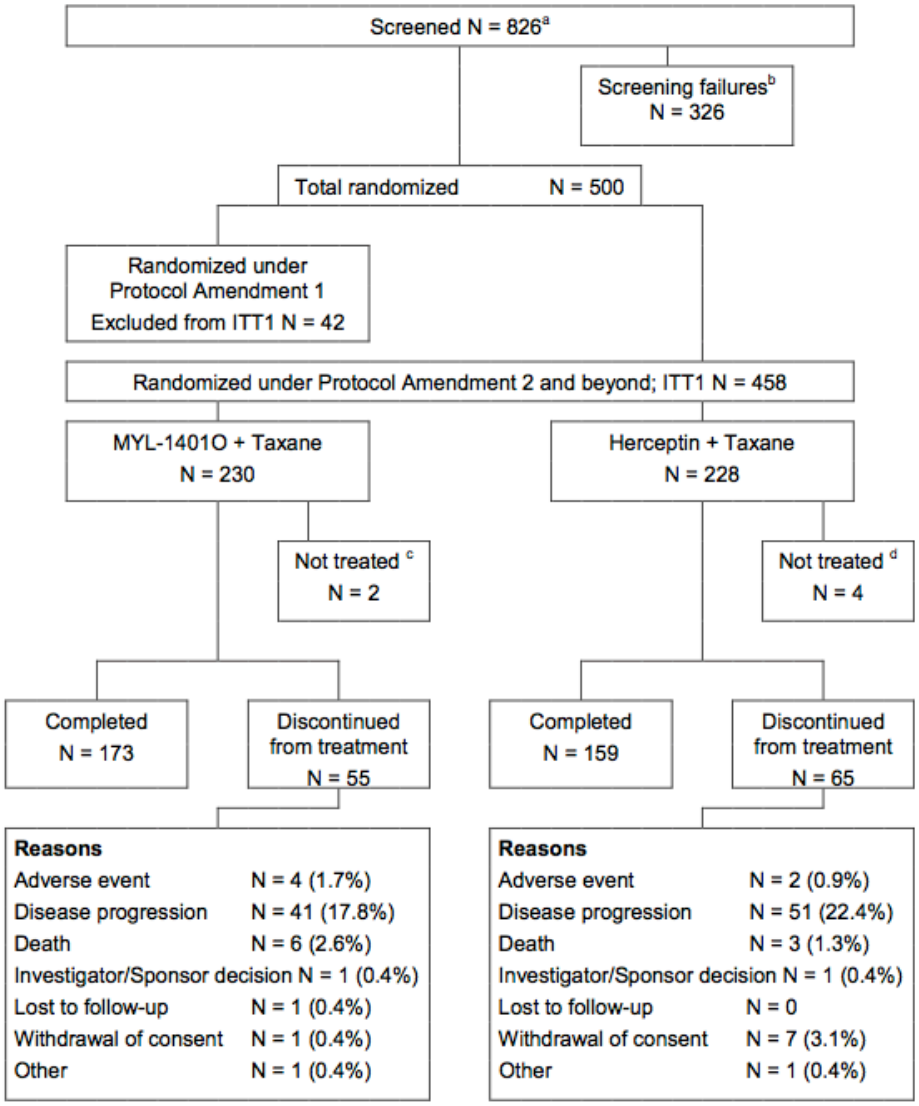
In both groups, the majority of patients was ≥50 years old with a higher percentage of patients in the MYL-1401O (71.5%) than the Herceptin arm (63.2%) falling into this category. The mean BSA (± SD) of patients was very similar in both treatment groups (MYL-1401O 1.73 ± 0.201 m^2, range: 1.3 m^2 to 2.2 m^2; Herceptin 1.74 ± 0.222 m^2, range: 1.1 m^2 to 2.4 m^2). In both treatment groups, the majority of patients were Caucasian (MYL-1401O 70.9%, Herceptin 70.6%). A little less than 30% of patients were Asian (28.5% versus 29.4%, respectively).

Generally, the demographic profile was similar between treatment groups with respect to age, race, height, weight, and BSA.

The ITT1 population was unchanged from Part 1 to Part 2. A total of 320 patients of the ITT1 entered Part 2 (169 patients in the MYL-1401O arm and 151 patients in the Herceptin arm).

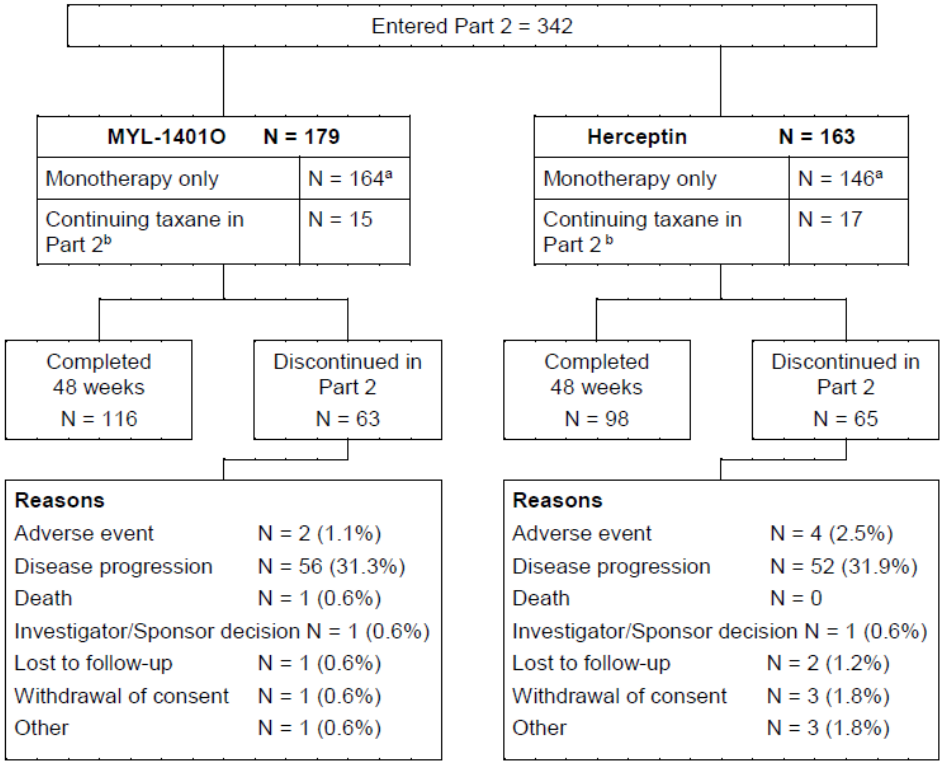
Likewise, the ITT2 population was unchanged from Part 1 to Part 2. A total of 342 patients of the ITT2 entered Part 2 (179 patients in the MYL-1401O arm and 163 patients in the Herceptin arm).

Finally, the PP population was also unchanged from Part 1 to Part 2. A total of 316 patients of the PP entered Part 2 (166 patients in the MYL-1401O arm and 150 patients in the Herceptin arm).



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 6: 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 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.*

Figure 7: Participant flow in Part 2 of the study, Safety population

Table 7: 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.

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.

Concomitant medicine use was rampant with almost 100% of all patients using these drugs. Most commonly used 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.

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 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. However, less patients on monotherapy used concomitant medications compare to those on combination therapy in Part 1.

Summary of main efficacy results

Primary Efficacy Analysis

The primary objective of Part 1 was to compare the best ORR at Week 24 in patients treated with MYL-1401O plus taxane compared with patients treated with Herceptin plus taxane, whereby the 2-sided 90% CI for the ratio of best ORRs at Week 24 had to be entirely within the equivalence range of 0.81 to 1.24 in order to confirm equivalence.

The results of the primary efficacy analysis are summarized in Table 8. At Week 24, the ratio of the ORRs was 1.09 with a 90% CI of (0.974, 1.211), a range which lays entirely within the pre-defined equivalence boundaries. Thus, therapeutic equivalence of MYL-1401O and Herceptin was statistically confirmed per FDA's recommendation in this study.

Table 8: 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

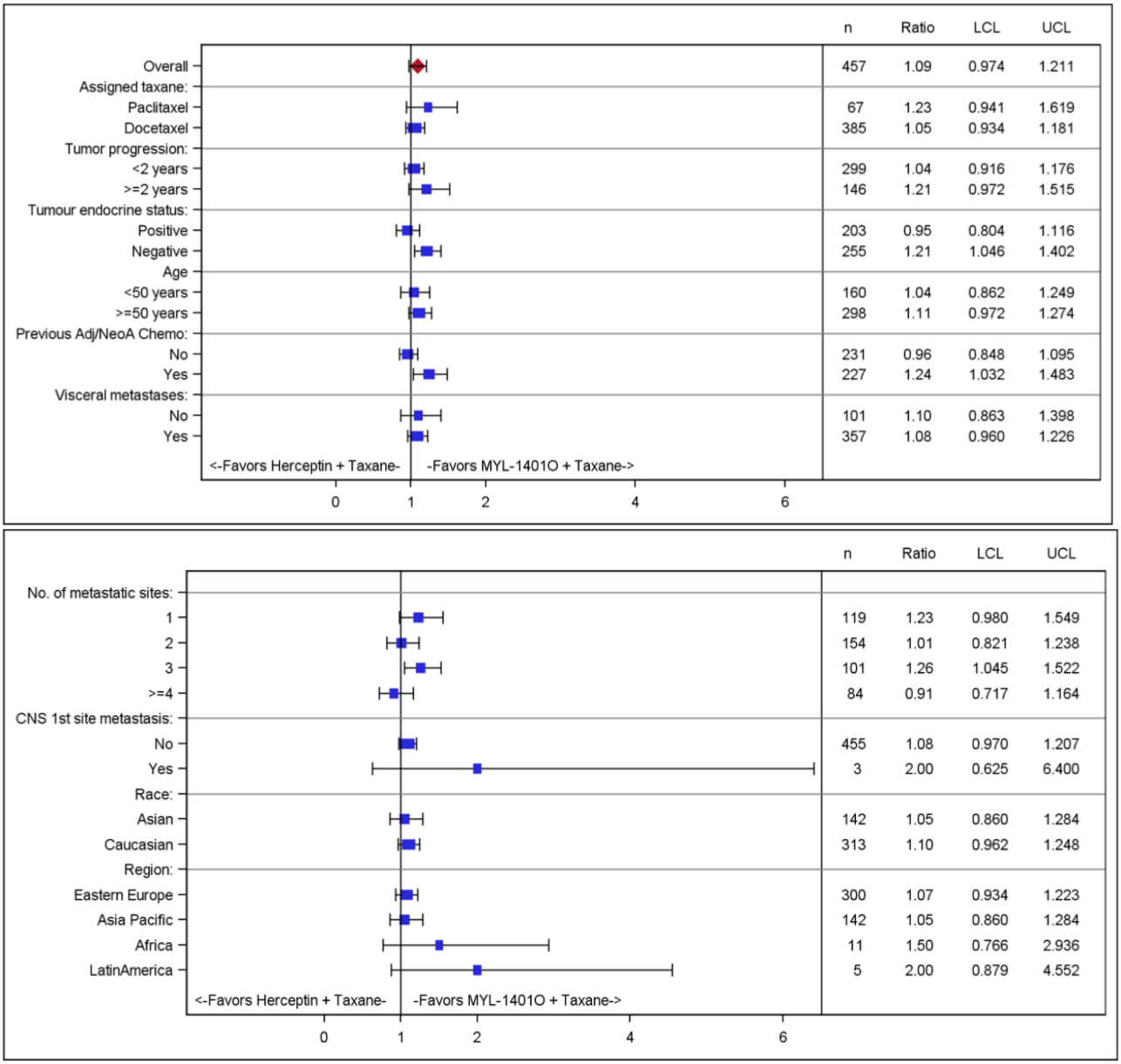
The equivalence of both treatments was also evaluated using the 2-sided 95% CI for the difference in best ORRs at Week 24 being entirely within the equivalence range of (-15%, 15%). The results of Study MYL-Her-3001 showed that the difference in best ORR between both treatment arms (MYL-1401O minus Herceptin) was 5.5% with a 95% CI of (-3.08%, 14.04%). Thus, therapeutic equivalence of MYL-1401O and Herceptin was also statistically confirmed per EMA's recommendation.

Table 9: 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

Subgroup analyses of best ORR were also performed by stratification factors (assigned taxane, tumour progression, tumour endocrine status), age, previous adjuvant/neoadjuvant chemotherapy or HER2 targeted treatment, visceral metastases, number of metastatic sites, CNS as first site of metastasis, race and geographic region (Eastern Europe, Asia Pacific, Africa, Latin America). Results generally supported the ORR ratio and difference findings, though three subgroups did seem to indicate a better response with MYL-1040O (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.



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.

Figure 8: Ratio of Best Overall Response Rate (ORR) at Week 24 Overall and by Subgroup: ITT1 Population

Sensitivity Analyses

The primary efficacy 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 and confirming the therapeutic equivalence between MYL-1401O and Herceptin.

Lastly, 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 I 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

Secondary analyses included TTP, PFS and OS at W24 and W48, as well as DR at Week 48.

Time to Tumour Progression

In the MYL-1401O arm, 35 patients (15.2%) had tumour progression compared to 44 patients (19.3%) in the Herceptin arm and according to the log-rank test, the time-to-event curves for both treatment arms were not statistically significantly different (p = 0.192). K-M estimates were non-descript due to the fact that only a relatively small number of patients presented with tumour progression at Week 24.

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

Until W48 41.3% and 43.0% of MYL-1401O and Herceptin subjects, respectively, had tumour progression, and log-rank test showed no significant difference in the time-to-event curves, see **Figure 9**. K-M estimates indicated a median TTP of 11.1 months in both treatment arms. Of note is the fact that at W48 over 50% of patients had not yet shown progressive disease, which means that most likely a longer TTP will be observed at study end.

The average hazard ratio remained slightly lower with a longer TTP in benefit of MYL-1401O, though the difference was less pronounced at W48 than at W24, and thus remained statistically insignificant.

Table 10: Time to Tumour Progression (TTP) at Week 48, ITT1 Population

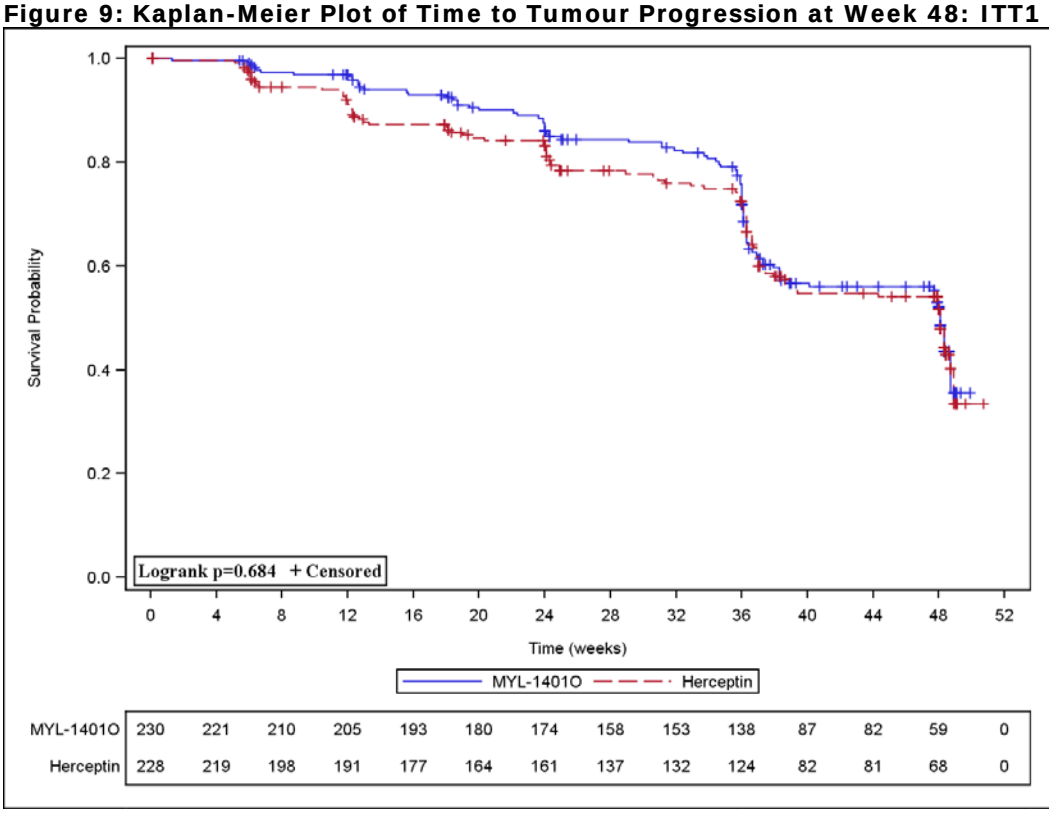
	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	230	228
Events, n (%)	95 (41.3)	98 (43.0)
Censored,[a] n (%)	135 (58.7)	130 (57.0)
Log-rank test: p-value	0.684	
Kaplan-Meier estimates [months]		
N	230	228
Mean (95% CI)	9.2 (8.82, 9.58)	8.8 (8.37, 9.26)
SE	0.19	0.23
Median (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 9: Kaplan-Meier Plot of Time to Tumour Progression at Week 48: ITT1

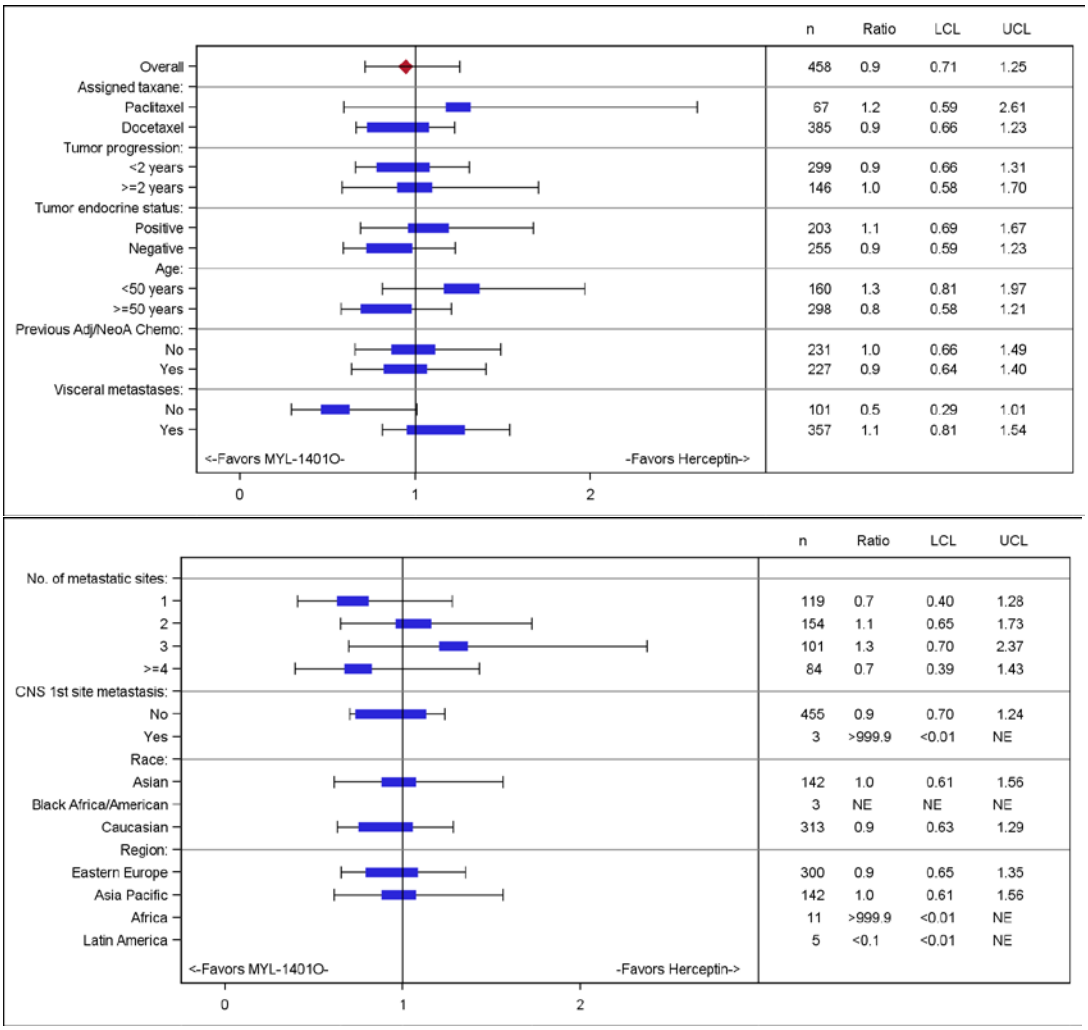


At 24 Weeks, the final model Cox regression model showed that previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment had a significant influence on TTP (hazard ratio 2.02, p = 0.003).

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 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), though due to the small number of patients with tumour progression the data were of limited clinical relevance.

Subgroup analysis (**Figure 10**) did not find any 95% CI of the TTP ratio that did not include '1' and thus no relevant subgroup differences exist.



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.

Figure 10: Time to Tumour Progression at Week 48 Overall and by Subgroup, ITT1 Population

Sensitivity analyses on TTP using the ITT2 and TP populations confirmed the above findings at W48.

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.

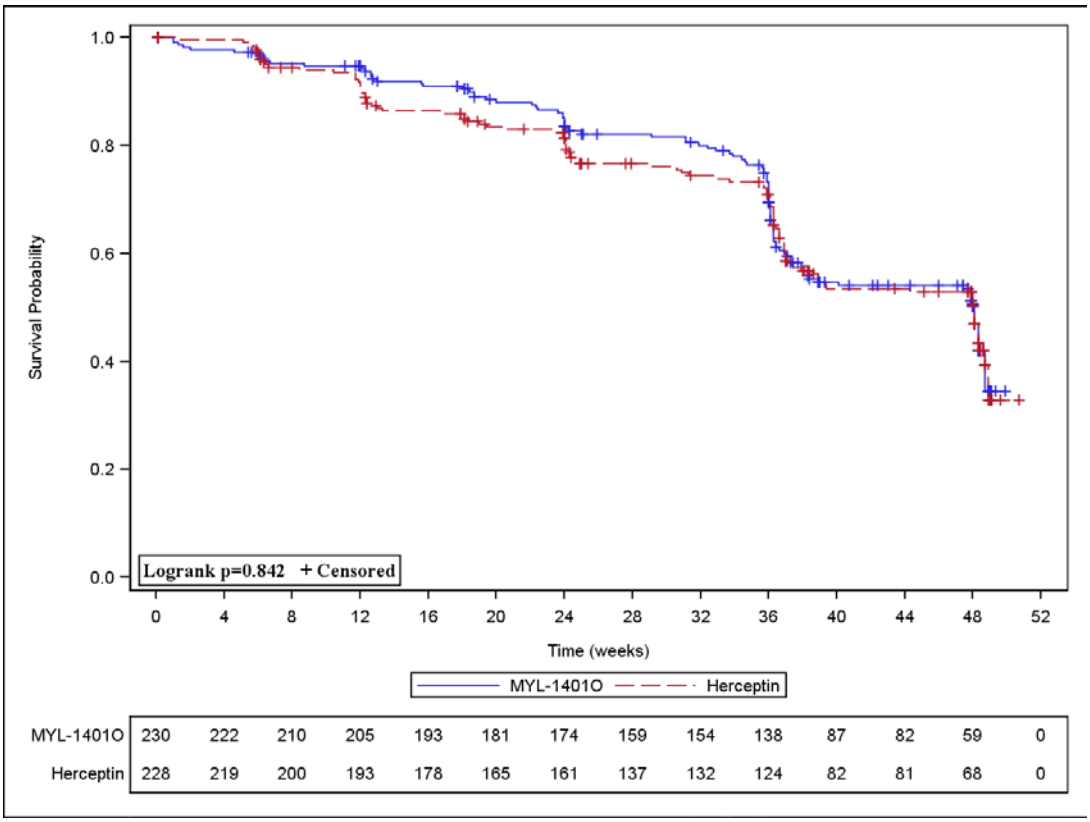
Until Week 48 (Table 24), 55.7% of MYL-1401O and 55.3% of Herceptin subjects still did not have progression of the disease (see **Table 11**). Log-rank testing showed that the time-to-event curves for both treatment groups were not different in a statistically significant way**.**

K-M estimate of median time for PFS was 11.1 months in both treatment arms. As more than 50% of patients in both treatment arms did not have tumour progression until Week 48 median PFS might still change when analysed using a later data cut-off.

Table 11: 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.



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.

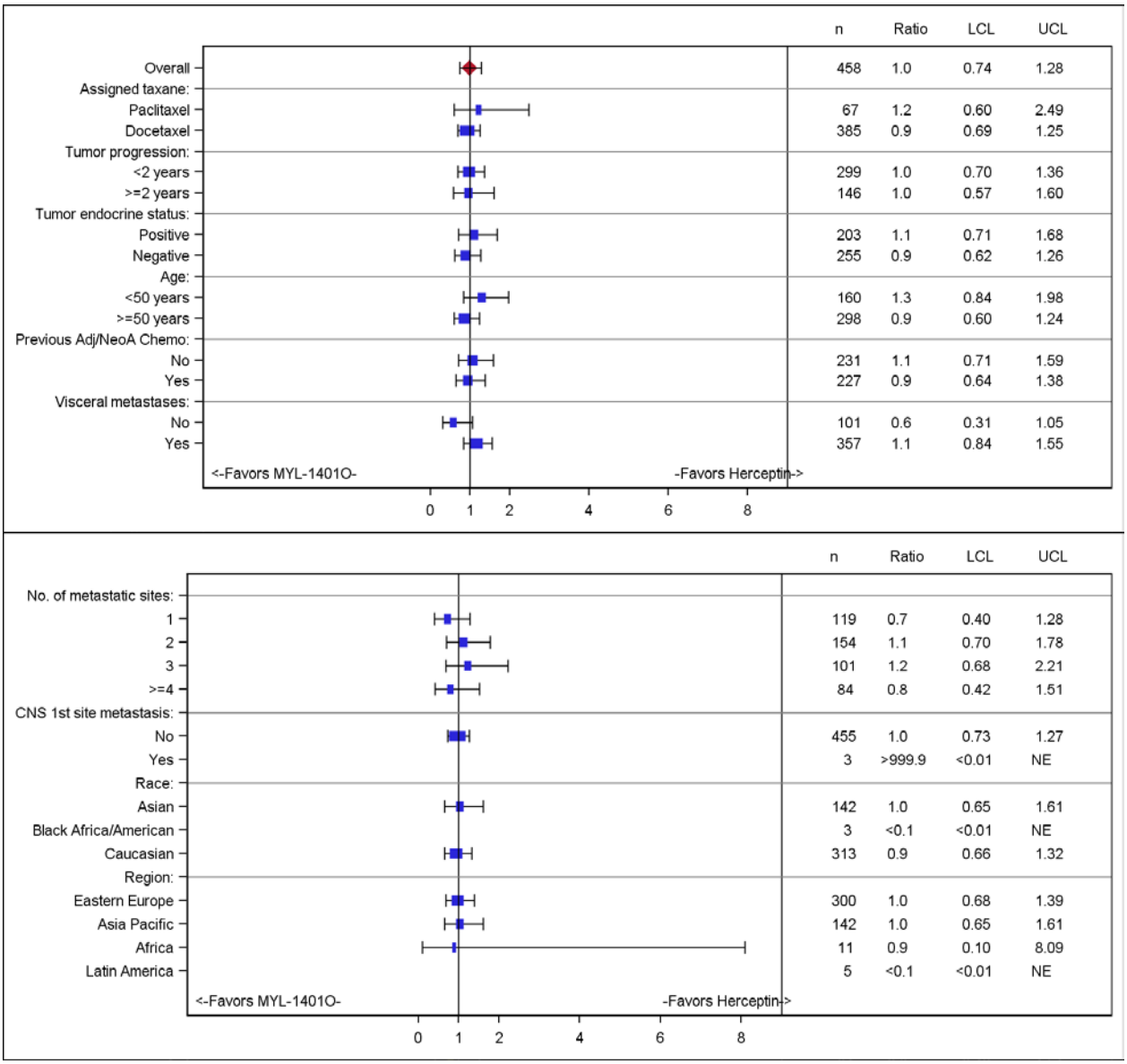
Figure 11: Kaplan-Meier Plot of Progression-Free Survival at Week 48, ITT1 Population

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 race1 had an influence on PFS, but due to the small sample size in these subgroup analyses the data were of limited clinical relevance.

Subgroup analysis (**Figure 12**) did not find any 95% CI of the TTP ratio that did not include '1' and thus no relevant subgroup differences exist.



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.

Figure 12: Progression-Free Survival at Week 48 Overall and by Subgroup, ITT1 Population

Sensitivity analyses on PFS using the ITT2 and TP populations confirmed the above findings at W48.

Overall Survival

In the MYL-1401O arm, 223 patients (97.0%) survived until Week 24 compared to 219 patients (96.1%) in the Herceptin arm, and according to the log-rank test, this differences 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 12), 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 18).

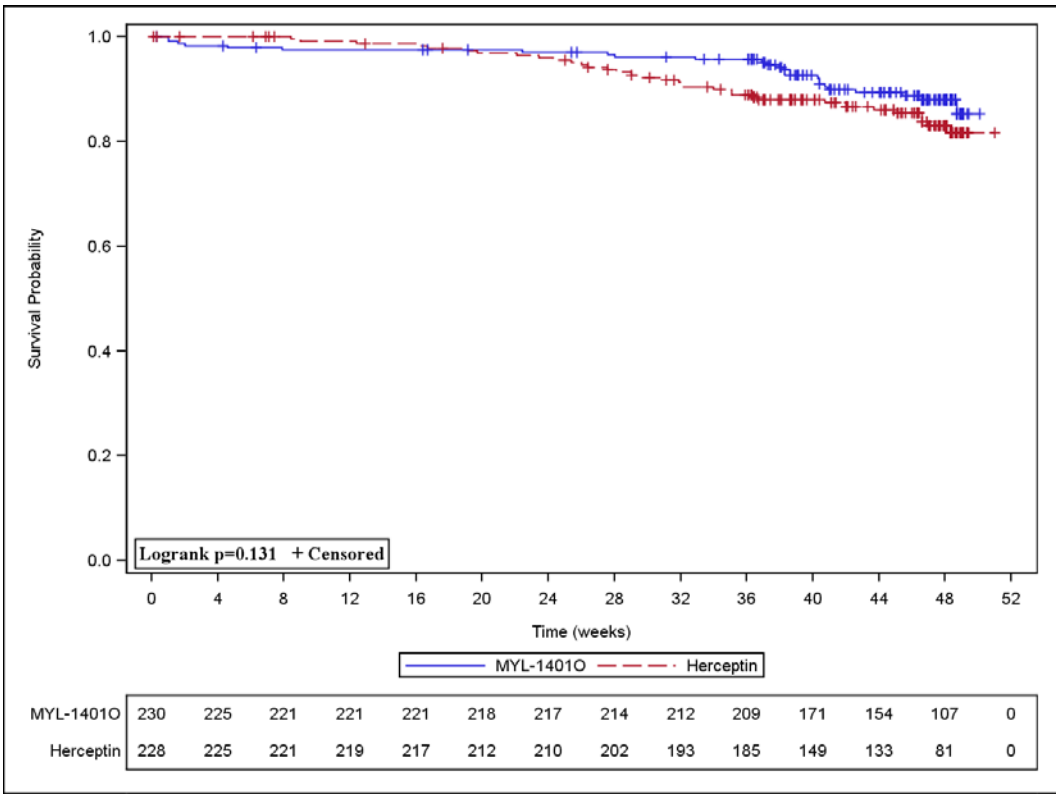
Note that for the Kaplan-Meier estimates for OS, the median was not reached, neither at W24 nor at W48, due to the relatively small number of patients in the ITT1 population who died prior to those time points. Thus, K-M estimates are of limited value up until the W48 data cut-off point.

At W48 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 conform the observation at W24. Likewise, the difference was again not statistically significant.

Table 12: 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.*



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.

Figure 13: Kaplan-Meier Plot of Overall Survival at Week 48, ITT1 Population

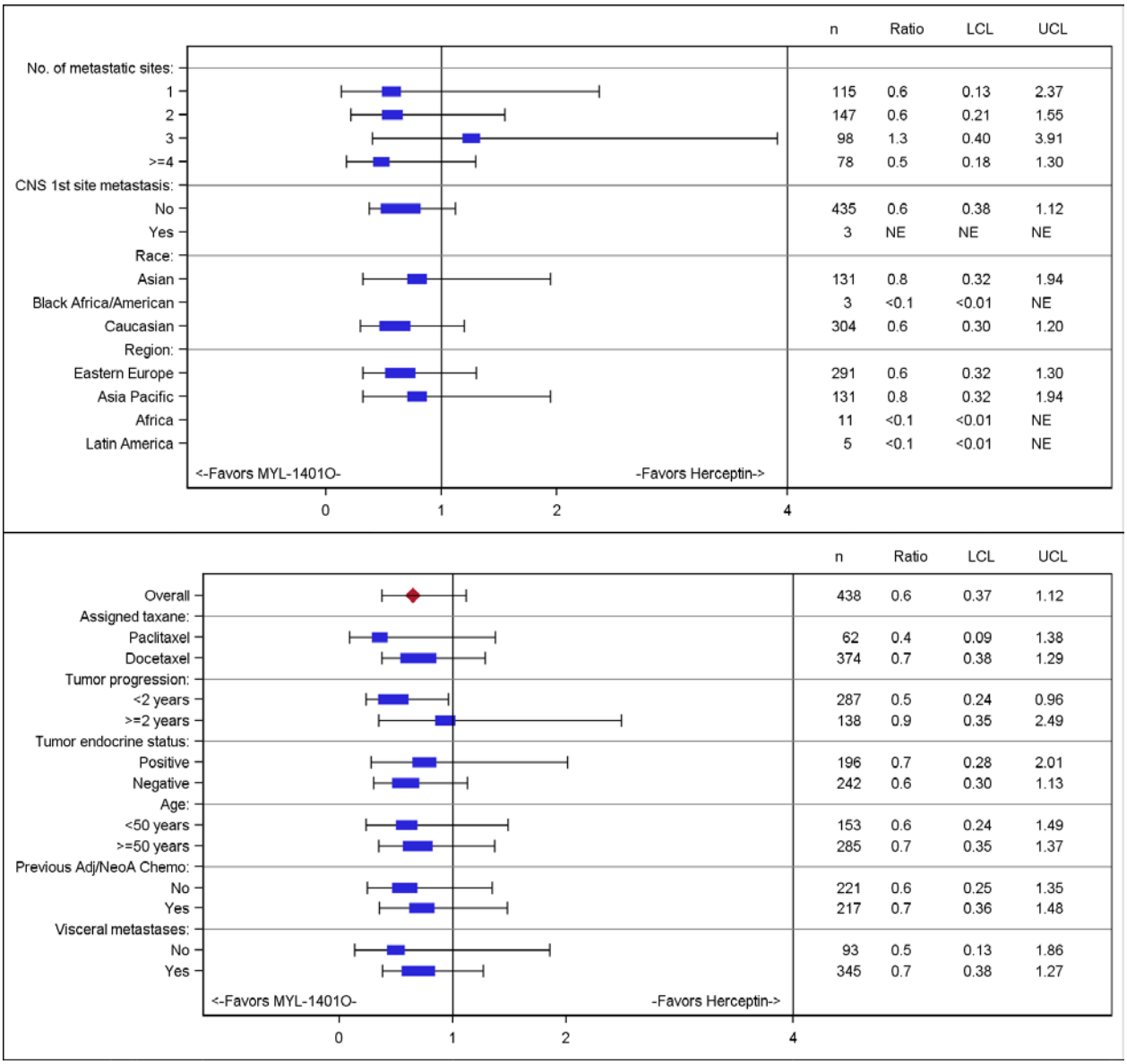
Cox regression analysis at W24 indicated that previous adjuvant/neoadjuvant chemotherapy/HER2 targeted treatment and race had an effect on the hazard ratio for OS and these parameters were thus included in the final model.

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 said final W48 model, tumour endocrine status and number of metastatic affected OS, though due to the small sample size in these subgroup analyses the data should be considered of limited clinical relevance.

A strange observation was made in the analysis of the 95% CI of the OS ratio (**Figure 14**), as the subgroup “tumour progression <2 years” CI at Week 48 did not encompass ‘1’ which indicates a relevant difference in ratio.

Upon analysis, no particular clinical explanation could be found. However, the Applicant claims that given the relatively small number of patients per subgroup, this aberrant result likely has no clinical or statistical significance. Given that this is the only result that deviates from the overall trend of similarity, and given that the aberration was not seen in the ITT2 and TP based sensitivity analyses, it is agreed that this isolated observation is likely an artefact without clinical significance.



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.

Figure 14: Overall Survival at Week 48 Overall and by Subgroup, ITT1 Population

Duration of Response

DR was defined as the time from the first documentation of objective tumour response to the date of first documentation of objective tumour progression or to death due to any cause, whichever occurred first.

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 13**. Log-rank testing did not show a statistically significant difference in the time-to-event curves for both treatment groups (**Figure 15**).

K-M estimate of median time to tumour progression or death after objective tumour response was 9.7 months in both treatment arms. However, since more than 50% of patients in both treatment arms did

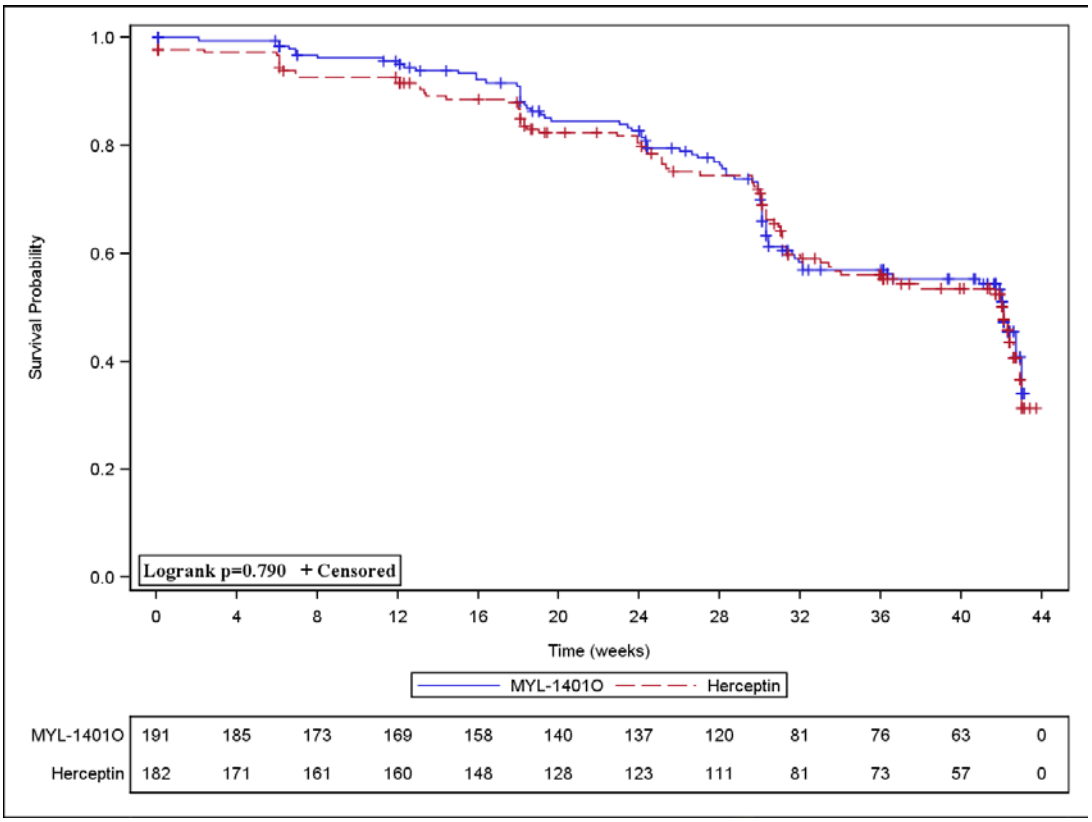
not have tumour progression or did not die until W48 the median duration of response might still change when applying a later data cut-off.

The stratified and unstratified hazard ratios MYL-1401O: Herceptin obtained from the Cox proportional hazard model were not significantly different for both hazard ratios. Thus, the average hazard rate for tumour progression or death after the tumour response as well as DR were not statistically significantly different in both treatment groups.

Table 13: 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.*

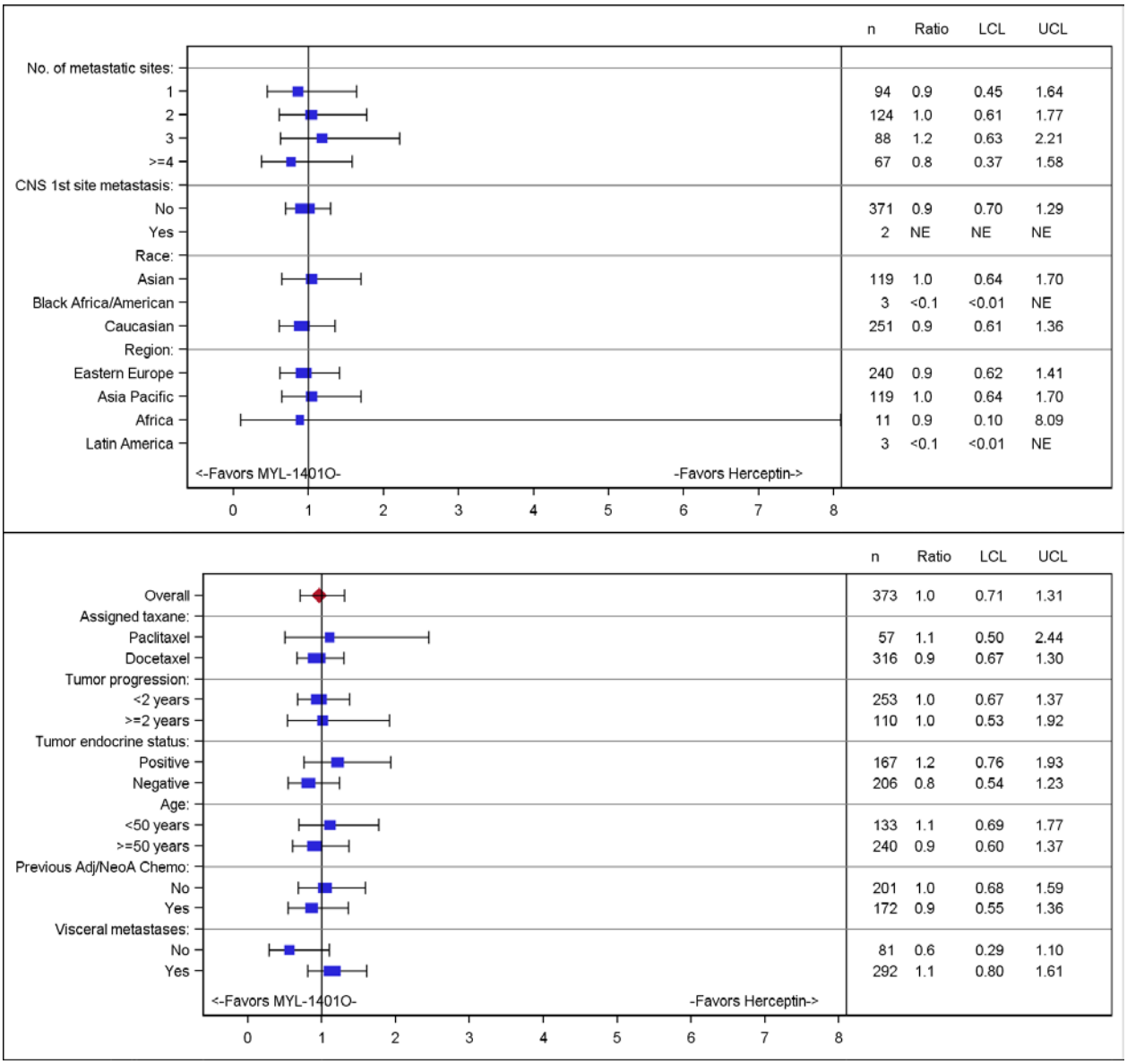


ITT: intent-to-treat
Numbers at risk are displayed at the bottom of the figure.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Figure 15: Kaplan-Meier Plot of Duration of Response at Week 48, ITT1 Population

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. However due to the small sample size in these subgroup analyses the data are of limited clinical relevance.

As shown in **Figure 16**, the 95% CI of the DR ratio included '1' for all subgroups at Week 48 and thus no relevant differences between the subgroups exist.



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.

Figure 16: Duration of Response at Week 48 Overall and by Subgroup, ITT1 Population

Exploratory analyses results

Disease Control Rate

Disease control was defined as confirmed CR, confirmed PR, or best response of SD according to RECIST Version 1.1 based on central tumour evaluation. 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.

Table 14: 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). Part 2 is still ongoing and results are not discussed in the D80 report. The endpoints for the primary and secondary objectives were to be analyzed at Week 24 in Part 1 and at Week 48 (only secondary) in Part 2.	
	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
	Herceptin (Part 2)		Herceptin. 24 weeks Safety: 163, ITT1: 151
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 analyzed 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 analyzed 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	*Only analyzed in Part 2.*
	Exploratory endpoint	Disease control rate	The sum of patients who had CR, PR, and SD according to RECIST 1.1. *Not analyzed in Part 2.*
	Exploratory endpoint	HER2/ECD	Baseline HER2/ECD assessed as a predictor for ORR, OS and TTP.
Database lock	Part 1: Not clearly specified in report, final assessment of final patient in Part 1: 25 January 2016 Part 2: Not clearly specified in report, final assessment of final patient in Part 2: 13 July 2016		
<u>Results and Analysis</u>			
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. 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)	Comparison groups	MYL-1401O - Herceptin (ITT1)
		Best ORR ratio	1.09
		90% CI	(0.974, 1.211)
		P-value	N/A
	Primary (ORR difference)	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
		N/A 95% CI - unstratified - stratified	N/A (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	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.

Clinical studies in special populations

Not Applicable.

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

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.

Furthermore, the BM200 trial was not statistically powered to conclusively evaluate similarity in efficacy between Bmab-200 and the reference product. ORR at 24 weeks in Study BM200-CT3-001-11 was based on imaging performed every 12 weeks whereas in Study MYL-Her-3001, tumour imaging was performed every 6 weeks.

Finally, the supportive study did not have a provision for confirmation of response and thus the measured ORR might not be a true representation of ORR as per RECIST Version 1.1.

Population

Given the comparison issues noted earlier no head-to-head comparison is done given the constraints explained earlier. In general both studies had an exclusive female population with ECOG-1 score, though the BM200 trial participants were younger and lither.

The majority of patients were treated with docetaxel as the complimentary taxane (MYL-study: 84%, BM200-study: 100%), with 14.6% in the MYL-study treated with paclitaxel and 1.3% receiving no taxane treatment at all.

Prior treatment

In the MYL-study less than 15% of patients used prior medications (13.4% in the MYL-1401O arm and 15.4% in the Herceptin arm), while in the BM200-study about 51% of patients (46% in the Bmab-200 arm and 56% in the Herceptin arm) had prior treatment.

At baseline, the most common prior medications in the former study were analgesics (3.7%) and drugs for the treatment of bone diseases (3.0%). In the BM200-trial the most common prior chemotherapies in both arms were anthracycline and anthracycline + taxane based, but all patients were naïve to chemotherapy for MBC.

Inclusion/exclusion criteria

Both studies included women at least 18 years of age, and patients in both studies must have had histopathologically confirmed MBC, measurable according to RECIST Version 1.1, with documentation of HER2 gene amplification by FISH or documentation of HER2- overexpression by IHC.

Prior systemic therapy in the metastatic disease setting including chemotherapy or HER2-targeted therapy (e.g., trastuzumab) was an exclusion criterion for both studies.

Study population

Baseline characteristics were broadly similar between both studies.

Population ethnicity

In the MYL-study the majority of patients were Caucasian, with a little less than one-third being of Asian descent. In the BM200-study on the other hand all patients and study centres were Indian.

Efficacy results

Given the differences between the study objectives and architectures comparison of efficacy outcomes is not meaningful.

Nonetheless the observed risk ratio in these 2 studies were more or less comparable and in line with the risk ratio reported with Herceptin (MYL-Her-3001, 69.6% versus 64% respectively; compared with 65.15% and 75% respectively in Study BM200-CT3-001-11).

The lower numerical ORR observed with Bmab-200 in the supportive study could be because of non-identified confounding factors while the slightly lower numerical ORR in the Herceptin group compared could be due to a slight imbalance in baseline characteristics.

Interpretation of the differences in the ORR between the 2 studies is also limited by the small sample size of Study BM200-CT3-001-11.

The disease control rates in the 2 studies were also comparable; 90.4% in the MYL-1401O arm versus 85.5% in the Herceptin arm in Study MYL-Her-3001 compared with 86.36% in the Bmab-200 arm versus 89.71% in the Herceptin arm in Study BM200-CT3-001-11.

Supportive study(ies)

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. Given all of the above, results of this trial are considered supportive only.

Study patients

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.

The medical baseline status of the ITT-FAS population is as follows:

Table 15: Disease History and Baseline Characteristics (ITT-FAS Population)

Variable	Statistics / Category	Bmab-200 N=67	Herceptin® N=68
ECOG performance status	0	21	20
	1	45	47
	2	1	1
Her2+ overexpression	IHC3+ or FISH+ or IHC2+ & FISH+	67	68
Survival Expectancy (months)	Mean ± SD	11.01 ± 7.38	10.51 ± 5.46
	Median	10	9
	Min, Max	(6, 60)	(6, 24)
Time from Diagnosis[a] (Days)	Mean ± SD	89.12 ± 190.85	60.56 ± 87.86
	Median	31	31
	Min, Max	(9, 1365)	(4, 491)
Stage of Disease	Stage IV	67	68
Sum of Longest Diameters for Target Lesions (mm)	Mean ± SD	99.54 ± 60.80	91.99 ± 52.96
	Median	88	79.5
	Min, Max	(15, 329)	(12, 236)
Histopathology	Atypical breast hyperplasia	1	-
	Breast adenocarcinoma	1	1
	Ductal Carcinoma	2	1
	Infiltrating ductal breast cancer	10	9
	Others/not specified	53	57

Note:
SD - Standard Deviation; (Min, Max)-(Minimum, Maximum)
a: of metastatic disease

Prior chemotherapy status for this analysis set is summarised in Table 16:

Table 16: Prior Treatments for Cancer (ITT-FAS Population)

Variable	Statistics /Category	Bmab-200 (N=67)	Herceptin® (N=68)
Prior adjuvant/ neoadjuvant therapy	No	36	30
	Yes	31	38
	• Anthracycline Based	14	21
	• Anthracycline Based+Taxane Based	13	15
	• Taxane Based	4	2

Patients were allowed to take concomitant medications as deemed allowed in the study protocol. The 10 most commonly used medications were: pheniramine, ranitidine, dexamethasone, granisetron, pantoprazole, paracetamol, ondansetron, domperidone, hydrocortisone and metoclopramide.

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 17: 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)	

The analysis of ORR indicates 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. Complete response was seen in 0 patients in the Bmab-200 arm, and in 1 patient in the Herceptin arm; in other words, there was no meaningful difference between the two treatment arms in the number of patients who progressed on treatment. This is further reflected in the overall clinical benefit rates discussed in the following section. The odds ratio for overall response rate was 1.60 (95% CI: 0.76, 3.39), again indicating that the treatment arms showed a similar response. Analysis of patients with stable disease indicates that the proportion of patients with stable disease at Week 12 and at Week 24 was comparable between the two treatment arms.

Evaluation of the PP subset gave similar results.

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.

Table 18: Clinical Benefit Rate by Treatment Group (ITT-FAS Population)

Variable	Bmab-200 N=66[a] [n(%)]	Herceptin® N=68 [n(%)]
Clinical Benefit Rate		
Patients with Clinical Benefit (CR+PR+SD)	57(86.36%)	61(89.71 %)
Patients with no Clinical Benefit	9(13.64 %)	7(10.29 %)
Difference in Clinical Benefit Rate	3.34%	
Odds Ratio (95% CI)	1.38(0.48,3.94)	

CR: complete response, PR: partial response, SD: stable disease

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).

Figure 17 shows a waterfall plot that charts the best change in the longest diameter in the lesion. The plot for both study arms looks similar, and the mean and median best change was similar between Bmab-200 and Herceptin arm.

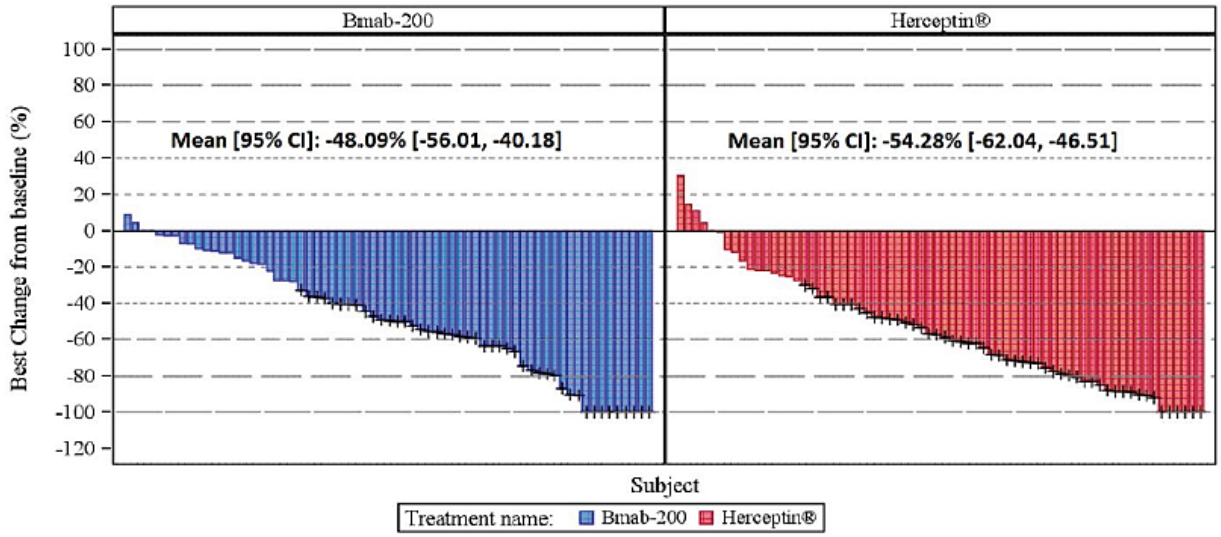


Figure 17: Best change in tumour size (%) from baseline to EOT by treatment

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy similarity evaluation in the framework of the current application for marketing authorization for the MYL-1401O trastuzumab biosimilar of Herceptin in the indications of metastatic breast cancer, early breast cancer and metastatic gastric cancer was conducted based on two trials. The Applicant aims to show similarity only for IV administration, SC administration is not applied for.

Pivotal trial characteristics

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 trial itself was split in two parts, with the D80 data package containing only data from the first part. Treatment in Part 1 was foreseen for 24 weeks during which 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).

The second part would also run for 24 weeks, and patients in this stage of the trial continue receiving the trastuzumab treatment they were assigned to in part 1 without a concomitant taxane, though if the investigator was of the opinion that temporary continuation of taxane treatment was more beneficial for the patient then continuing concomitancy was allowed, and this until disease progression, unacceptable toxicity, or death, whichever occurred first.

Concomitant chemotherapy

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 on the condition that the choice would apply for all trial subjects admitted to said site.

It is not entirely understood why this decision was made, as no explication was provided for this change. Given the comparability nature of the trail, as homogenous as possible populations should be used and thus the point of introducing more heterogeneity in this fashion is not entirely understood. Nonetheless, given that only a minority of patients (<20%) in the trial received paclitaxel and the fact that the decision to have only one taxane possible per study centre, thus ensuring that there is balance at least between arms, it is not expected that this issue will weigh heavily on the efficacy comparison outcome itself, though some uncertainty remains whether non-homogenous taxane use might affect the equivalence regions as calculated.

Following clarification by the Applicant it is agreed that the mixed taxane use is a more realistic representation of in practice treatment procedures. Likewise, at the time of study design different treatment protocols were in force in both US and EU, which necessitated the need for different taxane allowance in regards to region of investigation. Though a subgroup analysis hinted that combination with Paclitaxel may possibly not be equivalent with Herceptin, it is acknowledged that given the small

amount of patients having received paclitaxel versus docetaxel, and given that the study was not powered to investigate taxane subgroup analysis, these results cannot be taken at face value. Likewise, the analysis did at least hint that even if there would not be equivalence, then at least the combination would not be inferior to the Herceptin + paclitaxel combination. The type of taxane received (i.e., paclitaxel or docetaxel) was a stratification factor, along with hormonal status and tumour progression into metastatic phase ≥ 2 years OR < 2 years after primary diagnosis. Other stratification factors such as prior adjuvant trastuzumab, would have been desirable.

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. In total 32 patients (15 MYL-1401O and 17 Herceptin subjects) thus continued taxane treatment in Part 2, though all had switched to trastuzumab monotherapy by W48. 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. Tumour assessments were conducted every 12 weeks (±3 days).

Dosing

Dosing of the treatments was based on the dosing of the reference product, and taxanes were doses as prescribed in the product's SmPC.

The dose of 75 mg/m2 of docetaxel mimics the current use of this taxane (higher dose of 100 mg, though authorised, are not widely used due to the toxicity). In Cleopatra study, Docetaxel exposure revealed a median of 8 cycles in each group. The inclusion of paclitaxel, though increases the background noise, is probably capturing some clinicians' preferences for specific patients. Paclitaxel given as a Q3W dosing regimen is considered a more toxic and less efficacious regimen when compared with a weekly administration schedule.

Protocol amendments

Throughout the clinical development of the MYL-HER-3001 study numerous protocol amendments were made, some with non-negligible impact on the conduct of the study.

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 Protocol Amendment 1. The protocol was amended and Protocol Amendment 2 limited recruitment 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 are included in the intent-to treat-1 (ITT1) population. The primary efficacy analysis was conducted on the ITT1 population.

Part of the recruited population was randomized in their respective study arms under Protocol Amendment 1, whereas the great majority were randomized slightly later under Protocol Amendment 2. In effect this meant that the latter were grouped in an ITT population, called ITT1, which was in itself a sub-group of the full ITT population, referred to as ITT2. All pivotal analyses were performed based on results in ITT1, whereas ITT2 and PP populations were used for sensitivity analyses of the

primary outcomes. Thus, The ITT-2 population (ITT2) consisted of all randomized patients, including 42 patients enrolled under protocol Amendment 1. PP population was defined at the end of Part 1 and was a subset of ITT1.

Patients whom finished part 1 of the study and had stable disease could enter part 2. As the primary goal of part 2 was safety analysis the whole population was regarded as the safety population for analysis purposes, while secondary efficacy variables were analysed on the ITT1 sub-population, with sensitivity analyses done on the ITT2 and PP subpopulations. For these three latter populations, the defining composition elements did not change between parts 1 and 2.

Nonetheless, there is a lack of a well-documented and rationalized protocol amendment chain at the moment, and the numerous amendments that have been effected make it hard to have any comments on the actual protocol itself in its final form. Of concern is that the protocol was apparently never updated to include the information necessary for the additional primary analyses that was advised by CHMP.

Upon request the amendments were provided individually, and after review changes effected were deemed logical, especially as most important updates were made following requests by regulatory bodies (FDA, EMA) to adapt study elements to be in line with more state-of-the-art knowledge. Likewise, the Applicant updated the final protocol to include the EMA requested analyses.

Inclusion criteria

The patients that were deemed eligible for enrolment had to have histologically confirmed diagnosis of breast cancer with at least 1 metastatic targetable lesion, and not having received prior systemic therapy in the metastatic disease setting. HER2 gene amplification needed to be confirmed by fluorescent in situ hybridization (FISH), or alternatively HER2-overexpression had to be confirmed by immunohistochemistry.

The choice for MBC as target in a biosimilarity exercise has some limitations in terms of homogeneity of patient population or sensitivity. It could be debated whether the neoadjuvant EBC setting evaluating the pathological clinical response (pCR) might be more appropriate in regards to these aspects. Nevertheless, the choice of MBC is acceptable per se and is considered sufficiently sensitive to establish clinical similarity as long as effort is made to control and minimise heterogeneity.

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%, biosimilar arm vs Herceptin group respectively, had previously received trastuzumab.

Sample size & randomization

As a sample size of sample size to 410 patients (205 per treatment group) was necessary to achieve 80% power, a total of 500 patients were withheld through screening, with 249 patients assigned to the MYL-1401O arm. Of the former 185 completed Part 1 of the study (74.3%) while the Herceptin2 arm 171 (68.1%) did. When restricted to the ITT1 population the numbers look as follows: of the 230 randomized ITT1 MYL-1401O patients 75.2% completed Part 1 of the study, while of the 228 randomized Herceptin ITT1 patients 69.7% did the same.

Randomization was stratified according to a number of covariates such as ER/PgR status, type of taxane received, etc. Baseline characteristics and disease were generally comparable between arms.

For Part 2, a total of 342 patients, of which 179 MYL-1401O and 163 Herceptin subjects, continued on from Part 1. Of these 64.8% and 60.1%, respectively, attained the W48 endpoint. The vast majority of discontinuations (37% of all subjects in total) was due to disease progression with no imbalance apparent between treatment groups.

All of the patients entering Part 2 were part of the ITT2 population, whereas the ITT1 population encompassed 169 MYL-1401O (94.4%) and 151 Herceptin (92.6%) patients. The Part 2 PP population consisted of 166 (92.7%) and 150 (92.0%) subjects respectively.

Endpoints

Proposed primary endpoint and timing of the efficacy analysis are acceptable for the purpose of comparability exercise. ORR is considered sensitive enough to show the difference exists. The primary endpoint chosen for this trial was best ORR, analyzed by measuring if the ratio of best ORR fell within a predefined equivalence margin as discussed with the FDA. EMA for their part requested an additional analyses of the difference of best ORR, with its own equivalence margin. Given the importance of said equivalence margins, it is not fully clear how the use of mixed taxanes might affect them.

Regarding the equivalence margins, (-15%, 15%), as the CHMP SA already stated, these intervals appear overall acceptable. However, for FDA equivalence was declared if the CI was completely within the equivalence range of (0.81, 1.24). Even though the primary endpoint of the study was tested under the FDA premise, a sensitivity analysis applying the CHMP SAWP advice was carried out. The company justifies the choice of these margins because the 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, which is considered clinically significant. This justification can be debatable, and a narrower margin had been preferable (12-14%).

One point of concern was the fact that the validation of use of ORR for margin calculation had been done using literature data that was a mix of PFS and TTP weighted outcomes. Normally it is not very straightforward to translate one to the other, but as the Applicant correctly pointed out in their response to this concern fatality numbers in trials concerning MBC treated with trastuzumab are generally very low, making the PFS and TTP values almost synonymous in practice. Coupled with the fact that all studies but one used TTP as weighted outcome it can indeed be agreed that in this particular exercise the mixing of PFS/TTP endpoints will not likely have influenced the robustness of the validation.

Secondary endpoints were TTP, PFS, OS and in Part 2 additionally DR. These secondary endpoints are endorsed. DCR and HER2/ECD as a predictor of PFS, TTP and OS were exploratory variables.

Supportive studies

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. Efficacy endpoints in this trial were only of a secondary exploratory nature and aimed to compare 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.

It 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 terms of formulation, from MYL-1401O.

A total of 132 patients were planned to be enrolled, with final enrolment count being 135 patients. The latter 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.

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

Immunogenicity

A full analysis of immunogenicity is provided in the safety part of this overview, and it was noted that both ADA and Nab titres were low and similar in both arms during the study. Moreover, as far as efficacy is concerned no diminution or suppression of response was observed in relation to ADA positive status.

Efficacy data and additional analyses

Baseline characteristics

The participant flow, beyond these two ITT populations, did not reveal important concerns in both groups of treatment. Within the ITT1, the biosimilar arm seems to show less 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%). The protocol deviations leading to exclusion from the PP population seems to be evenly balanced, with the highest difference in terms of lack of post-baseline tumour assessment. But in any case, the absolute numbers are low and the impact in the final results probably minor.

Regarding the baseline and disease characteristics, overall there are not big differences between arms. Only slight tendencies in terms of ECOG, tumour progression into metastatic phase, presence of visceral disease and number of metastatic sites. The actual weight of these “imbalances” is not easy to determinate, even though overall seems to favour to the biosimilar arm.

Primary endpoint

The pivotal MYL-HER-3001 comfortably met the primary endpoints, as both ORR ratio and difference analyses (1.09, 90% CI [0.974, 1.211] and 5.5%, 95% CI [-3.08, 14.04]) fell squarely within the predefined equivalence margins of (0.81, 1.24) and (-15, 15) respectively.

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 endpoints

Secondary endpoint analyses (ran on ITT1, ITT2 and PP populations for sensitivity analysis reasons) was aimed at TTP, PFS and OS factors, and found no statistical differences in either.

Both PP and ITT2 populations are also within the 15% interval. The results seem to be robust, as the investigator assessments are in line with the main analysis. All the secondary variables appear to show a better result for the biosimilar. Both, TTP and PFS, point out a better outcome for MYL-1401O. Nevertheless, the number of events is still too low so as to reach any conclusion (17% in TTP and 19% for PFS). This idea is also observed in the main analysis in terms of ORR (69.6% vs 64%). Furthermore, when the 95%CI is observed, it seems that patients treated with MYL-1401O could obtain a better result (-3.08 /14.04), in the same way as in the PP population (95%CI; -4.59%, 12.61%). The subgroups analyses of ORR point out in the same direction, with some subgroups where

the biosimilar seem to show a better outcome, especially in tumour endocrine status negative (stratification factor), previous adjuvant/neoadjuvant chemotherapy, subgroup of patients with 3 metastatic sites. However, given the confirmed similarity of secondary endpoints even in W48, as well as the similarity shown in PK factors, the relatively low numbers involved and the fact that slight baseline differences may disproportionately affect these relatively small subgroup analyses it is believed that it would be unreasonable to further pursue these odd observations as their clinical impact is considered to be of no concern given the favourable results in the major primary and secondary endpoints.

The overall observation of there not being any 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.

One odd and unexplainable point of non-equivalence was seen in the OS for <2 years tumour progression subgroup, and this in favour of MYL-1401O. No clinical explanation is readily apparent, but 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 but an aberrant artefact.

The W48 analysis of duration of response likewise indicated that no significant difference exists between MYL-1401O and Herceptin treated subjects.

Exploratory endpoints

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.

Supportive study

For the supportive BM200-CT3-001-11 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. It is worth however to highlight the difference of about 10% in the ORR between the Bmab-200 arm and the Herceptin arm. The mean as well as median number of cycles received by the patients in the two groups was similar.

The analysis of ORR indicates 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.

Of note, BM200-CT3-001-11 was not powered to confirm or deny similarity.

An odds ratio of 1.38 indicated that the arms showed a similar response, and the proportion of patients with clinical benefit at week 24 was comparable between the two treatment arms.

Progression free survival rates for both PFS and PP were also highly similar between both treatment arms.

Finally, 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.

A comparison between both trials has only very limited value due to the fact that the investigative products, as well as the endpoints, design as well as goals of both studies were wildly different. Based on a very high level comparison both trials are supportive of each other in regards to their respective efficacy findings.

3.3.7. Conclusions on clinical efficacy

The similarity in terms of ORR at week 24 has been shown with the a priori defined margin of similarity (15%). The results appear robust enough as different sensitivity analyses support the main one, including comparison according to stratification factors and analyses in the ITT2 and PP groups. While the trastuzumab biosimilar MYL-1401O seems at least as efficacious, in terms of ORR, as Herceptin, there is the likelihood that can show a higher antitumour activity, which in itself does not pose any concern, even though it could be a sign of lack of equivalence. Nonetheless, W48 data alleviated these concerns by showing strong evidence of similarity, which when taken into account together with the PK-PD similarity outcomes can be understood to confirm similarity in efficacy between investigative product and control.

For PFS, TTP and OS data preliminary W24 results do not indicate a significant difference in these factors between MYL-1401O and Herceptin, and this was confirmed using more mature data at the W48 endpoint. Likewise, analysis of duration of response at W48 did not indicate any significant difference between MYL-1401O and Herceptin treatment. However, there seem to be a tendency for a better result in those patients treated with the biosimilar (even clearer in some subgroups). This observation could be confirmed with the long-term variables still pending. Though a more thorough sub-analysis wasn't provided by the Applicant, given the continued similarity shown in both PK-PD and main primary/ secondary efficacy factors, the relatively low numbers involved and the fact that slight baseline differences may disproportionately affect these relatively small subgroup analyses it is believed that these differences are not likely to have a meaningful clinical impact and are more likely data artefacts.

The supportive BM200-CT03-001-11 trial was not powered to investigate similarity in efficacy, used a different investigative product composition and had a different design and endpoints. Thus, its value was very limited, but nonetheless on sufficiently broad level its findings were in line with those of the pivotal trial.

Though the similarity investigation was done in metastatic breast cancer patients, the confirmed similarity in efficacy, as well as the non-clinical, pharmacodynamic and -kinetic similarity between MYL-1401O and Herceptin support extrapolation towards all other indications currently approved for the latter.

3.3.8. Clinical safety

Main safety information for MYL-1401O were generated in the pivot 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 data is further supported by results from two other comparative studies, MYL-Her-1001 and MYL-Her-1002, in healthy male volunteers. The forth study, supportive Study BM200-CT3-001-11, was conducted in patients with HER2-positive MBC, but with another formulation which differs from MYL-1401O.

Of the 4 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

A total of 635 patients with HER2-positive MBC were exposed to MYL-1401O/Bmab-200 in studies MYL-Her-3001 and BM200-CT3-001-11. 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 19).

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 19). 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 19: 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 –	Mean dose	8.0 mg/kg	8.0 mg/kg

Part 1	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 20).

Table 20: 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 21).

Table 21: 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 22).

Table 22: 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/m^2/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). As shown in Table 23, 185 (74.3%) patients completed Part 1 in MYL-1401O and 171 (68.1%) patients in the Herceptin arm. The most common reason for discontinuation was disease progression (MYL-1401O 18.9% versus Herceptin 23.1%).

A total of 14 patients who completed Part 1 of the study did not enter Part 2 (MYL-1401O 6 patients, Herceptin 8 patients). Reasons for not entering Part 2 monotherapy were disease progression (MYL-1401O 4 patients/Herceptin 4 patients), withdrawal of consent (2/1), death (0/1), AE not due to disease progression (0/1), no reason (0/1).

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 23, 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 23: 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 24, 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 24: 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 25).
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 25).

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 25: 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 26 below.

Table 26: 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

Most patients (97.6%) reported at least 1 TEAE, most frequently in the SOCs of blood and lymphatic system disorders (66.9%), followed by skin and subcutaneous tissue disorders (65.9%), general disorders and administrative site conditions (53.8%), Nervous system disorders (41.8%), and gastrointestinal disorders (40.2%). At the PT level, the most frequently reported TEAEs were alopecia (56.4%), followed by neutropenia (56.0%), and diarrhea (20.9%). 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. However, the numerical difference in between the 2 treatment groups could be attributed to the differences in medical history, age, previous chemotherapy, use of concomitant medications and trastuzumab exposure. Of note, most of these differences were driven by Part 1 of the study in patients who were receiving combination therapy. 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%). Although the exposure to paclitaxel and to trastuzumab was higher in the MYL-1401O arm, it is difficult to attribute the reason for the differences, confounding factors like previous and concomitant medical disorders, symptoms related with different metastatic sites, and unbalanced use of medications could contributed to some differences. These differences were seen in Part 1 of the study. 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) indicating that the differences seen between arms through 48 weeks were due to Part 1 of the study and possibly attributable to concomitant taxane therapy.

In terms of severity, the majority of TEAEs were Grade 1 or Grade 2 in severity (Table 27). 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 (65.6% in the MYL-1401O arm and 65.9% in the Herceptin arm). The most frequently reported TEAEs of Grade 3 or greater overall were neutropenia and leukopenia, which occurred in similar frequencies between treatment arms (Table 28). 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 27: Number of Patients with Treatment-Emergent Adverse Events by Maximum Severity (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

TEAE CTCAE Grade	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) 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 28: 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) n (%)	MYL-1401O (N = 247) Events	Herceptin (N = 246) n (%)	Herceptin (N = 246) Events	Overall (N = 493) n (%)	Overall (N = 493) 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 29).

Table 29: 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 30). However, Grade 2 (moderate) and Grade 3 (severe) TEAEs were less frequent in Bmab-200 arm than Herceptin arm. For note: the number of Grade 4 TEAE was not provided by the applicant.

Table 30: 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 events and deaths

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 31). 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 31: 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 32). In both arms, the majority of patients with SAE had SAEs deemed unrelated to study drug (Bmab-200, 15.15%; Herceptin, 17.65%).

Table 32: 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) (Table 33).

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.

Table 33: Listing of Patients with TEAE with Fatal Outcome (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

Patient Number	TEAE System Organ Class	TEAE Preferred Term	Study Day Onset	Study Drug Relationship T: trastuzumab P: paclitaxel D: docetaxel
MYL-1401O + Taxane Arm				
	Respiratory, thoracic and mediastinal disorders	Respiratory failure	7	T: Possible D: Not related
	Blood and lymphatic system disorder	Pancytopenia	7	T: Not related D: Definite
	Hepatobiliary disorders	Hepatic failure	7	T: Not related D: Not related
	Cardiac disorders	Cardiac failure	157	T: Unlikely D: Unlikely
	Respiratory, thoracic and mediastinal disorders	Respiratory failure	157	T: Unlikely D: Unlikely
(monotherapy in Part 2)	Respiratory, thoracic and mediastinal disorders	Dyspnea	229	T: Not related D: Not applicable
	General disorders and administrative site conditions	Multi-organ failure	13	T: Not related D: Not related
(monotherapy in Part 2)	Cardiac disorders	Carditis	340	T: Unlikely D: Not applicable
Herceptin + Taxane Arm				
	General disorders and administrative site conditions	Death	59	T: Unlikely D: Probable
	Respiratory, thoracic and mediastinal disorders	Respiratory failure	76	T: Possible P: Not related
	Infections and infestations	Pneumonia	160	T: Unlikely D: Unlikely
	Infections and infestations	Sepsis	160	T: Unlikely D: Unlikely
	Hepatobiliary disorders	Hepatic failure	4	T: Not related D: Definite
	Metabolism and nutrition disorders	Tumour lysis syndrome	4	T: Not related D: Not related

TEAE: treatment-emergent adverse events
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0.
Source: Table 14.3.2.11.1b, Listing 16.2.7.7b

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 (Table 30). 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 buy slightly higher in MYL-114O (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.

Table 34: Infusion-related Reactions, Allergic-like Reactions, and Hypersensitivity (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

TEAE Category	MYL-1401O (N = 247)		Herceptin (N = 246)		Overall (N = 493)	
Preferred Term	n (%)	Events	n (%)	Events	n (%)	Events
Total TEAE						
Infusion related reaction	17 (6.9)	30	12 (4.9)	20	29 (5.9)	50
Anaphylactic reaction	2 (0.8)	2	0	0	2 (0.4)	2
Drug hypersensitivity	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Hypersensitivity	5 (2.0)	6	7 (2.8)	7	12 (2.4)	13
Grade 3 or greater						
Infusion related reaction	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Anaphylactic reaction	2 (0.8)	2	0	0	2 (0.4)	2
Drug hypersensitivity	1 (0.4)	1	0	0	1 (0.2)	1
Hypersensitivity	0	0	1 (0.4)	1	1 (0.2)	1
Serious adverse event						
Infusion related reaction	0	0	1 (0.4)	1	1 (0.2)	1
Anaphylactic reaction	2 (0.8)	2	0	0	2 (0.4)	2
Drug hypersensitivity	1 (0.4)	1	0	0	1 (0.2)	1
Hypersensitivity	0	0	2 (0.8)	2	2 (0.4)	2
Related TEAE						
Infusion related reaction	9 (3.6)	10	6 (2.4)	6	15 (3.0)	16
Anaphylactic reaction	1 (0.4)	1	0	0	1 (0.2)	1
Drug hypersensitivity	0	0	0	0	0	0
Hypersensitivity	2 (0.8)	2	2 (0.8)	2	4 (0.8)	4

n: number of patients with TEAEs, TEAE: treatment-related 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.
AE with missing severity grade are 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 (MYL-1401O or Herceptin) alone.
Source: Table 14.3.2.2.1b, Table 14.3.2.3.1b, Table 14.3.2.4.1b, Table 14.3.2.9.1b

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.

For the excipients, please refer to the safety discussion.

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%) (Table 31). 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.

Table 35: Potential Pulmonary Toxicity (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

TEAE Category	MYL-1401O (N = 247)		Herceptin (N = 246)		Overall (N = 493)	
Preferred Term	n (%)	Events	n (%)	Events	n (%)	Events
Total TEAE	32 (13.0)	41	30 (12.2)	43	62 (12.6)	84
respiratory events						
Dyspnoea	17 (6.9)	20	18 (7.3)	24	35 (7.1)	44
Dyspnoea exertional	3 (1.2)	5	2 (0.8)	4	5 (1.0)	9
Pneumonia	7 (2.8)	8	10 (4.1)	11	17 (3.4)	19
Pneumonitis	4 (1.6)	5	2 (0.8)	3	6 (1.2)	8
Pulmonary fibrosis	1 (0.4)	1	0	0	1 (0.2)	1
Respiratory failure	2 (0.8)	2	1 (0.4)	1	3 (0.6)	3
Grade 3 or greater						
Dyspnoea	3 (1.2)	3	2 (0.8)	2	5 (1.0)	5
Dyspnoea exertional	0	0	0	0	0	0
Pneumonia	3 (1.2)	3	5 (2.0)	5	8 (1.6)	8
Pneumonitis	0	0	2 (0.8)	2	2 (0.4)	2
Pulmonary fibrosis	0	0	0	0	0	0
Respiratory failure	2 (0.8)	2	1 (0.4)	1	3 (0.6)	3
Serious adverse event						
Dyspnoea	2 (0.8)	2	0	0	2 (0.4)	2
Dyspnoea exertional	0	0	0	0	0	0
Pneumonia	6 (2.4)	6	5 (2.0)	5	11 (2.2)	11
Pneumonitis	1 (0.4)	1	2 (0.8)	2	3 (0.6)	3
Pulmonary fibrosis	0	0	0	0	0	0
Pulmonary fibrosis	0	0	0	0	0	0
Respiratory failure	2 (0.8)	2	1 (0.4)	1	3 (0.6)	3
Related TEAE						
Dyspnoea	4 (1.6)	4	3 (1.2)	3	7 (1.4)	7
Dyspnoea exertional	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Pneumonia	0	0	1 (0.4)	1	1 (0.2)	1
Pneumonitis	2 (0.8)	2	1 (0.4)	2	3 (0.6)	4
Pulmonary fibrosis	0	0	0	0	0	0
Respiratory failure	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2

n: number of patients with TEAEs, TEAE: treatment-related 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.
AE with missing severity grade are considered to be Grade 3.
Treatment-related includes TEAEs possibly, probably, or definitely related to trastuzumab or relationship unknown.
In addition to the above listed PTs, 1 related TEAE of pulmonary congestion was reported for 1 patient (0.4%, 1 event) in the Herceptin group.
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 14.3.2.14b, Table 14.3.2.3.1b, Table 14.3.2.4.1b, Table 14.3.2.9.1b, Table 14.3.2.2.1b

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 event 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.

Table 36: Cardiac Toxicity (Safety Population; Study MYL-Her-3001 – parts 1 & 2)

TEAE Category	MYL-1401O (N = 247)		Herceptin (N = 246)		Overall (N = 493)	
Preferred Term	n (%)	Events	n (%)	Events	n (%)	Events
Total TEAE cardiac disorders	12 (4.9)	13	10 (4.1)	10	22 (4.5)	23
Cardiac failure	6 (2.4)	6	1 (0.4)	1	7 (1.4)	7
Cardiomyopathy	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Cardiotoxicity	2 (0.8)	2	0	0	2 (0.4)	2
Carditis	1 (0.4)	1	0	0	1 (0.2)	1
Congestive cardiomyopathy	0	0	1 (0.4)	1	1 (0.2)	1
Left ventricular dysfunction	2 (0.8)	2	3 (1.2)	3	5 (1.0)	5
Left ventricular failure	0	0	1 (0.4)	1	1 (0.2)	1
Metabolic cardiomyopathy	1 (0.4)	1	3 (1.2)	3	4 (0.8)	4
Grade 3 or greater						
Cardiac failure	3 (1.2)	3	0	0	3 (0.6)	3
Cardiomyopathy	0	0	0	0	0	0
Cardiotoxicity	0	0	0	0	0	0
Carditis	1 (0.4)	1	0	0	1 (0.2)	1
Congestive cardiomyopathy	0	0	0	0	0	0
Left ventricular dysfunction	2 (0.8)	2	1 (0.4)	1	3 (0.6)	3
Left ventricular failure	0	0	0	0	0	0
Metabolic cardiomyopathy	0	0	0	0	0	0
Serious adverse event						
Cardiac failure	2 (0.8)	2	0	0	2 (0.4)	2
Cardiomyopathy	0	0	0	0	0	0
Cardiotoxicity	0	0	0	0	0	0
Carditis	1 (0.4)	1	0	0	1 (0.2)	1
Congestive cardiomyopathy	0	0	0	0	0	0
Left ventricular dysfunction	0	0	0	0	0	0
Left ventricular failure	0	0	0	0	0	0
Metabolic cardiomyopathy	0	0	0	0	0	0
Related TEAE						
Cardiac failure	4 (1.6)	4	1 (0.4)	1	5 (1.0)	5
Cardiomyopathy	0	0	1 (0.4)	1	1 (0.2)	1
Cardiotoxicity	2 (0.8)	2	0	0	2 (0.4)	2
Carditis	0	0	0	0	0	0
Congestive cardiomyopathy	0	0	1 (0.4)	1	1 (0.2)	1
Left ventricular dysfunction	1 (0.4)	1	0	0	1 (0.2)	1
Left ventricular failure	0	0	0	0	0	0
Metabolic cardiomyopathy	1 (0.4)	1	3 (1.2)	3	4 (0.8)	4

n: number of patients with TEAEs, TEAE: treatment-related 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.
AE with missing severity grade are considered to be Grade 3.
Treatment-related includes TEAEs possibly, probably, or definitely related to trastuzumab or relationship unknown.
In addition to the above listed PTs from the Cardiac disorders SOC the following results were obtained for the PT ejection fraction decreased: TEAEs (all unrelated) MYL-1401O 12 patients (4.9%, 16 events), Herceptin 7 patients (2.8%, 8 events), overall 19 patients (3.9%, 24 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).
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 14.3.2.13b, Table 14.3.2.3.1b, Table 14.3.2.4.1b, Table 14.3.2.9.1b, Table 14.3.2.2.1b

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) (Cf. Table 36).

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. However, the applicant proposed that it may be because a smaller proportion of patients in the Bmab-200 arm (40.3%) had been exposed to anthracycline therapy for primary adjuvant/neoadjuvant therapy compared with the Herceptin arm (52.9%).

Hematologic toxicity

In Study BM200 CT3-001-11, seven (10.61%) patients in the Bmab-200 arm and 7(10.29%) patients in the Herceptin arm reported at least 1 TEAE related to the SOC Blood and lymphatic system disorders. The reported TEAEs in this SOC in the Bmab-200 arm were anemia (7.58%), thrombocytopenia (3.03%), leukopenia (1.52%), and eosinophilia (1.52%). The reported hematological TEAEs in the Herceptin arm were anemia (8.82%) and disseminated intravascular coagulation (1.47%). Of these, disseminated intravascular coagulation reported in the Herceptin arm was fatal. Febrile neutropenia, which is a common AE for Herceptin when given with docetaxel, was not reported in this study. This is likely because all patients received prophylactic pegfilgrastim in each cycle of chemotherapy.

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.

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.

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-l401O 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.

Febrile neutropenia, which is a very common AE for Herceptin, was not reported in this study. This is likely because prophylactic pegfilgrastim (peg-G-CSF) was administered to all patients (in each cycle of chemotherapy prior to docetaxel infusion) to prevent haematological toxicity. This might explain less neutropenia events, and less leukopenia and anaemia events reported in BM200-CT3-001-11 compared to MYL-HER-3001. Although the use of G-CSF prophylactic treatment varies widely in clinical practice, both in the timing of therapy and in the patients to whom it is offered, recommendations has been published for its optimal use (Aapro et al, 2011).

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, the clinical significance of this observation is thought to be minimal as 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

In accordance with the EMA guideline "Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues" (EMA/CHMP/BMWP/403543/2010), analyses in the special populations are not relevant in the present MAA as the biosimilar relies on the information already known of the reference product.

For note, 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 Applicant considers differences 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.
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 37 presents a summary of the ADA results by visit and treatment.

Table 37: 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. According to the applicant, 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).

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. As can be seen from Table 37, the number of positive patients which was 5.9 and 9.2% at baseline in the MYL-1401O and Herceptin groups declined over time. The overall incidence of ADA-positive samples was low. The maximum proportion of ADA-positive patients post-baseline was seen at Week 6 and was 2.5% in the MYL-1401O arm and 3.0% in the Herceptin arm. At the Week 48 time-point, none of the patients in either arms were ADA-positive.

With regard to NAb analysis, confirmed positive ADA samples were further tested using a validated cell based NAb assay. Table 38 presents a summary of the NAb results by visit and treatment.

Table 38: 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 39). 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.

Table 39: 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 38) had pre-existing antibodies against the test and reference product prior to study entry, an additional analysis that excluded these subjects was conducted. Table 40 presents a summary of the treatment-induced ADA-positive samples by visit and treatment.

Table 40: 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 41. The treatment-induced ADA rate in the MYL-1401O arm was 1.7% (4 patients) and 1.8% (4 patients) in the Herceptin arm. The treatment-induced NAb rate was 0.4% (1 patient) and 0.9 % (2 patients) in the MYL-1401O and Herceptin arms respectively. Also 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 41: 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 42.

Table 42: 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.

The titer evolution for patients with ADA positive samples post-baseline is shown in Table 43.

Table 43: Summary of the titers of ADA-Positive samples by Visit and Treatment (safety population, Study MYL-Her-3001) during part 1 (cycle 1 to 9) and part 2 (cycle 13 & 17). Nab positivity or negativity is indicated (+ or -, respectively).

Patient number (treated with MYL-14010)	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Total of ADA-positive samples / Nab - positivity
Cycle1, Wk0	1 / -	0	0	0	3.9 / -	0	**2 / 0**
Cycle3, wk6	3.1 / -	1.9 / -	1.4 / -	0	1.5 / -	1.9 / -	**5 / 0**
Cyle5, wk12	7.4 / -	6.5 / -	0	0	NP	0	**2 / 0**
Cycle7, wk18	2 / -	5.6 / -	0	0	NP	0	**2 / 0**
Cycle9, wk24	0	8.1 / -	0	1 / -	NP	0	**2 / 0**
Cycle13, wk36	11 / -	11.5 / +	NP	1 / -	NP	NP	**3 / 1**
Cycle17, wk48	NP	NP	NP	0	NP	NP	**0 / 0**

Patient number (treated with Herceptin)	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Titer / NAb	Total of ADA-positive samples / Nab - positivity
C1, Wk0	0	6.9 / -	3 / +	0	2.4 / -	3.2 / -	5.2 / -	0	1.9 / -	**6 / 1**
C3, wk6	0	2.6 / +	5.4 / +	2.8 / -	1.7 / +	2.6 / -	1.7 / -	0	0	**6 / 3**
C5, wk12	0	0	0	NP	0	0	1.1 / -	1 / -	0	**2 / 0**
C7, wk18	0	0	0	NP	0	0	NP	0	1 / -	**1 / 0**
C9, wk24	0	NP	0	NP	0	0	NP	0	0	**0***
C13, wk36	1 / -	NP	NP	NP	NP	0	NP	0	NP	**1 / 0**
C17, wk48	NP	NP	NP	NP	NP	NP	NP	NP	NP	**0**

Data from listing 16.2.8.1.7b, CSR MYL-Her-3001. This table does not include samples that were ADA-positive only at baseline. NP: data is not provided (end of study). *Inconsistency with another table where there is 1 ADA positive sample at cycle 9 wk24 in Herceptin arm. All other values (ADA and Nab) are consistent with previously presented tables.

During the treatment with MYL-14010, 6 patients had ADA-positive samples (Table 43). 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. One patient 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 44.

Table 44: 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.

ADA and ORR

Considering the low incidence of ADA-positive patients across both treatment groups and the transient nature of the positive response, any correlation to efficacy has been considered of limited value by the applicant. However, a summary and analysis of best ORR at Week 48 for patients with at least 1 ADA assessment (PP population) has been provided. ORR is independent of ADA as ORR is different in both treatment groups. Note that due to the small numbers of patients, the result may not be meaningful.

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 49 below).

Table 45: 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 (

Table 46 below). In corroboration, these two ADA-positive patients did not experience any infusion reactions over the duration of the trial.

Table 46: Summary of ADA Titres at Screening, Week 12, and Week 24 (Study BM200-CT3-001-11).

Visit	Titres*	Bmab-200 N=66 [n(%)]	Herceptin® N=68 [n(%)]
Screening	Non Diluted	3(4.54 %)	0(0.00%)
	1:4 Dilution	0(0.00%)	2(2.94 %)
	1:8 Dilution	1(1.52 %)	2(2.94 %)
Week 12	Non Diluted	1(1.52 %)	0(0.00%)
	1:4 Dilution	1(1.52 %)	0(0.00%)
	1:8 Dilution	0(0.00%)	0(0.00%)
Week 24	Non Diluted	1(1.52 %)	0(0.00%)
	1:4 Dilution	0(0.00%)	0(0.00%)
	1:8 Dilution	0(0.00%)	0(0.00%)

The clinical trial was not powered to pick up 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 is 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.

Safety related to drug-drug interactions and other interactions

NA

Discontinuation due to AES

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%) (Table 43; CSR MYL-Her-3001 table 14.3.2.6.1.1b). 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 (CSR MYL-Her-3001 table 14.3.2.6.2.1b) (Cf. discrepancy in safety discussion).

Table 47: 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 authorization for another formulation (which was used in Study BM200 CT3-001-11) in India in October 2013. 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 analyzed 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.

3.3.9. 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, however. Moreover, a fourth supportive clinical study (BM200-CT3-001-11) was conducted with another formulation (Bmab) 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, the Applicant's dossier includes safety data through 48 weeks (Parts 1 & 2) of Study MYL-Her-3001. 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.

Patient exposure

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 doesn't 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 trough 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.

Safety 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. Because of confounding factor, and because these differences

have not been seen in part 2 (monotherapy), it is difficult to know if these differences are clinically relevant.

For note, in the Herceptin arm, there is a discrepancy between overall number (parts 1 and 2) and numbers given separately by study parts (see below). There are 7 patients in part 1 with TEAEs leading to study drug discontinuation and there are 8 patients in part 2: total of 15 patients (instead of 16 patients as seen in 14.3.2.6.1.1b). There is no discrepancy for the MYL-1401O arm. The applicant should further address the discrepancy in regard to the number of patients that discontinued Herceptin due to TEAEs in the study MYL-Her-3001 (the overall number over 48 weeks and separately by study parts) and update the related tables accordingly. 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 (myl-Her-3001 CSR- table 14.3.2.6.1.1a.). 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 (myl-Her-3001 CSR- table 14.3.2.6.2.1a.). 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 (myl-Her-3001 CSR- table 14.3.2.6.1.2b.). 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) (myl-Her-3001 CSR- table 14.3.2.6.2.2b.).

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%) 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 related TEAE in MYL-1401O (including 4 cardiac failure), and 6 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. Most of the cardiac events occurred during Part 1 while patients received combination therapy. Cardiac dysfunction in an important identified risk in the RMP, and careful monitoring of patient's cardiac function during treatment is already planned to minimise the impact of this risk. As a trend to a higher incidence of significant cardiac toxicity has been observed, the Applicant should provide narratives for patients with cardiac toxicity and discuss the observed rates of great 3 or greater events in view of historical data.

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).

Immunogenicity

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. 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-14010 and Herceptin).

Finally, the analyse 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. 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).

Please refer to the PK section concerning the immunoassays to measure ADA and Nab, their validation, and the relation between ADA and the trastuzumab clearance.

Excipients

The Applicant discussed the current knowledge on the safety profile of one of the excipient when included in IV formulations at clinical relevant doses and the observed hypersensitivity reactions. While initially considered as immunologically safe, this type of excipient, 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 one excipient. Two cases of a reaction after receiving IM injections of medroxyprogesterone (Depo-Provera), containing a similar excipient 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. Therefore, given that cases of immediate-type PEG hypersensitivity are reported with increasing frequency but not always recognised as such, awareness of PEG's allergenic potential should be raised and better product labeling of Ogivri containing relatively large amounts of this excipient should be discussed by the Applicant.

The dose of one of the excipient used 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.

3.3.10. Conclusions on clinical safety

The data up to 48 weeks in the pivotal trial MYL-Her-3001 indicate similar safety profile between biosimilar candidate MYL-1401O and reference product Herceptin. 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 immunogenicity observed in this study with MYL-1401O is similar to Herceptin's immunogenicity and to the reported immunogenicity of trastuzumab in the literature.

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.

3.3.11. Extrapolation of efficacy and safety

The populations that will be exposed to MYL-1401O in the marketplace will be patients with HER2-positive MBC, early breast cancer, and metastatic gastric cancer.

The mechanism of action of trastuzumab is the same in all 3 indication and the target receptor involved is also the same in early breast cancer, metastatic gastric cancer and MBC (i.e., HER2).

The dosage is also similar for all 3 indications, and trastuzumab is administered by the same route in all indications and has been demonstrated to be safe and effective in the additional indications of early breast cancer and metastatic gastric cancer.

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 1 active site other than the HER2 targeting area.

Results of the physico-chemical, structural, and biological characterization data and the comparative preclinical studies indicate similarity between MYL-1401O and Herceptin. A further decrease in residual uncertainty has been established through in vitro functional tests and in vivo animal studies.

Results of the PK studies MYL-Her-1001 and MYL-Her-1002 further reduce the residual uncertainty.

From the efficacy perspective, extrapolation to other indications appears to be justified.

Ogivri seems to demonstrate similarity to Herceptin in terms of safety based on available data up to 24 weeks. The results are comparable to data published for the reference product. Key adverse reactions for Herceptin are cardiac dysfunction, infusion-related reactions, haematological toxicity (in particular neutropenia) and infections (Herceptin SmPC).

In regard to cardiotoxicity, patients treated with Herceptin are at increased risk for developing congestive heart failure (CHF). These events have been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy (Herceptin SmPC). Herceptin is indicated, following anthracycline based chemotherapy, in MBC and EBC. A meta-analysis including breast cancer studies including 58 studies (29,598 patients) reported that severe cardiotoxicity occurred in 3.00% (95% CI 2.41-3.64), 2.62% (95% CI 1.97-3.35), and 3.14% (95% CI 2.12-4.37) of overall, early (EBC) and metastatic (MBC) breast cancer patients, respectively (Mantarro et al., 2016).

In MGC, Herceptin is approved to be used in combination with capecitabine or 5-fluorouracil and cisplatin. The pivotal investigating Herceptin in MGC, reported no difference in the occurrence of cardiac events between the trastuzumab plus chemotherapy and chemotherapy alone groups (17 [6%] vs. 18 [6%]) and cardiac failure occurred in <1% in both treatment groups (Bang et al., 2010).

Infusion reactions occur frequently in patients receiving Herceptin. It is estimated that approximately 40 % of patients who are treated with Herceptin will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions (Herceptin SmPC).

In the ToGa study (for MGC), 17 (6%) patients experienced at least one typical infusion-related AE of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 Grade ≥ 3 on the day of or the day after a trastuzumab. None of them was fatal. The proportion of patients experiencing these events generally decreased with each infusion: 41% of patients in the FP+H arm reported a typical infusion-related event on the day of or the day after the first infusion, while only 2% of patients reported such an AE after the eighth infusion (EMA/842364/2009).

In regard to haematological toxicity, febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly during trastuzumab treatment (Herceptin SmPC). Slightly higher levels of febrile neutropenia were reported in the MBC indications, compared to the other indications, but these were likely related to the concomitant chemotherapy.

In conclusion, it is challenging to determine whether there are major cross-indication differences in terms of safety events for trastuzumab, due to differences in patient populations, study designs and concomitant medication use. While some differences in terms of clinical safety have been reported between indications, these are likely to be the result of the use of concomitant medication and other factors aforementioned rather than differences related to trastuzumab. There are no clear differences in key trastuzumab adverse events that may preclude extrapolation of safety outcomes obtained in the HER2-positive MBC indication.

3.4. Risk management plan

The Applicant updated the Summary of safety concern in the RMP (RMP Version 3, signed on 31 March 2017).

Safety Specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 48: Summary of the safety concerns as proposed by the applicant

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Administration-related reactions • Haematological toxicity • Oligohydramnios • Pulmonary disorders
Important potential risks	• Infections
Missing information	• Treatment in male breast cancer patients

Pharmacovigilance Plan

Not applicable, as routine pharmacovigilance only is proposed and there are no studies or other additional activities from the pharmacovigilance plan, whether ongoing, planned or completed.

Risk minimisation measures for Ogivri

Table 49: Summary table of additional Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Cardiac dysfunction	Text in SmPC: • Warning in Section 4.4 that patients treated with trastuzumab are at increased risk for developing CHF or asymptomatic cardiac dysfunction and that these events may be moderate to severe and have been associated with death. In addition, advice for caution in risk patients and recommendation to assess cardiac function in all patients prior to, during and after treatment with trastuzumab. Information that the safety of continuation or resumption of Ogivri in patients who experience cardiac dysfunction has not been prospectively studied and recommendation that symptomatic cardiac failure developing during trastuzumab therapy should be treated with standard medicinal products. • In Section 4.8, inclusion of congestive heart failure (NYHA Class II-IV) as a common undesirable effect, as well as irregular heart beat, palpitations, cardiac flutter and ejection fraction decreased (very common); cardiomyopathy and supraventricular tachyarrhythmia (common); pericardial effusion (uncommon); and cardiogenic shock, pericarditis, bradycardia, gallop rhythm present (frequency not known). Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.	*None*
Important identified risk: Administration related reactions	Text in SmPC: • Contraindication in section 4.3 for patients with hypersensitivity to trastuzumab, murine proteins, or to any of the excipients • Warning in section 4.4 that serious infusion-related reactions including anaphylaxis may occur, including fatal cases. Description of the more common reactions and their typical temporality to administration. Recommendations regarding premedication and symptomatic treatment. • In section 4.8, infusion-related reaction is listed as a very common undesirable effect together with the most typical signs and symptoms such as dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, respiratory distress, urticaria and angioedema. Anaphylactic reactions and anaphylactic shock are also listed (frequency unknown). Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.	None
Important identified risk: Haematological	Text in SmPC: • In section 4.8, haematological toxicities including anaemia, neutropenia, leukopenia, thrombocytopenia and febrile	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
toxicity	neutropenia are listed as very common undesirable effects, and information is provided that the risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.	
Important identified risk: Oligohydramnios	Text in SmPC: • Warning in section 4.6 that cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Recommendation that women should use effective contraception during treatment with Ogivri and for 7 months after treatment, and to advise women who become pregnant of the possibility of harm to the foetus and to closely monitor pregnant woman treated with trastuzumab or within 7 months following the last dose. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.	None
Important identified risk: Pulmonary disorder	Text in SmPC: • Contraindication in section 4.3 in patients suffering from severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy. • Warning in section 4.4 that severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting and that these events have occasionally been fatal. Information that in addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Description of risk factors for pulmonary disorders and advice for caution regarding pneumonitis in patients being treated concomitantly with taxane. • In section 4.8, various potentially severe pulmonary events are listed as common or very common undesirable effects, including dyspnoea, pleural effusion, asthma and lung disorder. Pneumonitis is listed as a rare undesirable effect. Additionally, pulmonary events listed as reported in the postmarketing setting include lung infiltration, pulmonary fibrosis, (acute) respiratory distress and failure, and (acute) pulmonary oedema (frequency not known). Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	experienced in the administration of cytotoxic chemotherapy.	
Important potential risk: Infections	Text in SmPC: • In section 4.8, infection is listed as a very common undesirable effect. Neutropenic sepsis (common), pneumonia (common), sepsis (uncommon), and several other infectious disorders are additionally listed. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.	None
Missing information: Treatment in male breast cancer patients	Text in SmPC: • In section 5.3, mention that no long-term animal studies have been performed to determine the effects of trastuzumab on fertility in males. Other routine risk minimization measures: • Prescription only medicine. • Restricted medical prescription: The SmPC advises in section 4.2 that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.	None

Public summary of the RMP

The public summary of the RMP may require revision.

PRAC Outcome

The RMP as proposed by the applicant could be approvable if the following 2 points are addressed with the next RMP update:

-inclusion of “Medication Errors” as important potential risk, due to the risk of errors in route of administration as subcutaneous presentations of trastuzumab are available on the market.

-inclusion of “Safety of concomitant use with docetaxel 75mg/m2 versus 100mg/m2” as missing information in the RMP in view of the fact that in pivotal Phase III trial patients were assigned to 75 mg/m2 docetaxel, thereby avoiding exposure to trastuzumab plus higher dose of docetaxel (100 mg/m2). Annual analysis of the safety profile of Ogivri when used concomitantly with docetaxel 75 mg/m2 versus usage with docetaxel 100 mg/m2 should be presented within scheduled PSUR”

3.5. Pharmacovigilance system

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

3.6. New active substance status

Not applicable.

4. Orphan medicinal products

Not applicable.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

Ogivri is developed as a biosimilar to Herceptin. The approval is sought for intravenous use in all approved indications of the reference product according to the Herceptin Summary of Product Characteristics (SmPC):

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 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 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 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 sections 4.4 and 5.1).

5.1.2. Available therapies and unmet medical need

NA

5.1.3. Main clinical studies

The applicant has submitted three different pivotal studies.

- Study MYL-Her-1001 was a single-center, 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-center, 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.

5.2. Favourable effects

From the quality perspective the Applicant demonstrated that the manufacturing processes for Ogivri DS and DP are adequately controlled and properly validated. Ogivri DS and DP have been thoroughly characterised and are sufficiently controlled. The proposed shelf lives for Ogivri DS and DP are supported by the performed stability studies. The biosimilarity analysis revealed that from a quality point of view MYL-1401O DP can be considered as biosimilar to EU Herceptin.

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, no major issues were noted in regards to similarity of MYL-1401O and Herceptin. The submitted primary PK analysis shows 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, we can observe that the terminal half-life, Vz and CL parameters were also similar across the groups. A population pharmacokinetic (PopPK) analyses has been carried out for protocol MYL-HER 3001 and the derived parameters showed good concordance between the 2 products.

PD findings do not contradict the available data for the overall comparability exercise.

Immunogenicity was overall low and comparable between MYL-1401O and Herceptin across clinical trials, and not associated with attenuated efficacy responses.

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, shows that the differences in the response rates according to RECIST 1.1 criteria (69.6% and 64.0% MYL-1401O and Herceptin respectively) are within the pre-defined equivalence margin [-15; +15] (5.5% with a 95% CI of -3.08%, 14.04%) based on central tumour evaluation. Primary efficacy analyse based on the best ORR ratio was within the predefined equivalence margins of [0.81; 1,24] (1.09, 90% CI [0.974, 1.211]), as per FDA requirements.

Furthermore, both PP and ITT2 populations are also within the 15% interval. The results seem to be robust, as the investigator assessments are 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 included the TTP, PFS, OS and DR analysed by Kaplan-Meier plot, unadjusted log-rank tests, Cox proportional hazard modelling and uni- and multivariate analysis. All the secondary variables appeared to show a better result for the biosimilar in Part 1, though the results were not yet robust due to the fact that there were very little disease progressions/deaths in the first part of the Phase III study. Further secondary analysis effectuated in Part 2 (after 48 weeks of treatment in total) confirmed the initial results of similarity in secondary endpoints as noted at W24; with tumour progression (TTP) having occurred in 41.3% and 43.0% of MYL-1401O and Herceptin patients respectively (p = 0.684), 55.7% and 55.3% not having tumour progression (PFS, p = 0.842) and 89.1% and 85.1% (p = 0.439) of subjects respectively surviving (OS) until W48. 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.

5.3. Uncertainties and limitations about favourable effects

In spite of the fact that the ORR result is within the predefined intervals (15% and 0.81-1.24), there could be a tendency in favour of the MYL-1401O in terms of TTP and PFS. The analysis of these secondary variables seems to offer a better result for the biosimilar. This idea appears to be reinforced when the upper bound of the CI for the ORR is observed. The latter, would be clearer if a narrower interval than 15% had been selected (12%-14%). Nonetheless, analysis of PFS, TTP, OS and DR using more mature data at W48 do indicate that there is no statistically significant difference between treatments for these endpoints. However, less than 50% of patients entering Part 2 of the study died or had disease progression at W48, thus changes in these parameters could still occur past the 48th week.

Thus overall the tendency in favour of the MYL-1401O seems to have been diluted at the week 48, with lower upper CI at this time. However, only patients who had at least SD after the first part of the study were allowed to receive MYL-1401O in monotherapy, adding some uncertainties when it comes to comparing these two parts. Some of the differences observed at baseline, such as number of metastatic sites, presence of visceral disease, ECOG, etc. could have possibly influenced the initial impression.

Regarding the subgroup analysis in terms of ORR, there are some subgroups where the biosimilar seem to show a better outcome, especially in tumour endocrine status negative (stratification factor), previous adjuvant/neoadjuvant chemotherapy, subgroup of patients with 3 metastatic sites.

There was a slight imbalance in the baseline disease characteristics with regards to ECOG score and visceral metastases between treatment groups, which are factors that could influence the ORR further down the line. However, analysis of these observations showed them to be statistically insignificant, and thus no impact on outcomes is expected.

The design of the efficacy pivotal trial encompasses two different parts. Part 1, where trastuzumab is given along with a taxane, and part 2 (still on-going) where patients with at least stable disease are treated with trastuzumab in monotherapy (MYL-1401O or Herceptin). However, supporting the above idea that MYL-1401O could be more efficacious than Herceptin, is the fact that more patients treated with the biosimilar reached the part 2 of the study (71.8% vs 64.9%).

Primary efficacy sensitivity analyses by stratification factor indicated that paclitaxel treatment might favour the MYL-1401O treatment arm. However, the low number of paclitaxel treated patients compared to the number of docetaxel treated patients does not allow to draw conclusion on whether this observation is spurious or indication of an actual effect.

With regard to the supportive efficacy study (Study BM200-CT3-001-11), no firm conclusions can be drawn from this trial, since a different formulation was used for MYL-1401O and the study was not designed to evaluate similarity in efficacy between Bmab-200 and the reference product. However, it is worth highlighting the difference in the ORR, 65.15% in the Bmab-200 arm and 75.00% in the Herceptin arm. Of note, the formulation to be marketed and tested in the pivotal trial MYL-her-3001, is slightly different from the EU- approved and United States (US)-licensed Herceptin formulations (). However and having said that, from a quality and PK (similarity) perspective no differences have been found between the two formulations, so apparently, only the design of the study and chance may explain this result in terms of ORR.

Finally, there are some uncertainties regarding GMP compliance in select drug product manufacturing and testing sites. A valid GMP certificate is lacking for the drug product manufacturing site Biocon Ltd (Bangalore, India; DP manufacture, QC testing). A GMP inspection has been performed.

5.4. Unfavourable effects

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.

However, in the Myl-1401O arm compared to in the Herceptin arm, there were slightly more TEAE (but similar number of patients with TEAE). Overall, the SOCs with the most frequently reported TEAEs were blood and lymphatic system disorders, followed by skin and subcutaneous tissue disorders, general disorders and administrative site conditions, Nervous system disorders, and gastrointestinal disorders. At the PT level, the most frequently reported TEAEs were alopecia, followed by neutropenia, and diarrhea. 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, asthenia, arthralgia, and upper respiratory tract infection in the MYL-1401O arm and Herceptin arm respectively. However, the numerical difference in between the 2 treatment groups could be attributed to the differences in medical history, age, previous chemotherapy, use of concomitant medications and trastuzumab or paclitaxel exposure.

Moreover, in the MYL-1401O arm compared to in the Herceptin arm, there were more treatment-related TEAE and more patients with treatment-related TEAE.

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 (accelerated hypertension and pneumothorax spontaneous, both 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, 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).

5.5. Uncertainties and limitations about unfavourable effects

As seen before, although the safety profile has been shown overall similar between MYL-1401O and Herceptin at 48 weeks, there are slight differences in regard to safety findings (see before). However, these are mostly seen in part 1 in combination with taxanes (and not in part 2 monotherapy). 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, especially in studies that are not powered to evaluate statistically meaningful differences in AEs. It could be related to the 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.

Moreover, some remaining uncertainties should be discussed by the applicant: higher incidence of significant cardiac toxicity and risk associated with one excipient.

5.6. Effects Table

The Effects Table is not needed for biosimilars.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

For a biosimilar, the benefit-risk conclusion is based on the totality of evidence collected from the quality, non-clinical and clinical comparability exercise.

Proof of similarity for both efficacy and safety is intended in metastatic breast cancer setting. Furthermore, given that extrapolation to all other indications of Herceptin (early breast cancer and metastatic gastric cancer), similarity in qualitative, PK/PD and non-clinical qualities is crucial.

No major quality issues were identified during review. The lack of the GMP certificate for the manufacturing site is raised as major objection, however.

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. Antibody-Dependent Cell Phagocytosis (ADCP) comparison data have been requested. This is indeed considered as a major mechanism of action for the mAb trastuzumab. Finally, binding data to the other isoforms FCγRIIA131R and FcγRIIIa158V should be provided to ensure that both products have comparative activity.

As for pharmacokinetic aspects, no major issues were noted in regards to similarity of MYL1401O and Herceptin. The submitted PK analysis shows 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.

Likewise, pharmacodynamics assessment did not reveal any major differences between investigative and reference product.

In regards to similarity in clinical efficacy the primary endpoint was met. Efficacy data are showing that the similarity in terms of ORR at week 24 has been shown with the a priori defined margin of similarity (15%). The results appear robust enough as different sensitivity analyses support the main one. This outcome has been achieved in a study designed to show the similarity in terms of ORR at week 24, which is deemed enough to reach the response in the majority of patients and consistent with originator Herceptin pivotal study. ORR is also considered the most sensitive endpoint to show if a difference exists between MYL-1401O and Herceptin. In addition, the pattern of the response is quite similar between the study groups.

In stratified subgroup analyses of the primary endpoint there was a slight trend for better efficacy with paclitaxel + MYL-1401O, but large confidence intervals due to the relatively low numbers of patients do not allow to draw conclusions.

Finally, full analysis of the TTP, PFS, OS and DR confirmed the similarity outcomes seen at the W24 endpoint.

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 globally comparable.

5.7.2. Balance of benefits and risks

The biosimilarity claims by the Applicant are currently supported from a quality, non-clinical, pharmacokinetic and pharmacodynamics, as well as from a clinical efficacy point of view given that the Phase I W24 similarity data have now been supported by secondary endpoints results at, and from a long-term clinical safety and immunogenicity perspective (48 weeks). However, the balance of benefits and risks is currently regarded negative on quality grounds. A major objection on quality has been raised due to the lack of a valid GMP certificate for the manufacturing site Biocon Ltd (India).

Finally, regarding the potential extrapolation to other indications (EBC and MGC) this fact usually relies on a step-by-step-process covering a similar mechanism of action, receptor interactions, PK, efficacy and expected toxicities. Taking into account that (1) MBC, EBC, and MGC require a similar dosage of trastuzumab in all settings, (2) the active substance of the reference product interacts with one common receptor in the tested and non-tested therapeutic indications (HER2 and ADCC), (3) PK data do not reveal any concern, it is reasonable to believe that along as major objection on quality and all the remaining issues from efficacy and safety can be solved, no objections can be raised so far as to extrapolate for the rest of indications applied for.

5.7.3. Additional considerations on the benefit-risk balance

Not Applicable.

5.8. Conclusions

The overall B/R of Ogivri is currently considered negative since a major objection has been maintained for quality, relating to the lack of a valid GMP certificate for the manufacturing site Biocon Ltd (India).

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