THE E.U. RISK MANAGEMENT PLAN FOR HERCEPTIN®/TRASTUZUMAB

RMP version to be assessed as part of this application:

RMP Version number: 23.0

Data lock point for this RMP: 10 June 2021

Date of final sign off:

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Rationale for submitting an updated risk management plan (RMP):

The Marketing Authorization Holder (MAH) proposes to update the RMP with regards to the current statement on medication errors of Herceptin and Kadcyla (trastuzumab emtansine). This follows on from a EMA request received on 23 April 2021 instructing the MAH to include in the medication error statement the other trastuzumab-containing product Enhertu (trastuzumab deruxtecan). The MAH has revised the current statement to widen scope by including examples of INN (International nonproprietary name) of other trastuzumab-containing products and not limiting to brand names, which may change in the future.

Summary of significant changes in this RMP:

The MAH introduced the following updates to the trastuzumab RMP

- Part III.1:Routine pharmacovigilance activities: Pregnancy related adverse events (Oligohydramnios) re-ordered for better clarity.
- Medication error information was updated to ensure correct trastuzumab product and not other trastuzumab-containing products are administered.
- Annex 4 (Specific Adverse Drug Reaction Follow-up Forms) was updated to include updated guided questionnaire for medication error.

Other RMP versions under evaluation:

RMP Version number: None

Submitted on: Not applicable

Procedure number: Not applicable

Details of Currently Approved RMP:

Version number: 22.1.

Approved with procedure: EMEA/H/C/000278/II/1068

Date of approval (opinion date): 10 June 2021

See page 1 for signature and date

Leanne Angst-Wu (QPPV) Date

See page 1 for signature and date

[redacted] Date

PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or common name)	**Trastuzumab**
Pharmacotherapeutic group(s) (ATC Code)	**L01XC03**
Marketing Authorization Holder (or Applicant)	**Roche Registration GmbH, Germany**
Medicinal products to which this RMP refers	**One**
Invented name(s) in the European Economic Area (EEA)	**Herceptin®**
Marketing authorization procedure	**Central Authorization Procedure**
Brief description of the product including:	**Chemical Class:** Recombinant Humanized Monoclonal Antibody
	Summary of mode of action: Trastuzumab selectively targets the extracellular domain of human epidermal growth factor receptor 2 (HER2), a transmembrane tyrosine kinase receptor. Trastuzumab has been shown, both in *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.
	Important information about its composition: Trastuzumab is produced by a genetically engineered Chinese hamster ovary (CHO) cell line grown in large scale, which secretes trastuzumab into the culture medium. The antibody is then purified extensively using standard chromatographic and filtration methods.
Hyperlink to the Product Information	
Indication(s) in the EEA	**Current:** • ***Breast Cancer*** – Metastatic Breast Cancer (MBC): intravenous (IV) and subcutaneous (SC) (vial and single-use injection device [SID]). – Early Breast Cancer (EBC): IV and SC (vial and single-use injection device [SID]). • ***Metastatic Gastric Cancer (MGC)*** : IV only
	Proposed: Not applicable

Dosage in the EEA	**Current:** **IV formulation: *Metastatic breast cancer*** ***Three-weekly schedule*** The recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. ***Weekly schedule*** The recommended initial loading dose of Herceptin is 4 mg/kg body weight. The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight, beginning one week after the loading dose. ***Early breast cancer*** ***Three-weekly schedule*** The recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. ***Weekly schedule*** The recommended initial loading dose of Herceptin is 4 mg/kg followed by 2 mg/kg every week concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. ***Metastatic gastric cancer*** ***Three-weekly schedule*** The recommended initial loading dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. **Subcutaneous (SC) formulation:** The recommended dose for Herceptin subcutaneous formulation is 600 mg irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2-5 minutes every three weeks
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Herceptin is available as an IV formulation (150 mg single dose vials containing powder for concentrate for solution for infusion;

	reconstituted concentrate contains 21 mg/mL of trastuzumab; in addition, single dose vials (60 mg) and multi-dose vials are available outside of the EEA). It is also available as a SC formulation (600 mg fixed-dose vial containing solution for injection, which should not be reconstituted or diluted).
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the E.U.?	No

CHO = Chinese hamster ovary, EBC = Early Breast Cancer, EEA = European Economic Area, HER2 = human epidermal growth factor receptor 2, IV = intravenous, MBC = Metastatic Breast Cancer, MGC = Metastatic Gastric Cancer, SC = Subcutaneous, SID = Single–Use Injection Device.

ABBREVIATIONS

Abbreviation	Definition
AC–>T	doxorubicin plus cyclophosphamide followed by docetaxel
AC–>T+H	doxorubicin plus cyclophosphamide followed by docetaxel plus trastuzumab
AC–>T–>H	doxorubicin plus cyclophosphamide followed by docetaxel followed by trastuzumab
ADA	Anti-Drug Antibodies
ADRs	Adverse Drug Reactions
ADS	Annual Data Summary
AEs	Adverse Events
ARR	administration-related reactions
CHF	Congestive Heart Failure
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DHPC	Direct Healthcare Professional Communication
DSR	Drug Safety Report
ErbB2	erythroblastic oncogene B2
EBC	Early Breast Cancer
ECHO	echocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen Receptors
E.U.	European Union
E.U.-RMP	E.U. Risk Management Plan
FDA	United States Food and Drug Administration
GC	Gastric Cancer
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
HER-2	Human Epidermal Growth Factor Receptor-2
HLGT	High Level Group Terms
HLT	High Level Terms
IB	Investigator's Brochure
IBD	International Birth Date
ISR	Injection Site Reaction
INN	International nonproprietary name

IV	intravenous
LLN	Law of Large Numbers
LVEF	left ventricular ejection fraction
MAH	Marketing Authorization Holder
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary of Regulatory Activities
MGC	Metastatic Gastric Cancer
MI	Myocardial Infarction
MUGA	Multigated Acquisition Scan
Nab	Neutralizing Antibody
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAM	post-authorization measure
PBRER	Periodic Benefit Risk Evaluation Report
PFS	progression-free survival
PR	Progesterone Receptors
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
Q1W	once a week
Q3W	every three weeks
rHuPH20	recombinant human PH20 hyaluronidase
RMP	Risk Management Plan
ROW	Rest of World
SAEs	Serious Adverse Events
SC	subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SID	Single-use Injection Device
SmPC/SPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TAE	Targeted Adverse Event
TCH	docetaxel plus carboplatin plus trastuzumab
U.S.	United States
USPI	U.S. prescribing information

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 EARLY/METASTATIC BREAST CANCER

- Incidence

In Europe, breast cancer is the most commonly diagnosed form of cancer in women (463,800 new breast cancers in 2012 or 28.8% of total cancers reported in Europe) (Ferlay et al. 2013). There is an approximate 3-fold variation in risk among European Union (E.U.) countries; incidence rates range from 54 cases per 100,000 (Ukraine) to 147.5 cases per 100,000 (Belgium). Rates generally appear to be higher in western compared to Eastern Europe (Ferlay et al. 2013).

Globally, breast cancer is also the most common female cancer with an estimated 1.38 million cases in 2008. Worldwide, rates appear to vary by geographical region with the highest breast cancer rates in more developed, "Westernized" countries such as those in North America and Europe (Jemal et al. 2011)

It has been estimated that approximately 15%-20% of diagnosed breast cancers in women are Human Epidermal Growth Factor Receptor-2 (HER2)-positive breast cancers (Chia et al. 2008; Ross et al. 2009; Pathmanathan et al. 2012; Bilous et al. 2012)

Most breast cancers in the Western world (around 94%-95% of patients in the United States [US] and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al. 2012) i.e., only around 5%-6% of new cases are locally advanced (T4) or metastatic at diagnosis.

- Prevalence

The global 5-year limited duration prevalence of breast cancer is 5.2 million patients (Bray et al. 2013). The prevalence of HER2 positivity varies considerably, ranging from 9% to 74%, with an average of 22% (Chia et al. 2008). Factors that contribute to this variability include stage of disease (metastatic versus. non-metastatic), specimen type (e.g., frozen, paraffin, etc.) and assay type (e.g., fluorescence in situ hybridization [FISH], immunohistochemistry [IHC], etc.) and center (tertiary hospitals tend to report the highest rates of HER2 positivity). However most investigators tend to believe that the

true range of HER2 positivity falls within the range of 15%-20% (Chia et al. 2008; Ross et al. 2009; Pathmanathan et al. 2012; Bilous et al. 2012).

- Demographics:

The incidence rate rises rapidly between 35 and 39 years of age, then levels off to a plateau after 80 years of age (Benson et al. 2009; Smigal et al. 2006).

Breast cancer is rare in men, accounting for less than 1% of all malignancies (Fentiman et al. 2006). The average age of diagnosis of breast cancer in men is 67 years.

Among patients newly diagnosed with breast cancer, 28% of those aged 20-29 years were HER2-positive, while only about 10% of those aged >75 years were HER2-positive (Clarke et al. 2012). Estimation of HER2-positive breast cancer in men significantly varies in the literature (5%-56%) (Onami et al. 2010) (Barh ,2009). Although racial differences in the incidence of different breast cancer sub-types have been described (Kwan M et al. 2009), notably for triple-negative breast cancer, no particular racial differences have been described for HER2-positive disease.

- The main existing treatment options:

Treatment of newly diagnosed, non-metastatic breast cancer:

Breast cancer is treated with a multidisciplinary approach involving surgical oncology, radiation oncology, and medical oncology, which has been associated with a reduction in breast cancer mortality. Because ductal carcinoma in situ (DCIS) and invasive breast cancer are managed differently, the discussion is restricted to invasive breast cancer. The treatment approach depends on the stage at presentation.

Non metastatic breast cancer is broadly considered in two categories:

- Early stage –includes patients with stage I, IIA, or a subset of stage IIB disease (T2N1);
- Locally advanced –includes a subset of patients with stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease.

Early-stage breast cancer

Surgery is the main modality of local treatment for breast cancer, and surgery and/or radiotherapy can control loco-regional disease in the majority of patients. Conventionally, adjuvant systemic therapy is given after loco-regional therapy to eradicate micrometastatic disease and reduce the chances of distant (and local) relapse. Neoadjuvant therapy (also called 'primary systemic' or 'pre-operative' therapy) is given prior to surgery and has become a standard treatment option for many patients with newly diagnosed breast cancer. Although originally developed for patients with large and/or inoperable tumors to enable definitive surgery to be performed, neoadjuvant therapy is also now used in patients with operable EBC at high risk of recurrence (e.g.,

HER2+ positive tumors, node positive disease) to try to avoid a mastectomy and enable breast-conserving surgery to take place. Neoadjuvant therapy is also the primary modality of therapy for patients with inflammatory breast cancer, regardless of tumor size (Dawood et al. 2011)

Following definitive local treatment, adjuvant systemic therapy may be offered based on primary tumor characteristics, such as tumor size, grade, number of involved lymph nodes, the status of estrogen receptors (ER) and progesterone receptors (PR), and expression of the HER2 receptor.

Tumor characteristics predict which patients are likely to benefit from specific types of therapy. For example, hormone receptor-positive patients benefit from the use of endocrine therapy. In addition, patients with HER2-positive cancers benefit from treatment using HER2-directed treatment.

For patients with early-stage breast cancer, treatment is based on tumor characteristics, patient status, and patient preferences:

- Patients with hormone receptor-positive breast cancer should receive endocrine therapy. Whether they also should receive adjuvant chemotherapy depends on patient and tumor characteristics.
- Chemotherapy is offered to patients with early-stage hormone receptor-positive cancers that have high-risk characteristics, such as high-grade tumor, large tumor size (≥2 cm), pathologically involved lymph nodes, and/or high 21-gene recurrence score (≥31).
- For patients with ER/PR and HER2-negative disease (triple-negative breast cancer), it is recommended to administer adjuvant chemotherapy if the tumor size is ≥0.5 cm. Because these patients are not candidates for endocrine therapy or treatment with HER2-directed agents, chemotherapy is their only option for adjuvant treatment, following or before radiotherapy. Patients with a triple-negative breast cancer <0.5 cm in size may forego adjuvant chemotherapy in most cases, due to minimal, if any, survival advantage.
- Patients with HER2-positive breast cancer with a tumor size >1 cm should receive a combination of chemotherapy plus HER2-directed therapy. The management of small (≤1 cm) HER2-positive breast cancers is controversial.
- Following chemotherapy, patients with ER-positive disease should also receive adjuvant endocrine therapy.

Locally advanced breast cancer

Locally advanced breast cancer is best managed with multimodality therapy employing systemic and loco-regional therapy.

Most patients with locally advanced breast cancer should receive neoadjuvant systemic therapy. The goal of treatment is to induce a tumor response before surgery and enable breast conservation. Neoadjuvant therapy results in long-term distant disease-free

survival and overall survival (OS) comparable to that achieved with primary surgery followed by adjuvant systemic therapy. Selection of treatment in the neoadjuvant setting is outlined below:

- For most patients HR-positive disease, chemotherapy in the neoadjuvant setting rather than endocrine therapy is recommended. Chemotherapy is associated with higher response rates in a shorter time period. For select patients with hormone-positive disease, neoadjuvant endocrine therapy may be an appropriate option.
- For patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, a HER2-directed agent (e.g. trastuzumab with or without pertuzumab) should be added to the chemotherapy regimen.

All patients should undergo surgery following neoadjuvant systemic therapy, even if they have a complete clinical and/or radiological response. In addition, patients who experience progression while on neoadjuvant systemic therapy should proceed with surgery, rather than switching the chemotherapy regimen.

The use of postoperative (adjuvant) systemic therapy is guided by the patient's clinical status and tumor characteristics:

- Patients who did not receive neoadjuvant systemic therapy should receive adjuvant treatment. The use of chemotherapy, biologic therapy, and/or endocrine therapy is guided by the same principles used to determine treatment for early-stage breast cancer.

For patients who received the full course of planned neoadjuvant chemotherapy

- Patients with HR-positive breast cancer should receive endocrine therapy to reduce the risk of breast cancer recurrence and breast cancer-related mortality. There is no evidence that the addition of further chemotherapy in the form of adjuvant treatment improves OS. The selection of endocrine therapy is made according to menopausal status.
- Patients with HR-negative breast cancer would typically not receive further chemotherapy in the adjuvant setting, as there is no evidence that the addition of adjuvant chemotherapy improves OS. These patients should begin post treatment surveillance.
- In some exceptional cases where the tumor progressed during neoadjuvant therapy or if the complete neoadjuvant therapy could not be delivered at the normal levels of intensity, adjuvant chemotherapy should be discussed and considered.
- Patients with HER2-positive breast cancer should receive one year of trastuzumab with or without pertuzumab following completion of surgery without the addition of further chemotherapy.

Patients treated with neoadjuvant endocrine therapy who undergo surgery should continue endocrine therapy in the adjuvant setting. Whether or not to administer

adjuvant chemotherapy should be individualized; up-to-date online article accessed 23 November 2017 (Taghian A et al. 2020).

Although metastatic breast cancer is unlikely to be cured, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies. Median OS approaches two years, with a range from a few months to many years.

The selection of a therapeutic strategy depends upon both tumor biology and clinical factors, with the goal being a tailored approach. Although a subset of patients with oligometastatic disease may benefit from an intensified loco-regional approach, most patients with metastatic breast cancer receive systemic medical therapy consisting of chemotherapy, endocrine therapy, and/or biologic therapies, and supportive care measures.

Therapeutic goals: the primary goals of systemic treatment for metastatic breast cancer are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life, despite the toxicity associated with treatment. The median survival for metastatic breast cancer is 18 to 24 months, though this varies widely based on subtype of tumor, sites of metastatic involvement, and burden of metastatic disease, and some patients experience long-term survival.

No prospective randomized clinical trials have demonstrated that systemic therapy prolongs survival compared with best supportive care alone. However, median survival for patients with metastatic breast cancer appears to have improved over time, a trend which has been attributed to the availability of new, more effective agents, including taxanes, aromatase inhibitors, and trastuzumab. As an example, patients from the British Columbia Breast Cancer Outcomes Database who were diagnosed between 1997 and 2001 had better two-year OS than patients diagnosed between 1991 and 1995 (45 versus 34 percent).

Treatment selection is based on the following factors:

- The aim of treatment is to palliate symptoms, prolong survival, and maintain quality of life.
- Patients with visceral metastases (especially if rapidly progressing) and/or a short disease-free interval generally have an aggressive phenotype, while patients with soft tissue and bone metastases have a more indolent phenotype.
- Hormone receptor status and HER2 overexpression are important in estimating prognosis and the likelihood of response to therapy.
    - Hormone receptor (ER and/or PR) status is the major determining factor for response to endocrine therapy.
    - Likewise, HER2 overexpression is required for response to HER2-directed therapies.

Based upon these principles, selection of treatment can be individualized. Endocrine therapy is best used for patients with HR-positive breast cancer and not for patients with hormone-negative breast cancer. HER2-directed therapy is only appropriate for patients with tumors that overexpress HER2. Lastly, chemotherapy is indicated for hormone-insensitive metastatic breast cancer (i.e., patients with HR-negative breast cancer and those with HR-positive breast cancer who have become resistant to endocrine therapy). It is less clear when to use endocrine therapy versus chemotherapy as initial treatment for patients with hormone receptor-positive metastatic breast cancer. Likewise, it is less obvious when to use single agent versus combination chemotherapy, how to best incorporate biologic therapies, and whether combined modalities are of benefit.

Treatment algorithms:

- *Hormone receptor-positive HER2-negative patients —*

In general, endocrine therapy is very likely to be beneficial for these patients, with fewer side effects compared with chemotherapy. Therefore, these should usually be used as initial treatment for patients with hormone receptor-positive disease. However, chemotherapy induces higher response rates than endocrine therapy. Therefore, patients with rapidly progressive, symptomatic disease or visceral metastases with end-organ dysfunction may be best treated with first-line chemotherapy. After chemotherapy response stabilizes (usually four to six months), a switch to maintenance endocrine therapy is a commonly employed strategy, which can reduce the treatment side effects without compromising overall survival. Given its generally favorable toxicity profile, first-line endocrine therapy is more appropriate for most patients except those with severe symptoms or rapidly progressive visceral involvement. If the disease progresses rapidly (within a few months) following initiation of first-line endocrine therapy, chemotherapy is generally recommended as a second-line therapy rather than switching to another endocrine strategy. If time to progression on first-line endocrine therapy is greater than six months, then a switch to second-line endocrine therapy at progression is reasonable.

- *Hormone receptor-positive HER2-positive patients —*

Therapeutic options for these patients include chemotherapy, endocrine therapy, and HER2-directed therapy. HER2-directed therapy has demonstrated improved survival for patients with tumors that overexpress HER2 and thus should be part of first-line therapy for these patients.

- *Hormone receptor-negative HER2-negative patients —*

Many patients with triple- (ER-, PR-, HER2-) negative breast cancer have a particularly aggressive subtype, and first-line chemotherapy is recommended. Whether chemotherapy agents are given in combination or sequentially should be determined based on symptoms and location and burden of disease, as well as patient-related factors (i.e. preferences, goals, and overall health) up-to-date online article (Hayes DF et al. 2016].

- Risk factors for the disease

Major risk factors for breast cancer in general include being female, older age, early menarche, late menopause, older age at first childbirth, alcohol consumption, family history of breast cancer, postmenopausal hormone use, having benign breast disease, and being overweight/obese (Adami et al. 2002). Height is positively associated with breast cancer risk (Adami et al. 2002).

HER2 overexpression is associated with increased tumor aggressiveness, higher rates of recurrence and increased mortality in node-positive patients, while the influence in node-negative patients is more variable (Borg et al,1990). Oral contraceptive use has been associated with increased risk of HER2 positive status in at least one study (Gammon et al. 1999).

- Natural history of the indicated condition in the (untreated) population:

Mortality: Breast cancer is the third leading cause of cancer death in Europe, with 131,200 new deaths reported in 2012. In the E.U., the mortality rates ranged from 16.7 per 100,000 in Spain to 29.5 per 100,000 in Belgium in 2012 (Ferlay et al. 2013). Approximately 20% of these deaths would be expected to be due to HER2-positive metastatic breast cancer, i.e., approximately 26,000 deaths in Europe and approximately 18,000 deaths in the E.U. HER2 overexpression is independently associated with poor prognosis, indicating a more aggressive form of breast cancer, with faster relapse times at all disease stages and shortened survival (Slamon et al. 1989). Among HER2-positive metastatic breast cancer patients in the post-trastuzumab era (since 30 October 1998), the median survival is approximately 3.5 years from time of initiation of first therapy in the metastatic setting (Olson et al. 2013).

Early Breast Cancer: Survival rates for early stages of breast cancer are high (>85%). In the U.S. and Europe, almost all women diagnosed with localised disease survive for at least 5 years, compared with only about a quarter of patients diagnosed with distant metastases (Jemal et al. 2007; Sant et al. 2004).

Metastatic Breast Cancer: Metastatic disease is associated with increased tumor burden and decreased survival. According to the U.S. population-based cancer registries that constitute the Surveillance, Epidemiology, and End Results (SEER) Programme of the National Cancer Institute (NCI), stage IV breast cancer is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al. 2001).

- Important co-morbidities:

The most common conditions among breast cancer patients are: previous solid tumors, diabetes, respiratory disease, psychiatric disease, angina, obesity, myocardial infarction (MI), and stroke (Piccirillo et al. 2008).

SI.2 METASTATIC GASTRIC CANCER

- Incidence

In Europe, gastric cancer (GC) is the sixth most common cancer overall, with approximately 140,000 new cases per year (Ferlay et al. 2013). Among E.U. countries, there is an approximately 5-fold variation in risk. The highest rates, among E.U. countries, are in Belarus (42.1 cases and 17.2 cases per 100,000 for men and women, respectively) and the lowest rates are seen in Sweden (7.4 cases and 4.1 cases per 100,000 for men and women, respectively) (Ferlay et al. 2013).

Despite the historic decline in incidence and mortality, worldwide, GC is the fifth most commonly diagnosed cancer (951,000 new cases in 2012), accounting for 6.8% of total cancer cases (Ferlay et al. 2015).

HER2 is overexpressed in 10-27% of all GC cases (Vakiani 2015).

- Prevalence

The global 5-year limited duration prevalence for GC is approximately 1.7 million patients (Bray et al. 2013). Based on the MAH's knowledge, there have been no epidemiologic studies reporting on the prevalence of HER2 positive GC.

- Demographics:

Men are more likely to develop GC. Incidence rates in Europe and globally are approximately 2-fold higher in men than women (Ferlay et al. 2015).

There is a positive association with age. In a report from the population-based Munich Cancer registry, 59% of the cohort was $\geq$ 70 years old (Schlesinger-Raab et al. 2015).

High risk areas (>20 cases per 100,000) include Eastern Asia and Central and Eastern Europe (Ferlay et al. 2015). Lower rates (<10 cases per 100,000) are seen in most countries in Africa, Northern America, Australia, and New Zealand (Ferlay et al. 2015).

HER2 overexpressing cancer of the stomach or gastroesophageal junction is estimated by the MAH to be 16% of all newly diagnosed patients.

- The main existing treatment options:

To date, the only potentially curative treatment for loco-regional GC is surgery (Roth 2003). Owing to increased detection of early GC, outcomes of GC patients have improved including mortality.

For those patients and for patients with recurrent disease after surgery, the main therapeutic option is chemotherapy (Ajani 2005; Cunningham et al. 2005; National Comprehensive Cancer Network 2006).

Because advanced GC is typically not curable with current therapy, the goal of therapy in this setting is symptom palliation and to prolong progression free and overall survival while maintaining quality of life.

- Risk factors for the disease:

Demographic, environmental and lifestyle risk factors associated with increased risk of GC include socioeconomic status (Uthman et al. 2013), race/ethnicity (Dixon et al. 2014; Lui et al. 2014), smoking (Crew and Neugut 2006; Han et al. 2013), alcohol consumption (Huang et al. 2014), *Helicobacter Pylori* infection (Herrero et al. 2014), diet such as consumption of salty foods (Lin et al. 2014), and obesity .

- Natural history of the indicated condition in the untreated population:

Mortality: Gastric cancer has poor prognosis and high mortality. In Europe, mortality rates are 14.6 per 100,000 in men and 7.0 per 100,000 in women. GC is the fourth most common cause of death from cancer and accounts for approximately 6.5% of all cancer deaths in men and 5.6% of all cancer deaths in women in Europe (Ferlay J,2013) Globally, 723,000 deaths due to GC were estimated to have occurred in 2012 (Ferlay et al. 2015).

Outcome of the untreated target disease: The 5-year OS rate increased from 64% to 73% from 1986 to 2006 according to a large retrospective analysis in Korea (Suh and Yang 2015). Relative risk of mortality in GC patients in Japan has been reported as 0.52-0.72 because of increased screening (Suh and Yang 2015). However, in Western Europe and North America, GC is often diagnosed at a stage beyond resectability and survival is low. The 5-year survival in all GC patients in Europe is reported to be 24% whereas in U.S. the 5-year survival rate has been reported to be approximately 27% (Dikken et al. 2012). Regardless of their geographic region, patients with unresectable disease due to locally advanced growth or metastatic spread have a poor prognosis, with overall 5-year survival, in the range of 1%-15% (De Vivo et al. 2000; Dassen et al. 2014).

While some studies show that HER2 positive patients have poor survival (Chen et al. 2013; Liang et al. 2014; Qiu et al. 2014), many others have also reported mixed evidence on the association of HER2 status and survival in GC patients (Tanner et al. 2005; Aizawa et al. 2014; Gomez-Martin et al. 2011; He et al. 2013; Jacome et al. 2014; Lorenzon et al. 2013; Ozen et al. 2013; Yoon et al. 2012).

- Important co-morbidities:

For gastric subcardia cancers, data from Netherlands (Eindhoven Cancer Registry) suggest that the most common co-morbid conditions are cardiovascular disease, hypertension, ulcerative disease, previous cancer, diabetes, chronic obstructive pulmonary disease, cerebrovascular disease, and liver disease.

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PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

1.1 TRASTUZUMAB IV FORMULATION

1.1.1 Toxicity

Single-Dose toxicity:

Single-dose acute toxicity studies were undertaken using intravenous bolus administration in mice sand rhesus monkeys. The absence of toxicity of several different preparations and formulations of trastuzumab could be demonstrated, as measured by standard parameters like food consumption, body weight, antibody formation, clinical chemistry and macro- and microscopic examination of standard organs/tissues.

Relevance to human usage: Yes

Discussion:

This data supports the use of trastuzumab in the target population. No safety concern has been identified.

Repeated-Dose toxicity:

The repeated-dose toxicity evaluation of trastuzumab is based on a four-week study in rhesus monkeys, and 12-week and 26-week studies in cynomolgus monkeys. In all the three studies, there was a minimal toxic response, with the only noteworthy observation having been injection-site trauma in the rhesus monkey.

Relevance to human usage: Yes

Discussion:

This data supports the use of trastuzumab in the target population. No safety concern has been identified.

Reproductive toxicity:

Owing to the lack of suitability of the species conventionally used (rat or rabbit), studies were undertaken in the cynomolgus monkey at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg of trastuzumab; and no evidence has been revealed of impaired fertility. Placental transfer of trastuzumab was observed during the

early and late days of gestation of the fetal development period (Days 20 to 50 and Days 120 to 150, respectively). Reproductive toxicity studies in female monkeys did not reveal any impaired fertility, embryo-toxicity, or effects on fetal development.

Relevance to human usage: Yes

Discussion:

The use of trastuzumab should be avoided during pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Embryofetal toxicity:

The non-clinical program revealed no direct toxicity of trastuzumab to juvenile and adult animals via the IV, SC or intrathecal route. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development, and the embryonic death in mutant mice lacking this receptor.

Relevance to human usage: Yes

Discussion:

In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab. This risk was not predicted by non-clinical IV route reproductive safety studies.

Mutagenicity:

The genotoxic potential of trastuzumab has been investigated both in vitro and in vivo. All tests gave clearly negative results. Genotoxicity testing is not required or recommended for biologics such as trastuzumab (International Conference on Harmonisation [ICH] S6[R1]). The genotoxicity assays cannot be validated for proteins as they are conducted under conditions that do not support protein stability and the proteins do not have nuclear access (in vitro or in vivo, i.e., non-genotoxic). Despite this the genotoxic potential of trastuzumab was investigated in the standard genotoxicity assays yielding negative results both in vitro and in vivo.

Relevance to human usage: Yes

Discussion:

This data supports the use of trastuzumab in humans.

1.1.2 General Safety Pharmacology

Cardiac dysfunction:

Preclinical investigations of trastuzumab associated with cardiac dysfunction, primarily on left ventricular ejection fractions and congestive heart failure (CHF), have been conducted by the MAH as well as independent investigators, and the results have suggested several possible mechanisms (De Keulenaer et al, 2010]: There may be a feedback loop involving neuregulin and erythroblastic oncogene B2 (ErbB2) (as a co-receptor) as part of a cell survival mechanism; trastuzumab may block or alter cell survival signaling; trastuzumab may down-regulate ErbB2 and thereby prevent cell survival signaling; cardiac physiological stress or damage can be exacerbated by trastuzumab; and/or there may be a direct effect of trastuzumab on cardiomyocytes.

It has been reported that HER2 signaling plays an important role in the sympathovagal control systems of the heart. In vitro studies showed that co-operation of neuregulin and the cholinergic system produced potent anti-adrenergic effects, resulting in a decrease in cardiac output and blood pressure. These findings suggest that resting sympathetic tone may be increased in patients treated with trastuzumab and in neuregulin-deficient mice [Sendur et al.2013]. However, the clinical implications of these findings, if any, have yet to be elucidated.

Relevance to human usage: Yes

Discussion:

Cardiac dysfunction has been observed in clinical trials. Cardiac dysfunction[1] is considered an important identified risk in humans

Intrathecal administration:

A small number of spontaneous cases have been received by the MAH in which it was reported that trastuzumab was administered to the patient intrathecally for the treatment of central nervous system (CNS) metastases. In response to this off-label use, the MAH has undertaken a study to investigate the safety and efficacy of intrathecal administration of trastuzumab in cynomolgus monkeys. A 4-week toxicology study with weekly intrathecal administration of trastuzumab was performed in cynomolgus monkeys at doses of 0, 3, or 15 mg, no trastuzumab-related effects on body weight, clinical signs, neurological function, clinical pathology, or anatomic pathology were noted. The applied

[1] Cardiac dysfunction was not initially identified in non-clinical studies but subsequently identified in clinical trials and subsequently re-assessed in non-clinical studies.

doses and cerebral spinal fluid (CSF) concentrations achieved in the repeat dose study exceeded those reported in patients after intrathecal administration.

Relevance to human usage: Yes

Discussion:

No safety concerns were identified in relation to intrathecal administration.

1.2 TRASTUZUMAB SC FORMULATION

1.2.1 Toxicity

Repeated-Dose Toxicity:

A 13-week study was performed to confirm whether the novel route of administration and the use of the novel excipient recombinant human PH20 hyaluronidase (rHuPH20) have an effect on the safety characteristics of trastuzumab. A 30 mg/kg dose was selected to achieve systemic exposure comparable to the systemic exposure at the highest tested dose of 25 mg/kg in the 26-week IV toxicity study. The achieved exposures were comparable. No adverse Herceptin SC formulation-related effects occurred for any parameters evaluated. The study results confirmed the favorable safety profile of trastuzumab and are in line with the toxicity studies conducted with trastuzumab IV.

Relevance to human usage: Yes

Discussion:

No direct relevance other than to support the use of Herceptin SC in the target population.

Local Tolerance:

A SC local tolerance study in rabbits was performed to specifically examine the local SC tolerance of trastuzumab in a formulation containing rHuPH20. The SC formulation to be used in humans was used in the study. There were no macroscopic or microscopic findings that were attributable to treatment with Herceptin SC.

Relevance to human usage: Yes

Discussion:

Absence of local reaction in rabbits or minipigs appropriately predicted tolerability in humans.

Preclinical Safety of IV vs. SC Trastuzumab:

For the purpose of bridging between trastuzumab IV and trastuzumab SC one 13-week repeat dose toxicity study in cynomolgus monkey for trastuzumab SC containing rHuPH20 was conducted. No toxicity was noted.

In this study. a mean systemic exposure (area under the concentration-time curve [AUC]: 1-7 days) of 47,400 µg.h/mL (Day 1) to 166,000 µg.h/mL (Day 78) was achieved at the dose of 30 mg/kg. Immunogenicity of Herceptin SC was noted to be low. Only 3 samples (all from the same animal) out of a total of 36 samples taken from 4 animals from the recovery phase were positive for anti-trastuzumab antibodies (neutralizing properties were not examined). The study is considered to be a valid study to assess potential toxicity of trastuzumab SC because the animals were continually exposed to trastuzumab during the treatment period.

Relevance to human usage: Yes

Discussion
Anti-Drug Antibodies (ADAs) have been observed clinically with both IV and SC formulations. No correlation has been identified between trastuzumab ADA status and trastuzumab pharmacokinetics, efficacy, or safety. The toxicity and toxicokinetic and immunogenicity results from all pre-clinical toxicity studies are relevant to support further use in humans.

1.3 RHUPH20 (HYALURONIDASE)

1.3.1 Toxicity

Repeated-dose toxicity:

Results from a 39-week toxicity study of rHuPH20 administered subcutaneously in cynomolgus monkeys with a recovery phase demonstrate the absence of toxicity and limited systemic exposure to rHuPH20 upon once-weekly repeated subcutaneous administration at a dose of 2 mg/kg.

Treatment-related minimal subcutaneous perivascular lymphoplasmacytic infiltration was present at the injection site of all animals administered 2 mg/kg rHuPH20 and in 1/4 males and 1/4 females administered 0.2 mg/kg rHuPH20 sacrificed at the end of treatment. The majority of the cells were plasma cells along with a few lymphocytes. At

the end of the recovery period, minimal subcutaneous perivascular lymphoplasmacytic infiltration was only present in a single male that had been administered 2 mg/kg rHuPH20, indicating substantial recovery. This result was not unexpected because subcutaneous perivascular lymphoplasmacytic infiltration is sometimes observed in cynomolgus monkeys that were injected subcutaneously with human proteins (Carbonatto et al. 2008). Consequently, this observation likely represents a nonspecific local response rather than a specific toxicity associated with rHuPH20. In view of the minimal severity of the finding and the general reaction to injection of a human protein, this finding was not considered to be adverse.

Relevance to human usage: Yes

Discussion

No direct relevance other than to support the use of rHuPH20 in the target population.

Immunogenicity to rHuPH20:

Immunogenicity in cynomolgus monkey after dosing with trastuzumab SC containing rHuPH20.

For the purpose of bridging between trastuzumab IV and trastuzumab SC one 13-week repeat dose toxicity study in cynomolgus monkey for trastuzumab SC containing rHuPH20 was conducted. No toxicity was noted.

Immunogenicity of rHuPH20: Following subcutaneous injections in the 13-week trastuzumab SC containing rHuPH20 study in cynomolgus monkey, seven out of 20 animals were considered positive for anti-rHuPH20 antibodies and the antibodies had neutralizing activity. However, neutralizing antibodies to rHuPH20 had no effect on the subcutaneous dispersion of the injection solution. Immunogenicity in cynomolgus monkey after dosing with rHuPH20 alone.

Cynomolgus monkey and human PH20 hyaluronidases are 89% homologous. This difference caused an immune reaction in cynomolgus monkeys toward rHuPH20. In the pivotal 39-week toxicity study in cynomolgus monkey, the reduction in hyaluronidase activity in plasma specimens following chronic repeated doses of 2 mg/kg was consistent with an increase in hyaluronidase neutralizing activity (neutralizing titre). Both total anti-rHuPH20 antibody (ADA) titre and neutralizing titre response correlated with dose and generally increased over time. These results were not unexpected because repeat administration of a human protein in cynomolgus monkeys can lead to an immunogenic response. After the 4-week recovery period, titres dropped by approximately 50% from peak levels. The presence of neutralizing activity was not correlated with adverse effects.

Relevance to human usage: Yes

Discussion:

Antibodies to rHuPH20 have been observed in humans. No correlation has been identified between trastuzumab ADA status and trastuzumab pharmacokinetics, efficacy, or safety. 'Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC' is considered as important potential risk in humans

Embryo-fetal toxicity in mice after treatment with rHuPH20:

Reproductive toxicology studies in mice with rHuPH20 revealed embryo-fetotoxicity at doses ≥ 9 mg/kg/day, and did not show teratogenic potential. This effect is considered to be related to the achieved high systemic exposure to rHuPH20 in mice and may have been related to disruption or degradation of hyaluronan in the developing embryos. rHuPH20 is a highly purified recombinant form of the naturally occurring human hyaluronidase enzyme. The enzyme breaks down hyaluronan which is an important glycosaminoglycan component of the cardiac jelly, critical for the formation of the heart during embryogenesis. Studies in hyaluronan synthase deficient mice (Camenish et al. 2000) and studies in whole embryos (Baldwin et al. 1994) in which hyaluronan was degraded and demonstrated the importance of hyaluronan during a specific time period in normal heart development.

Due to the low doses (<0.0025 mg/kg) of rHuPH20 in patients via trastuzumab SC, no systemic exposure was detected (m5-3-1 BP22023). The doses applied in mice were significantly higher (approximately 95-fold) than the doses in humans.

There is no clinical or scientific evidence of teratogenic effects in over 60 years of experience with animal derived hyaluronidase in humans.

Relevance to human usage: Yes

Discussion:

High systemic exposure to rHuPH20 in pregnant women via inadvertent IV administration of the SC formulation may lead to possible spontaneous abortion, stillbirth, or fetal growth restriction.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Due to the different designs of the pivotal studies (monotherapy versus. combination therapy, different comparators, different disease settings, different data collection, etc.) no pooled analyses were performed.

Clinical trials exposure is presented below by indication and by race, age, and sex, where appropriate. In Studies BO16348 (HERA) and BO18255 (ToGA), for Asian race, "Oriental" was used, and in the other studies, "Asian".

SIII.1 METASTATIC BREAST CANCER

SIII.1.1 Study H0648g

Table 1 Study H0648g Duration of Exposure

HER2−Positive Breast Cancer (H0648g)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin + AC	143	8.6 (0.4)	1–27	8.3
AC Alone	138	7.3 (0.4)	1–27	7.1
Herceptin + Paclitaxel	92	8.0 (0.5)	0–22	7.6
Paclitaxel Alone	96	4.6 (0.3)	0–13	4.0
Total	469	7.3 (0.2)	0–27	7.1

AC = Anthracycline + cyclophosphamide.

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)

Table 2 Study H0648g Duration of Exposure by Age Group

HER2-Positive Breast Cancer (H0648g)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
Herceptin + AC	124	19	8.9 (0.4)	6.8 (0.9)	1-27	2-16	8.7	6.7
AC Alone	117	21	7.5 (0.4)	6.3 (0.9)	1-27	1-16	7.3	6.4
Herceptin + Paclitaxel	81	11	8.1 (0.5)	7.2 (1.5)	0-22	0-14	7.6	6.9
Paclitaxel Alone	84	12	4.6 (0.3)	4.5 (0.8)	0-13	1-10	4.0	4.8
Total	406	63	7.4 (0.2)	6.3 (0.5)	0-27	0-16	7.3	5.5

AC = Anthracycline + cyclophosphamide.

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_age_above65) Database (FINAL)

Table 3 Study H0648g Duration of Exposure by Race

HER2−Positive Breast Cancer (H0648g)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin + AC				
Caucasian	127	8.7 (0.4)	1−27	8.5
Asian	1	6.2 (N/A)	6−6	6.2
Black	10	8.4 (1.5)	2−19	8.2
Other	5	6.7 (1.6)	2−12	7.3
AC Alone				
Caucasian	124	7.1 (0.4)	1−27	6.6
Asian	2	7.0 (1.7)	5−9	7.0
Black	6	8.4 (0.6)	6−10	8.1
Other	6	10.5 (2.8)	3−23	9.4
Herceptin + Paclitaxel				
Caucasian	83	8.0 (0.5)	0−22	7.6
Asian	3	7.8 (1.6)	5−10	8.5
Black	2	4.7 (2.3)	2−7	4.7
Other	4	8.3 (1.3)	5−10	8.9
Paclitaxel Alone				
Caucasian	86	4.6 (0.3)	0−13	4.0
Asian	1	3.9 (N/A)	4−4	3.9
Black	3	8.0 (3.0)	3−13	7.5
Other	6	3.5 (0.7)	2−6	3.3

AC = Anthracycline + cyclophosphamide, N/A = not applicable.

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_asian) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/h0648g/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

SIII.1.2 Study H0649g

Table 4 Study H0649g Duration of Exposure

HER2-Positive Breast Cancer (H0649g)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Total	222	4.8 (0.3)	0–24	3.0

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety) Database (FINAL)

Table 5 Study H0649g Duration of Exposure by Age Group

HER2-Positive Breast Cancer (H0649g)				
Age Group	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
≥18 to ≤65	198	4.8 (0.3)	0–24	3.0
>65	24	4.6 (0.7)	1–14	4.0

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_age_above65) Database (FINAL)

Table 6 Study H0649g Duration of Exposure by Race

HER2−Positive Breast Cancer (H0649g)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Caucasian	188	4.8 (0.3)	0–24	3.0
Asian	9	7.6 (1.9)	1–14	6.4
Black	9	2.0 (0.3)	1–3	2.1
Other	16	4.2 (1.4)	1–17	2.3

Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_asian) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)
Source: Biostatistics([redacted])
pgm(/immuno/her2/h0649g/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

SIII.1.3 Study M77001

Table 7 Study M77001 Duration of Exposure

HER2−Positive MBC(M77001)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Taxotere Alone	94	6.5 (0.4)	1–35	6
Taxotere plus Herceptin	92	12.2 (1.0)	1–43	10
Total	186	9.3 (0.6)	1–43	7

Table 8 Study M77001 Duration of Exposure by Age Group

HER2–Positive MBC (M77001)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
Taxotere Alone	83	11	6.5 (0.5)	6.2 (0.5)	1–35	3–8	6	6
Taxotere + Herceptin	83	9	12.3 (1.0)	11.2 (2.7)	1–43	3–25	10	7
Total	166	20	9.4 (0.6)	8.5 (1.3)	1–43	3–25	7	6

Table 9 Study M77001 Duration of Exposure by Race

HER2–Positive MBC (M77001)				
Race	Persons	Person Time (months) Mean (SE)	Range (months)	Median
Taxotere Alone				
White	85	6.6 (0.5)	1–35	6
Black/African American	4	5.6 (0.5)	5–7	5
American Indian/Alaska Native	1	4.8	5–5	5
Other	4	4.8 (1.2)	1–7	6
Taxotere + Herceptin				
White	91	12.2 (1.0)	1–43	10
Black/African American	1	13.5	13–13	13
American Indian/Alaska Native	-	-	-	-
Other	-	-	-	-

SIII.1.4 Study BO16216 (TANDEM)

Table 10 Study BO16216 (TANDEM) Duration of Exposure

HER2−Positive MBC (BO16216)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AnastrazoleAlone	104	6.7 (0.8)	1–63	3
Anastrazole plus Herceptin	103	13.5 (1.7)	2–72	6
Total	207	10.1 (1.0)	1 – 72	5

Table 11 Study BO16216 (TANDEM) Duration of Exposure by Age Group

HER2−Positive MBC (M77001)								
	Persons		**Person Time (months) Mean (SE)**		**Range (months)**		**Median**	
Age Group	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**
AnastrazoleAlone	83	21	7.0 (1.0)	5.7 (1.1)	2−63	1−21	4	3
Anastrazole plus Herceptin	80	23	14.6 (2.0)	9.7 (2.4)	2−72	3−46	7	5
Total	163	44	10.7 (1.1)	7.8 (1.4)	2−72	1−46	5	4

Table 12 Study BO16216 (TANDEM) Duration of Exposure by Race

HER2−Positive MBC (M77001)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Anastrazole Alone				
White	73	7.5 (1.1)	1–63	4
Black/African American	1	2.9 (N/A)	3–3	3
American Indian/Alaska Native	13	3.3 (0.4)	2–7	3
Asian	9	4.5 (0.9)	2–11	3
Other	8	7.5 (1.7)	2–16	7
Anastrazole plus Herceptin				
White	82	15.1 (2.0)	2–72	7
Black/African American	1	3.5 (N/A)	4–4	4
American Indian/Alaska Native	6	12.3 (5.8)	3–39	6
Asian	6	6.4 (2.3)	2–15	3
Other	8	5.1 (1.2)	2–10	3

SIII.2 EARLY BREAST CANCER

SIII.2.1 Study BCIRG 006 (H2296s)/GO00773

Table 13 Study BCIRG 006 (H2296s)/GO00773 Duration of Exposure

HER2−PositiveEBC: BCIRG 006 (H2296s)/GO00773				
Study arm	**Duration of exposure (months)**			
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AC→T	1041	5.8 (0.0)	1–9	5.9
AC→TH	1077	14.5 (0.2)	1–71	15.5
TCH	1056	12.4 (0.1)	1–79	12.8
Total	3174	11.0 (0.1)	1–79	12.7

AC→T = doxorubicin + cyclophosphamide followed by docetaxel;
AC→TH = doxorubicin + cyclophosphamide followed by docetaxel + Herceptin;
TCH = docetaxel + carboplatin + Herceptin
Source: Biostatistics([redacted])
pgm(/immuno/her2/bcirg006/rmp201309/programs/t_dur_safety) output (t_safety)
Database (FINAL).

Table 14 Study BCIRG 006 (H2296s)/GO00773 Duration of Exposure by Age Group

HER2−PositiveEBC: BCIRG 006 (H2296s)/ GO00773								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
AC→T	988	53	5.8 (0.0)	5.6 (0.1)	1−9	2−7	5.9	5.8
AC→TH	1033	44	14.5 (0.2)	13.6 (0.8)	1−71	3−34	15.5	15.5
TCH	1000	56	12.4 (0.1)	11.8 (0.5)	1−79	1−23	12.8	12.7
Total	3021	153	11.0 (0.1)	10.2 (0.4)	1−79	1−34	12.7	11.5

AC→T=doxorubicin + cyclophosphamide followed by docetaxel;
AC→TH=doxorubicin + cyclophosphamide followed by docetaxel + Herceptin;
TCH=docetaxel + carboplatin + Herceptin.Source: Biostatistics([redacted])
pgm(/immuno/her2/bcirg006/rmp201309/programs/t_dur_safety) output
(t_safety_age_18to65)Database (FINAL)Source: Biostatistics([redacted])
pgm(/immuno/her2/bcirg006/rmp201309/programs/t_dur_safety) output
(t_safety_age_above65)
Database (FINAL)

SIII.2.2 Study B-31/N9831 – Joint Analysis[1]

Table 15 Study B-31/N9831 – Joint Analysis Duration of Exposure

Adjuvant Treatment of HER2−Positive EBC (B-31/N9831 – Joint Analysis)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AC−>T	1655	6.4 (0.0)	0–11	6.2
AC−>T+H	2000	14.6 (0.1)	3–21	14.9
AC−>T−>H	364	20.2 (0.3)	6–33	20.7
Total	4019	11.4 (0.1)	0–33	9.3

AC−>T = doxorubicin plus cyclophosphamide followed by docetaxel;
AC−>T+H = doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin;
AC−>T−>H = doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin.

Source: Biostatistics [redacted] pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety) Database (FINAL)

[1] Data taken from the 8-year median follow-up report.

Table 16 Study B-31/N9831 – Joint Analysis Duration of Exposure by Age Group

Adjuvant Treatment of HER2−Positive EBC (B-31/N9831 – Joint Analysis)								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	**≥18 to ≤ 65**	**>65**	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**	**≥18 to ≤65**	**>65**
AC−>T	1551	104	6.4 (0.0)	5.9 (0.2)	0−11	0−9	6.2	5.8
AC−>T+H	1863	137	14.7 (0.1)	14.2 (0.3)	3−21	4−20	14.9	14.8
AC−>T−>H	346	18	20.3 (0.3)	19.7 (1.0)	6−33	14−24	20.7	19.9
Total	3760	259	11.5 (0.1)	11.1 (0.4)	0−33	0−24	9.3	9.1

AC−>T = doxorubicin plus cyclophosphamide followed by docetaxel;
AC−>T+H = doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin;
AC−>T−>H = doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin.

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65) Database (FINAL)

Source: Biostatistics([redacted]
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_age_above65)
Database (FINAL)

Table 17 Study B-31/N9831-Joint Analysis Duration of Exposure by Race

Adjuvant Treatment of Early HER2−Positive Breast Cancer (B-31/N9831 – Joint Analysis)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
AC−>T				
White	1358	6.4 (0.1)	0–11	6.1
Asian	47	5.9 (0.4)	0–9	5.8
Black	142	6.5 (0.2)	0–9	7.5
Hawaiian	16	7.1 (0.3)	5–9	7.9
Hispanic	72	6.6 (0.3)	0–11	7.9
Indian	4	4.7 (0.9)	2–6	5.3
Other	10	6.6 (0.6)	2–8	7.2
Unknown	6	5.8 (0.9)	2–8	5.7
AC−>T+H				
White	1682	14.7 (0.1)	3–21	14.9
Asian	68	14.0 (0.5)	5–19	14.8
Black	131	14.2 (0.4)	3–20	14.9
Hawaiian	12	16.8 (0.7)	12–20	17.6
Hispanic	75	14.2 (0.4)	6–19	15.0
Indian	6	14.3 (1.2)	9–18	14.8
Other	15	14.7 (1.0)	7–18	15.2
Unknown	11	13.5 (1.4)	4–18	14.5
AC−>T−>H				
White	313	20.4 (0.3)	6–33	20.7
Asian	11	19.1 (1.0)	15–23	18.4
Black	22	19.3 (1.2)	12–26	21.7
Hawaiian	1	23.1 ()	23–23	23.1
Hispanic	12	21.7 (1.8)	14–31	23.7
Indian	1	15.0 (N/A)	15–15	15.0
Other	4	17.4 (0.6)	16–18	17.5
Unknown	0	0	0	0
Total				
White	3353	11.5 (0.1)	0–33	10.2
Asian	126	11.2 (0.5)	0–23	10.7

Table 17 Study B-31/N9831-Joint Analysis Duration of Exposure by Race (cont.)

		Total		
Black	295	10.8 (0.3)	0–26	8.4
Hawaiian	29	11.7 (1.0)	5–23	8.6
Hispanic	159	11.1 (0.4)	0–31	8.8
Indian	11	10.9 (1.6)	2–18	14.6
Other	29	12.3 (1.0)	2–18	14.6
Unknown	17	10.8 (1.3)	2–18	12.6

AC–>T = doxorubicin plus cyclophosphamide followed by docetaxel;
AC–>T+H = doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin;
AC–>T–>H = doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin.

N/A= not applicable

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_white) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_asian) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_hawaiin) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_hispanic) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_indian) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/abcjoint/rmp201309/programs/t_dur_safety) output (t_safety_race_unknown) Database (FINAL)

SIII.2.3 Study BO16348 (HERA)*

Table 18 Study BO16348 (HERA) Duration of Exposure

Adjuvant Treatment of HER2−Positive Breast Cancer (BO16348 [HERA])				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Observation Only	1744	18.9 (0.2)	0–25	24
Herceptin 1 Year	1682	23.0 (0.1)	1–25	25
Herceptin 2 Year	1673	23.2 (0.1)	1–30	25
Remain in Observation	379	24.9 (0.0)	18–25	25
New Herceptin	896	14.8 (0.2)	1–26	13
Total	6374	20.9 (0.1)	0–30	25

*Data taken from the 8-year median follow-up report.

Table 19 Study BO16348 (HERA) Duration of Exposure by Age Group

Adjuvant Treatment of HER2−Positive Breast Cancer (BO16348 (HERA))								
	Persons		Person Time (months) Mean (SE)		Range (months)		Median	
Age Group	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65	≥18 to ≤65	>65
Observation Only	1642	102	18.8 (0.2)	19.7 (0.7)	0–25	0−25	23	25
Herceptin 1 Year	1588	94	23.1 (0.1)	22.0 (0.7)	1–25	1−25	25	25
Herceptin 2 Year	1583	90	23.3 (0.1)	22.1 (0.7)	1–30	1−26	25	25
Remain in Observation	341	38	24.9 (0.0)	24.9 (0.0)	18–25	24−25	25	25
New Herceptin	862	34	14.8 (0.2)	15.1 (1.1)	1–26	1−25	13	13
Total	6016	358	20.9 (0.1)	21.0 (0.4)	0–30	0−26	25	25

Table 20 Study BO16348 (HERA) Duration of Exposure by Race

Adjuvant Treatment of HER2−Positive Breast Cancer (BO16348 (HERA))				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Observation Only				
Other	273	19.4 (0.5)	0–25	25
White	1453	18.8 (0.2)	0–25	23
Oriental	7	20.8 (1.9)	13–25	24
American Indian/Alaska Native	-	-	-	-
Black/African American	6	16.8 (4.0)	1–25	19
Multiple	2	14.0 (11)	3–25	14
Native Hawaiian/Other Pacific Islander	2	21.0 (3.9)	17–25	21
Unknown	1	24.9	25–25	25
Herceptin 1 Year				
Other	262	23.3 (0.3)	1–25	25
White	1404	23.0 (0.1)	1–25	25
Oriental	6	24.9 (0.0)	25–25	25
American Indian/Alaska Native	1	12.6	13–13	13
Black/African American	8	24.9 (0.0)	25–25	25
Multiple	1	24.9	25–25	25
Native Hawaiian/Other Pacific Islander	-	-	-	-

Table 20 Study BO16348 (HERA) Duration of Exposure by Race (cont.)

Unknown	-	-	-	-
Herceptin 2 Year				
Other	264	23.0 (0.3)	1–27	25
White	1397	23.3 (0.1)	1–30	25
Oriental	5	23.4 (1.5)	18–25	25
American Indian/Alaska Native	1	24.9	25–25	25
Black/African American	5	24.9 (0.0)	25–25	25
Multiple	-	-	-	-
Native Hawaiian/Other Pacific Islander	1	24.9	25–25	25
Unknown	-	-	-	-
Remain in Observation				
Other	58	24.9 (0.0)	25–25	25
White	317	24.8 (0.0)	18–25	25
Oriental	-	-	-	-
American Indian/Alaska Native	-	-	-	-
Black/African American	2	24.9 (0.0)	25–25	25
Multiple	1	24.9	25–25	25
Native Hawaiian/Other Pacific Islander	1	24.9	25–25	25
Unknown	-	-	-	-
New Herceptin				
Oriental	5	22.2 (2.4)	13–25	24
Other	147	15.4 (0.5)	1–25	13
White	741	14.7 (0.2)	1–26	13

Table 20 Study BO16348 (HERA) Duration of Exposure by Race (cont.)

American Indian/Alaska Native	-	-	-	-
Black/African American	1	24.4	24–24	24
Multiple	-	-	-	-
Native Hawaiian/Other Pacific Islander	1	12.8	13–13	13
Unknown	1	12.7	13–13	13
Total				
Other	1004	21.1 (0.2)	0–27	25
White	5312	20.9 (0.1)	0–30	25
Oriental	23	22.7 (0.9)	13–25	25
American Indian/Alaska Native	2	18.7 (6.2)	13–25	19
Black/African American	22	22.7 (1.3)	1–25	25
Multiple	4	19.5 (5.5)	3–25	25
Native Hawaiian/Other Pacific Islander	5	20.9 (2.5)	13–25	25
Unknown	2	18.8 (6.1)	13–25	19

SIII.2.4 Study BO22227 (HannaH)

Table 21 Study BO22227 (HannaH) Duration of Exposure*

HER2−Positive Breast Cancer (BO22227 HannaH)				
	Persons	**Person Time (months) Mean**	**Range (months)**	**Median**
Herceptin IV	298	12.2	1.0–15.2	12.8
Herceptin SC (vial)	297	12.2	1.0–15.2	12.8
Total	595	12.2	1.0–15.2	12.8

* Data taken from updated Clinical Study Report with data cut off of 9 July 2012

Table 22 Study BO22227 (HannaH) Duration of Exposure by Age

HER2−Positive Breast Cancer (BO22227 HannaH)								
	Persons		**Person Time (months) Mean (SD)**		**Range (months)**		**Median**	
Age Group	**>18 to ≤65**	**≥65**	**>18 to ≤ 65**	**≥65**	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**
Herceptin IV	275	23	12.2 (2.6)	11.7 (3.2)	1.0–15.2	2.3–14.2	12.8	12.7
Herceptin SC (vial)	264	33	12.2 (2.6)	12.0 (2.6)	1.0–15.2	3.7–14.1	12.8	12.7
Total	539	56	12.2 (2.6)	11.9 (2.8)	1.0–15.2	2.3–14.2	12.8	12.7

Duration of Safety Observation is calculated from date of first study treatment to 28 days after last dose of treatment

Program : $PROD/cd10326o/j22227o/stdmdursa.sas Output $PROD/cd10326o/j22227o/reports/stdmdursa_SAF.lst 27SEP2013 17:

Table 23 Study BO22227 (HannaH) Duration (in Months) of Exposure by Race

	Trastuzumab IV (N=298)	Trastuzumab SC (N=297)	Total (N=595)
American Indian or Alaska Native n	3	3	6
Mean	11.0	10.7	10.9
SD	4.38	4.26	3.87
Median Q1-Q3	13.1	13.1	13.1
Min-Max	6.0-14.0	5.8-13.2	6.0-13.2
Asian n	61	64	125
Mean	12.2	12.3	12.2
SD	2.07	2.26	2.16
Median Q1-Q3	12.7	12.8	12.7
Min-Max	12.6-12.9	12.7-13.1	12.6-13.0
Black Or African American n	6	10	16
Mean	13.4	11.4	12.2
SD	0.24	3.28	2.72
Median Q1-Q3	13.3	12.8	13.2
Min-Max	13.2-13.4	10.3-13.8	12.7-13.6
OTHER n	20	20	40
Mean	12.3	12.5	12.4
SD	2.56	0.90	1.89
Median Q1-Q3	12.7	12.8	12.7
Min-Max	12.7-13.3	12.7-13.0	12.7-13.2
White n	208	200	408
Mean	12.1	12.1	12.1
SD	2.77	2.76	2.76
Median	12.8	12.9	12.8
Q1-Q3	12.7-13.2	12.7-13.2	12.7-13.2
Min-Max	1.0-15.2	1.0-15.2	1.0-15.2

Duration of Safety Observation is calculated from date of first study treatment to 28 days after last dose of treatment

Program : $PROD/cd10326o/j22227o/stdmdursr.sas

Output : $PROD/cd10326o/j22227o/reports/stdmdursr_SAF.lst

27SEP2013 17:10

Page 1 of 1

SIII.2.5 Study MO16432 (NOAH)

Table 24 Study MO16432 (NOAH) Duration of Exposure

Neoadjuvant–Adjuvant HER2–Positive Breast Cancer (MO16432)				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin with or without Chemotherapy (HER2+)	115	12.5 (0.2)	2–25	13
Chemotherapy Alone (HER2+)	113	10.1 (0.5)	2–26	8
Chemotherapy Alone (HER2–)	99	7.5 (0.1)	1–9	8
Total	327	10.2 (0.2)	1–26	8

HER2 = Human Epidermal Growth Factor Receptor 2.

Table 25 Study MO16432 (NOAH) Duration of Exposure by Age

Neoadjuvant–Adjuvant HER2–Positive Breast Cancer (MO16432)								
	Persons		Person Time (months) Mean (SD)		Range (months)		Median	
Age Group	>18 to ≤65	≥65	>18 to ≤65	≥65	>18 to ≤65	≥65	>18 to ≤65	≥65
Herceptin with or without Chemotherapy (HER2+)	106	8	12.4 (0.2)	13.5 (1.1)	2–25	8–19	13	13
Chemotherapy Alone (HER2+)	97	16	9.9 (0.6)	11.4 (1.5)	2–26	8–23	8	8
Chemotherapy Alone (HER2–)	88	11	7.6 (0.1)	6.8 (0.6)	1–9	2–8	8	8
Total	291	35	10.1 (0.2)	10.5 (0.9)	1–26	2–23	8	8

HER2 = Human Epidermal Growth Factor Receptor 2.

Table 26 Study MO16432 (NOAH) Duration of Exposure by Race

Neoadjuvant–Adjuvant HER2–Positive Breast Cancer (MO16432)				
Race	**Persons**	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Herceptin with or without Chemotherapy (HER2+)				
White	115	12.5 (0.2)	2–25	13
Chemotherapy Alone (HER2+)				
White	113	10.1 (0.5)	2–26	8
Chemotherapy Alone (HER2−)				
White	99	7.5 (0.1)	1–9	8
Total				
White	327	10.2 (0.2)	1–26	8

HER2 = Human Epidermal Growth Factor Receptor 2.

SIII.2.6 Study MO22982 (PrefHER)

Table 27 Exposure to Trial Drug following randomization (Cohorts 1 and 2; Safety Population)

Cohort 1	SC SID Period (N=242)	IV Period (N=241)	IV Continuation (N=226)	SID Self-Admin (N=43)	Overall (N=244)
Number of Cycles					
n	242	241	226	43	244
Mean (SD)	3.9 (0.45)	4.0 (0.27)	5.5 (2.63)	2.3 (0.67)	13.3 (3.43)
Median	4.0	4.0	5.0	2.0	13.0
25th, 75th percentile	4.0, 4.0	4.0, 4.0	3.0, 7.0	2.0, 3.0	11.0, 16.0
Min, Max	1, 4	1, 4	1, 10	1, 4	1, 18
Total Number of Cycles (n (%))					
1	5 (2.1)	1 (0.4)	4 (1.8)	3 (7.0)	1 (0.4)
2	1 (0.4)	2 (0.8)	25 (11.1)	27 (62.8)	0 (0.0)
3	1 (0.4)	1 (0.4)	31 (13.7)	11 (25.6)	2 (0.8)
4	235 (97.1)	237 (98.3)	32 (14.2)	2 (4.7)	2 (0.8)
5	0 (0.0)	0 (0.0)	39 (17.3)	0 (0.0)	3 (1.2)
6	0 (0.0)	0 (0.0)	20 (8.8)	0 (0.0)	2 (0.8)
Total Number of Cycles (n (%))					
7	0 (0.0)	0 (0.0)	25 (11.1)	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)	11 (4.9)	0 (0.0)	5 (2.0)
9	0 (0.0)	0 (0.0)	4 (1.8)	0 (0.0)	2 (0.8)
10	0 (0.0)	0 (0.0)	35 (15.5)	0 (0.0)	27 (11.1)
11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (11.5)
12	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (12.7)
13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	36 (14.8)
14	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (9.0)
15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (8.2)
16	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.0)
17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.9)
18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	51 (20.9)

Table 27 Exposure to Trial Drug following randomization (Cohorts 1 and 2; Safety Population) (cont.)

Roche: MO22982/CIL-TS/FINAL/EXP01P.SAS
Produced: 16 March 2016, 11:20
Source: Listing 16.2.5.1.1
Notes: [1] Percentages are based on the number of patients in the respective group.
Source: Abridged by PDRD from mainoutput Adapted from Table 14.1.13.1 *EXP01P*

Table 27 Exposure to Trial Drug following randomization (Cohorts 1 and 2; Safety Population) (cont.)

Cohort 2	SC Vial Period (N=237)	IV Period (N=237)	IV Continuation (N=10)	SC Vial Cont. (N=208)	Overall (N=239)
Number of Cycles					
n	237	237	10	208	239
Mean (SD)	3.9 (0.54)	3.9 (0.31)	3.4 (1.96)	5.5 (2.93)	12.7 (3.64)
Median	4.0	4.0	3.0	5.0	13.0
25th, 75th percentile	4.0, 4.0	4.0, 4.0	2.0, 4.0	3.0, 8.0	10.0, 15.0
Min, Max	1, 5	1, 4	1, 7	1, 10	1, 18
Total Number of Cycles (n (%))					
1	7 (3.0)	2 (0.8)	2 (20.0)	19 (9.1)	3 (1.3)
2	1 (0.4)	0 (0.0)	1 (10.0)	19 (9.1)	0 (0.0)
3	2 (0.8)	6 (2.5)	3 (30.0)	21 (10.1)	1 (0.4)
4	226 (95.4)	229 (96.6)	2 (20.0)	23 (11.1)	0 (0.0)
5	1 (0.4)	0 (0.0)	0 (0.0)	30 (14.4)	4 (1.7)
6	0 (0.0)	0 (0.0)	1 (10.0)	20 (9.6)	1 (0.4)
Total Number of Cycles (n (%))					
7	0 (0.0)	0 (0.0)	1 (10.0)	21 (10.1)	7 (2.9)
8	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.8)	11 (4.6)
9	0 (0.0)	0 (0.0)	0 (0.0)	7 (3.4)	17 (7.1)
10	0 (0.0)	0 (0.0)	0 (0.0)	38 (18.3)	19 (7.9)
11	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (8.8)
12	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (10.5)
13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	32 (13.4)
14	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (8.8)
15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (9.2)
16	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.2)
17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.9)

Table 27 Exposure to Trial Drug following randomization (Cohorts 1 and 2; Safety Population) (cont.)

18	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	38 (15.9)

Roche: MO22982/CIL-TS/FINAL/EXP01P.SAS
Produced: 16 March 2016, 11:20
Source: Listing 16.2.5.1.1
Notes: [1] Percentages are based on the number of patients in the respective group.
Source: Abridged by PDRD from mainoutput,Adapted from Table 14.1.13.1 EXP01P

SIII.2.7 Study MO28048 (SafeHER)

Cohort A (SC vial): Planned/enrolled/treated: 1800/1867/1864: Study treatment: Manual SC injection presentation: Herceptin SC 600 mg/5 mL vial containing a ready to use solution with a nominal content of 600 mg of Herceptin.

Cohort B Single-use Injection Device (SID): Planned/enrolled/treated: 700/710/709: Study treatment: Device presentation: Herceptin SC 600 mg/5 mL pre-filled SID. The cartridge included in the device contains a nominal content 600 mg of Herceptin.

Table 28 Study MO28048 (SafeHER): Number of Cycles Administered: Safety Population

Table 14.1.13.1 Study Drug Exposure – Number of Cycles
(Safety Population)

	Cohort A (N=1864)	Cohort B (N=709)	Cohort B (Selfadmin) (N=550)	Overall (N=2573)
Number of Cycles				
n	31681	12246	7614	43927
Mean (SD)	17.0 (3.38)	17.3 (2.88)	13.8 (4.29)	17.1 (3.25)
Median	18.0	18.0	16.0	18.0
Min, Max	1, 19	1, 18	1, 17	1, 19
Total Number of Cycles (n (%))				
1	18 (1.0)	6 (0.8)	15 (2.7)	24 (0.9)
2	10 (0.5)	3 (0.4)	7 (1.3)	13 (0.5)
3	9 (0.5)	1 (0.1)	6 (1.1)	10 (0.4)
4	23 (1.2)	5 (0.7)	9 (1.6)	28 (1.1)
5	14 (0.8)	4 (0.6)	7 (1.3)	18 (0.7)
6	9 (0.5)	1 (0.1)	9 (1.6)	10 (0.4)
7	13 (0.7)	6 (0.8)	12 (2.2)	19 (0.7)
8	16 (0.9)	2 (0.3)	12 (2.2)	18 (0.7)
9	4 (0.2)	4 (0.6)	10 (1.8)	8 (0.3)
10	5 (0.3)	1 (0.1)	8 (1.5)	6 (0.2)
11	8 (0.4)	2 (0.3)	19 (3.5)	10 (0.4)
12	17 (0.9)	6 (0.8)	14 (2.5)	23 (0.9)
13	4 (0.2)	0	27 (4.9)	4 (0.2)
14	9 (0.5)	4 (0.6)	38 (6.9)	13 (0.5)
15	9 (0.5)	3 (0.4)	59 (10.7)	12 (0.5)
16	11 (0.6)	2 (0.3)	119 (21.6)	13 (0.5)

Table 28 Study MO28048 (SafeHER): Number of Cycles Administered: Safety Population (cont.)

17	19 (1.0)	8 (1.1)	179 (32.5)	27 (1.0)
18	1663 (89.2)	651 (91.8)	0	2314 (89.9)
19	3 (0.2)	0	0	3 (0.1)

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/EXP0XP.SAS
Produced: 17 August 2015, 5:57 Page 1 of 1
Source: Listing 16.2.5.1.1 and 16.2.5.1.2
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Total number of cycles includes the cycles with missing and delayed doses

Table 29 Study MO28048 (SafeHER) :Demographics: Safety Population

Table 14.1.4.1 Demographics
(Safety Population)

	Cohort A (N=1864)	Cohort B (N=709)	Overall (N=2573)
Race (n (%))			
White	1421 (76.2)	556 (78.4)	1977 (76.8)
Black	25 (1.3)	6 (0.8)	31 (1.2)
Asian	295 (15.8)	83 (11.7)	378 (14.7)
Other	65 (3.5)	24 (3.4)	89 (3.5)
N/A (per local regulations)	50 (2.7)	39 (5.5)	89 (3.5)
Unknown	8 (0.4)	1 (0.1)	9 (0.3)
Ethnicity (n (%))			
Hispanic or Latino	366 (19.6)	129 (18.2)	495 (19.2)
Chinese	78 (4.2)	8 (1.1)	86 (3.3)
Indian (Indian subcontinent)	36 (1.9)	22 (3.1)	58 (2.3)
Japanese	1 (0.1)	1 (0.1)	2 (0.1)
Mixed	22 (1.2)	15 (2.1)	37 (1.4)
Other	1307 (70.1)	511 (72.1)	1818 (70.7)
Unknown	54 (2.9)	23 (3.2)	77 (3.0)
Gender (n (%))			
Male	4 (0.2)	0	4 (0.2)
Female	1860 (99.8)	709 (100.0)	2569 (99.8)

Table 29 Study MO28048 (SafeHER) :Demographics: Safety Population (cont.)

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/DEM0XP.SAS
Produced: 17 August 2015, 5:50 Page 1 of 3
Source: Listing 16.2.4.1
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Weight categories are based on overall safety population

Table 29 Demographics: Safety Population (cont.)

Table 14.1.4.1 Demographics
(Safety Population)

	Cohort A (N=1864)	Cohort B (N=709)	Overall (N=2573)
Age (years)			
n	1864	709	2573
Mean (SD)	54.0 (12.01)	53.0 (11.33)	53.7 (11.83)
Median	54.0	52.0	53.0
Min, Max	20, 88	27, 83	20, 88
Unknown	0	0	0
Age category (n (%))			
<75 years	1768 (94.8)	686 (96.8)	2454 (95.4)
>=75 years	96 (5.2)	23 (3.2)	119 (4.6)
Height (cm)			
n	1848	694	2542
Mean (SD)	160.9 (7.48)	161.7 (7.13)	161.1 (7.39)
Median	161.0	162.0	161.0
Min, Max	140, 186	131, 182	131, 186
Unknown	16	15	31
Weight (kg)			
n	1861	705	2566
Mean (SD)	68.64 (14.272)	68.76 (14.168)	68.67 (14.241)
Median	67.00	67.00	67.00
Min, Max	33.6, 144.0	39.0, 150.0	33.6, 150.0
Unknown	3	4	7

Table 29 Study MO28048 (SafeHER) :Demographics: Safety Population (cont.)

Source: Listing 16.2.4.1
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Weight categories are based on overall safety population

Table 29 Demographics: Safety Population (cont.)

Table 14.1.4.1 Demographics
(Safety Population)

	Cohort A (N=1864)	Cohort B (N=709)	Overall (N=2573)
Weight categories			
(<45kg)	31 (1.7)	9 (1.3)	40 (1.6)
P10 (<=53.0 kg)	226 (12.1)	68 (9.6)	294 (11.4)
Q1 (<=59.0 kg)	501 (26.9)	176 (24.8)	677 (26.3)
Q2 (>59.0 kg:<=67.0 kg)	454 (24.4)	187 (26.4)	641 (24.9)
Q3 (>67.0 kg:<=77.0 kg)	442 (23.7)	183 (25.8)	625 (24.3)
Q4 (>77.0 kg)	464 (24.9)	159 (22.4)	623 (24.2)
Unknown	3 (0.2)	4 (0.6)	7 (0.3)
Region			
Western Europe	992 (53.2)	440 (62.1)	1432 (55.7)
Eastern Europe	293 (15.7)	98 (13.8)	391 (15.2)
Africa	62 (3.3)	12 (1.7)	74 (2.9)
Asia Pacific	324 (17.4)	96 (13.5)	420 (16.3)
Americas	193 (10.4)	63 (8.9)	256 (9.9)

Source: Listing 16.2.4.1
Notes: [1] Percentages are based on the number of patients in the respective group
[2] Weight categories are based on overall safety population

SIII.3 HER2 POSITIVE GASTRIC CANCER

SIII.3.1 Study BO18255 (ToGA)

Table 30 Study BO18255 (ToGA) Duration of Exposure

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Fluoropyrimidine/Cisplatin	290	8.3 (0.3)	0–31	8.9
Herceptin/Fluoropyrimidine/Cisplatin	294	11.7 (0.5)	1–48	10.5
Total	584	10.0 (0.3)	0–48	9.9

Table 31 Study BO18255 (ToGA) Duration of Exposure by Age

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))								
	Persons		**Person Time (months) Mean (SD)**		**Range (months)**		**Median**	
Age Group	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**	**>18 to ≤65**	**≥65**
Fluoropyrimidine/Cisplatin	206	84	8.5 (0.3)	8.0 (0.5)	0–31	1−29	8.9	8.8
Herceptin/Fluoropyrimidine/Cisplatin	202	92	11.8 (0.5)	11.6 (0.8)	1–48	1−45	10.6	10.1
Total	408	176	10.1 (0.3)	9.9 (0.5)	0–48	1−45	10.0	9.4

Source: Biostatistics([redacted] pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_age_18to65)Database (FINAL)

Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_age_above65) Database (FINAL)

Table 32 Study BO18255 (ToGA) Duration of Exposure by Race

HER2–Positive Advanced Gastric Cancer (BO18255 (ToGA))				
	Persons	**Person Time (months) Mean (SE)**	**Range (months)**	**Median**
Fluoropyrimidine/ Cisplatin				
Oriental	158	9.3 (0.4)	1–31	10.0
Caucasian	105	7.4 (0.3)	1–17	7.6
Black	2	8.2 (1.7)	7–10	8.2
Other	25	5.9 (0.8)	0–15	6.1
Herceptin/ Fluoropyrimidine/ Cisplatin				
Oriental	151	12.2 (0.6)	1–46	11.2
Caucasian	115	11.3 (0.7)	1–48	10.2
Black	1	8.2 (N/A)	8–8	8.2
Other	27	11.1 (1.5)	1–30	8.8
Total				
Oriental	309	10.7 (0.4)	1–46	10.2
Caucasian	220	9.4 (0.4)	1–48	9.0
Black	3	8.2 (1.0)	7–10	8.2
Other	52	8.6 (0.9)	0–30	6.6

Source: Biostatistics([redacted])
pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_race_black) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_race_other) Database (FINAL)

Source: Biostatistics([redacted])
pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_race_caucasian) Database (FINAL)

Table 33 Study BO18255 (ToGA) Duration of Exposure by Sex

HER2−Positive Advanced Gastric Cancer (BO18255 (ToGA))								
	Persons		Person Time (months) Mean (SD)		Range (months)		Median	
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Fluoropyrimidine/Cisplatin	218	72	8.2 (0.3)	8.7 (0.5)	0–31	1−26	8.8	9.1
Herceptin/Fluoropyrimidine/Cisplatin	226	68	12.1 (0.5)	10.5 (0.9)	1–48	1−39	10.6	9.7
Total	444	140	10.2 (0.3)	9.6 (0.5)	0–48	1−39	10.0	9.2
Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_sex_male) Database (FINAL) Source: Biostatistics([redacted]) pgm(/immuno/her2/toga/rmp201309/programs/t_dur_safety) output (t_safety_sex_female) Database (FINAL)								

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 34 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity	Treatment with trastuzumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients[a]	No	Hypersensitivity is contraindicated in E.U.-SmPC.
Severe dyspnea	Treatment with trastuzumab is contraindicated in patients with severe[b] dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy	No	Severe dyspnea is contraindicated in E.U.-SmPC.
Serious cardiac illness or medical conditions Serious cardiac illness or medical conditions including history of or existing (CHF), history of myocardial infarction (MI), other cardiomyopathy, poorly controlled hypertension, uncontrolled arrhythmia	Heart failure has been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline containing chemotherapy.	No	In Section 4.4 of the E.U. SmPC Special warnings and precautions of use, treatment of patients with these pre-existing conditions with Herceptin is not recommended. Cardiac dysfunction is classified as important identified risk in humans (see SVII. 3 and SVIII).
Low Left Ventricular Ejection Fraction (LVEF) Patients with low left ventricular ejection fraction (<50% or <55%,	Patients are thought to be at increased risk of cardiac toxicity associated with Herceptin administration	No	LVEF <55% included in Section 4.4 Special Warnings and Precautions for Use, E.U. SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
depending on the patient population)			Cardiac dysfunction is classified as important identified risk in humans (see SVII. 3 and SVIII).
Pregnant or lactating women Women of childbearing potential or less than one year after menopause (unless surgically sterile) who are unable or unwilling to use adequate contraceptive measures during study treatment	At the design stage of the initial pivotal trials in the MBC setting, it was not known whether Herceptin can affect reproductive capacity or cause harm to the fetus. Reproduction studies in cynomolgus monkeys observed placental transfer of Herceptin during the early and late fetal development period. In the post marketing setting cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus have been reported in pregnant women receiving Herceptin. Therefore women of childbearing potential should use effective contraception during treatment with Herceptin and for at least 7 months after treatment has been concluded. Pregnant women should not be treated with Herceptin. It is not known whether Herceptin is secreted in human milk. As human immunoglobulin G (IgG) is secreted in human milk,	No	Prevention of pregnancy by using adequate contraceptive measures during Herceptin treatment is considered appropriate. Section 4.6 (Fertility, pregnancy, and lactation) of the current E.U. SmPC adequately covers this information.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	and the potential for absorption and harm to the infant is unknown, women should not breast feed during Herceptin therapy and for 7 months after the last dose.		
Clinically significant infections	Patients may not be able to tolerate myelosuppressive chemotherapy and are at increased risk of infectious complications associated with myelosuppression.	No	No specific warning or exclusion included in the E.U. SmPC since assessment of patients' fitness for chemotherapy is part of routine oncology practice.
Evidence of Central Nervous System (CNS) metastases	Patients were excluded due to concerns that monoclonal antibodies like trastuzumab cross the blood brain barrier poorly and such patients also tend to have aggressive disease and may have insufficient time to benefit from treatment in a trial setting	No	This exclusion criterion was not related to the safety of the patient population
Life expectancy less than 3 months	In clinical trials, patients with short life expectancy are usually excluded.	No	This exclusion criterion was not related to the safety of the patient population. Not applicable for Herceptin use outside of clinical trials
Current significant or uncontrolled gastrointestinal (GI) bleeding	Patients with gastrointestinal (GI) bleeding may not be able to comply with study assessments as GI bleeding is often a symptom of progression of disease. Further to this, these patients may not tolerate myelosuppressive	No	No specific warning or exclusion included in the E.U. SmPC since assessment of patient's fitness for chemotherapy is part of routine oncology practice.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	chemotherapy. Serious adverse events (SAEs) with GI bleeding and gastric perforation have been reported in patients treated with Herceptin.		
Active infection with HIV, HBV or HCV	Patients may not be able to tolerate myelosuppressive chemotherapy and are at increased risk of infectious complications associated with myelosuppression.	No	No specific warning or exclusion included in the E.U. SmPC since assessment of patient's fitness for chemotherapy is part of routine oncology practice. This concern is not considered by the MAH to be a sufficient reason to limit physician, options in treatment of patients with active infections with trastuzumab.

AE=Adverse events, CHF=congestive heart failure, CNS=Central Nervous System, E.U.- SmPC=European Summary of Product Characteristics, GI=gastrointestinal, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IgG= Immunoglobulin G; LVEF= left ventricular ejection fraction, MI=Myocardial infarction, SAE=Serious Adverse Events

[a] Includes rHuPH20 as excipient in SC formulation

[b] E.U. SmPC

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

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

Adverse events with long latency (up to 10 years) considered related by the reporter can be identified:

Patients treated with Herceptin IV in clinical trials have been followed up for 10 years in Study BCIRG 006 (H2296s)/GO00773 and for 11 years in BO16348 (HERA) study.

Long-term safety of Herceptin SC 5-year follow-up is now complete in Studies BO22227 (HannaH) and MO28048 (SafeHER). In the Study BO22227 (HannaH), the overall safety profile of Herceptin SC was consistent with the known safety profile for Herceptin IV. No new safety signals were observed, and similar incidences of cardiac adverse events (AEs) were observed in the lower weight patient quartiles in the Herceptin SC treatment arm compared with the corresponding group in the Herceptin IV treatment arm.

MO28048 (SafeHER) final analysis demonstrated that the safety and tolerability during treatment of Herceptin SC 600 mg Q3W for patients with HER2+ EBC are consistent with the known safety profile of Herceptin IV/SC in patients with HER2+ EBC. The safety results of the final analysis were consistent with those reported in the primary analysis. Likewise, the safety results for vial administration with a handheld syringe (Cohort A) and SID administration (Cohort B) were consistent. No new safety signals have been observed during the final analysis. A limited number of new AEs/SAEs/Cardiac AEs were observed during the follow-up period. The overall safety profile of Herceptin SC continues to be consistent with the known safety profile for Herceptin IV.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 35 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of special population	Exposure
Pregnant women	Not included in clinical development program
Breastfeeding women	Not included in clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in clinical development program

Patients with renal impairment	Not included in clinical development program
Patient with cardiovascular impairment	Not included in clinical development program
Patients with respiratory impairment	Not included in clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Immuno-compromised patients	Not included in clinical development program
Population with relevant different ethnic origin	There were no restrictions to study enrolment regarding race and ethnicity; however, based on higher incidence of breast cancer in the western world, fewer patients from the Asian region were included in breast cancer (BC) trials compared to Caucasian patients. However, this is reversed in the MGC/ metastatic gastroesophageal junction (MGEJC) indication due to the higher incidence of gastric cancer (GC) in Asia
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable
Other:	
Male Patients	*Metastatic GC/GEJ cancer:* BO18255 (ToGA) = 594 patients BO27798 (HELOISE) = 296 patients *Breast Cancer:* Male patients were usually excluded from the Herceptin breast cancer program as male breast cancer is a rare disease accounting for <1% of all male tumours.
Children	Not included in clinical development program
Elderly	1188 patients. Refer to Module SIII for study wise details on elderly patient exposure.

BC=Breast Cancer; GC=Gastric cancer; GEJ=Gastroesophageal junction; MGC=Metastatic gastric cancer; MGEJ=Metastatic Gastroesophageal junction

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

SV.1.1.1 Worldwide Exposure from Marketing Experience (Excluding the United States and Japan)

The estimation of the market exposure to trastuzumab during this reporting period and cumulatively was estimated based on the number of vials sold and average dose per patient over the course of treatment.

The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]). The sales data are provided on a monthly

basis; therefore, the exposure is available from the IBD to the point nearest the DLP (i.e., 30 September 2020).

Daily dose is calculated based on the mean dose and mean patient weight, which is reported by treating physicians in Roche market research. Daily dose calculations incorporate non-used portion of drug for non-reusable 150 and 60 mg vials. Mean treatment duration days is reported by treating physicians in market research and country affiliates' input. The number of patients exposed is calculated by dividing the total number of milligrams by the mean milligram per patient.

The assumptions for calculation of EEA and Rest of World ROW patient exposure along with demographic breakdowns are provided as follows:

- The patient exposure data in the EEA presented assumes 64% of Herceptin IV volume is for use in patients with EBC, 30% is for use in the MBC setting, and 6% is for use in the metastatic gastric setting. For Herceptin SC, 83% is for use in patients with EBC and 17% is for use in the MBC setting.
- The patient exposure data in ROW assumes 72% of Herceptin IV volume is for use in patients with EBC, 26% is for use in the MBC setting, and 2% is for use in the metastatic gastric setting. For Herceptin SC, 89% is for use in patients with EBC and 11% is for use in the MBC setting.
- The duration of treatment is 349 days in the EBC setting and 365 days in the MBC setting (Herceptin in first line MBC is mainly used with Perjeta with a treatment longer than in all the other lines). In the MGC setting, the duration of treatment is 189 days.

All information above is updated for each reporting interval (if needed) based on the most recent market research in EU 5 (France, Germany, Italy, Spain, and United Kingdom) and country's affiliates input.

No estimated pediatric exposures are available based on data from five E.U. markets (France, Germany, Italy, Spain, and United Kingdom). No consistent data is available on the sex of patients.

SV.1.1.2 Cumulative Patient Exposure from Marketing Experience in the United States

The assumptions for calculation of US patient exposure along with demographic breakdowns are provided below.

- The patient exposure data presented are based on a patient model that assumes 74% of U.S. sales is for use in patients with EBC, 22% of sales is for use in the MBC setting, and 4% of sales is for use in the metastatic gastric setting. Patient exposure is calculated from actual vials sold divided by vials per patient estimates from the patient model.

- According to data obtained via patient tracking activities, approximately 26% of patients receiving trastuzumab for EBC, 35% of patients receiving trastuzumab for MBC, and 41% of patients receiving trastuzumab for metastatic gastric cancer in the United States are 65 years or older.
- Patient tracking data also suggests that 23% of patients are receiving trastuzumab weekly and 66% of patients are receiving trastuzumab on a 3-weekly regimen and 10% receive it on another dosing schedule (primarily Q1W to Q3W).
- Epidemiology data indicates 0.8% of patients with breast cancer are male, and 68% of gastric cancer patients are male. Overall, approximately 5% of trastuzumab patients are male.
- The vial size changed in the United States during the time interval. The MAH discontinued the 440-mg vial and started selling Herceptin in 150-mg vials in May 2017. Therefore, the MAH reports separate patient numbers exposed to the two vial sizes during the time interval.
- HER2-positive breast cancer or gastric cancer is extremely rare in patients <18 years old. Therefore, estimated pediatric exposures in the U.S. are not available.

1.3.1.1 Cumulative Patient Exposure to Herceptin from Marketing Experience in Japan

Exposure in the breast cancer indication from September 1998 to 3 April 2011 comes from the re-examination of application data in Japan. The exposure since 4 April 2011 comes from the EPI database, an online library of epidemiological data for approximately 180 diseases for the United States, 5 major European countries and Japan; and 80 indications for Brazil, Russia, India, and China. Data is also available for Mexico and Turkey. The age and sex component ratio of the patients exposed cumulatively since the IBD cannot be provided because the re-examination application data does not have the information. Exposure split by indication is also not available. Because only breast cancer was recorded as the indication, it is not possible to split the Japanese exposure into EBC and MBC patients.

The estimated number of patients exposed to Herceptin in gastric cancer was calculated by using the EPI database and information about the age and sex component ratio.

The methodology used for calculating cumulative patient exposure was as follows:

1. Calculate the ratio of the total dose for each indication from sales assumption data.
2. Calculate the total dose for each indication using the ratio of each indication (from Step 1) and total sales data during the period.
3. Calculate the dose per patient per indication from 2014 sales assumption data.
4. Calculate patient exposure for each indication by dividing the results in Step 2 by the results in Step 3.

SV.1.2 Exposure

Since the IBD, an estimated cumulative total of 3.46 million patients have received Herceptin (Table 36) from marketing experience.

An estimated 3,264,791patients have received Herceptin for breast cancer 191,035 patients have received Herceptin for MGC (Table 36).

For all regions, the exposure in breast cancer can be further broken down into exposure in EBC and MBC (1,903,561patients and 1,169,211 patients, respectively) (Table 36).

Table 36 Cumulative Patient Exposure from Marketing Experience by Region

	Region			
Indication	Worldwide excluding the United States and Japan	United States	Japan	Total
EBC	1,319,867	529,949	53,746	1,903,561
MBC	797,826	331,717	39,668	1,169,211
EBC or MBC [a]	21,064	0	170,955	192,019
Total BC	2,138,757	861,666	264,369	3,264,791
MGC	87,793	54,007	49,235	191,035
Total	**2,226,549**	**915,673**	**313,604**	**3,455,826**

BC = breast cancer; EBC = early breast cancer; MBC = metastatic breast cancer; MGC = metastatic gastric cancer.

[a] Exposure via the Patient Access Program is included.

Note: Rounding errors may be introduced in the total figure

An estimated 300,233 patients have received the SC formulation of Herceptin (600 mg solution for injection in vial) (Table 37). Of these patients, 247,349 patients have been treated for EBC; 52,816 patients have been treated for MBC and 68 patients have been treated for MGC.

An estimated 3,058,994 patients have received the IV formulation of Herceptin (Table 37).

Dose is unknown for most of these patients and estimates have only been available for the U.S. market based on the regimen for the IV formulation only (Table 38). In the United States, the Q3W regimen has been used more frequently than the Q1W regimen.

Table 37 Cumulative Patient Exposure from Marketing Experience by Formulation

Indication	Herceptin Formulation		
	Intravenous	Subcutaneous	Unknown
EBC	1,613,777	247,349	42,434
MBC	1,084,587	52,816	31,808
EBC or MBC [a]	192,019	0	0
Total BC	2,890,383	300,165	74,242
MGC	168,611	68	22,357
Total	**3,058,994**	**300,233**	**96,599**

BC = breast cancer; EBC = early breast cancer; MBC = metastatic breast cancer;
MGC = metastatic gastric cancer.
Note: Rounding errors may be introduced in the total figure.
[a] Exposure via the Patient Access Program is included.

Table 38 Cumulative Exposure from Marketing Experience by Dose and Dosing Regimen

Indication	Dose (mg)					Dosing Regimen of Herceptin IV Formulation (USA)		
	60 mg	150 mg	440mg	600 mg	Unk	Q1W	Q3W	Unknown
EBC	790	293,328	349,954	223,968	1,035,520	123,708	341,460	64,779
MBC	247	111,736	114,672	38,734	903,822	82,929	232,204	16,586
EBC or MBC [a]	0	0	0	0	192,019			
Total BC	1,037	405,064	464,627	262,702	2,131,361	206,637	573,663	81,365
MGC	57	34,227	24,442	68	132,241	7,843	33,226	12,939
Total	**1,094**	**439,291**	**489,069**	**262,770**	**2,263,602**	**214,480**	**606,889**	**94,303**

BC = breast cancer; EBC = early breast cancer; MBC = metastatic breast cancer;
MGC = metastatic gastric cancer; Q1W = once a week; Q3W = every 3 weeks.
Note: Rounding errors may be introduced in the total figure.
[a] Exposure via the Patient Access Program is included.

Table 39 Cumulative Patient Exposure from Marketing Experience by Patient Sex and Age

Indication	Sex			Age (years)			
	Male	**Female**	**Unknown**	**2 to ≤16**	**>16 to 65**	**>65**	**Unknown**
EBC	4,239	525,708	1,373,613	0	385,339	134,598	1,373,612
MBC	2,654	329,062	837,494	0	222,042	119,207	837,494
EBC or MBC [a]	0	0	192,019	0	0	0	192,019
Total BC	6,893	854,770	2,403,126	0	607,380	253,804	2,403,125
MGC	36,724	17,283	137,028	0	32,149	22,340	137,028
Total	**43,617**	**872,054**	**2,540,154**	**0**	**639,529**	**276,144**	**2,540,153**

BC = breast cancer; EBC = early breast cancer; MBC = metastatic breast cancer; MGC = metastatic gastric cancer.
Note: Rounding errors may be introduced in the total figure.
[a] Exposure via the Patient Access Program is included.

PART II: MODULE SVI - ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of hemoglobin levels. The lack of evidence of such side-effects make it highly unlikely that trastuzumab is misused for illegal purposes. To date, no reports of misuse of Herceptin for illegal purposes have been received.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not Applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not Applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not Applicable.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Information on important identified risks

1.4 CARDIAC DYSFUNCTION

Medical Dictionary for Regulatory Activities (MedDRA) Terms:

Cardiac Failure Standardised MedDRA Query (SMQ)—Wide

Potential mechanisms:

- There may be a feedback loop involving neuregulin and ErbB2 (as a co-receptor) as part of a cell (myocyte) survival pathway.
- Trastuzumab may block or alter cell survival signalling.
- Trastuzumab may down-regulate ErbB2 and thereby prevent cell survival signalling.
- Cardiac physiological stress or damage can be exacerbated by trastuzumab

Evidence source(s) and strength of evidence:

- MBC: Studies M77001 and BO16216.
- EBC: Joint Analysis (NSABP B-31 and NCCTG N9831), Studies BCIRG 006 (H2296s)/GO00773, BO16348, MO16432, BO22227, MO22982, MO28048, and BO20652
- GC: BO18255. QTc-study H4613g (HerQLes).
- Global Safety Database

Characterization of the risk:

Patients treated with Herceptin are at increased risk of developing CHF (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin.

Background incidence/ prevalence:

- Metastatic Breast Cancer, First-line HER2-positive

The incidence of symptomatic CHF (Grades 3 or 4) for:

Non-trastuzumab containing regimens:

- Without anthracyclines: 0.3% to 1% (Slamon et al. 2001, Johnston et al. 2009)
- With anthracyclines: 3% to 4.7% (Slamon et al. 2001, O'Brien et al. 2004)

Trastuzumab containing regimens:

- Without anthracyclines: 2% to 4% (Slamon et al. 2001, Seidman et al. 2002).
- With concurrent anthracyclines: 16% (Slamon et al. 2001).

- Metastatic Breast Cancer, Second-line HER2-positive

Based on three lapatinib studies, the incidence of symptomatic CHF (Grades 3 or 4) was <1% for non-trastuzumab containing regimens (Blackwell et al. 2012; Capri et al. 2010; Burstein et al. 2003). In a pooled analysis of 3,689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was:

Anthracyclines: 0.5%

Herceptin: 0.1%

Neither anthracyclines or trastuzumab: 0.1%

- Early Breast Cancer, HER2-positive

Based on a review of three adjuvant Herceptin trials (NASBP B-31, NCCTG N9831, HERA) with anthracycline and non-anthracycline containing regimens, the incidence of symptomatic CHF (defined as NYHA Class III or IV) was:

0.8% to 3.8% for Herceptin containing regimens (Herceptin was given sequentially or concurrently).

0% to 0.9% for non-Herceptin containing regimens

Prevalence: Not available [(Tan-Chiu et al. 2005; Perez et al. 2008 ; Piccart-Gebhart et al. 2005)

- Advanced Gastric Cancer

Incidence

A recent randomised trial reported a 1.1% incidence of decreased LVEF (unspecified criteria) among HER2+ patients with advanced GC not treated with Herceptin (Van Cutsem et al. 2009).

Prevalence:

Not available

Frequency with 95% CI:

Frequency data for studies M77001, BO16216 and BO18255 is presented in Section 1.1 of. Annex 7 Table 1, Table 2, Table 3 and Table 4 respectively. For BCIRG 006 (H2296s)/GO00773: Please refer to Table 7 to Table 10 in Annex 7.

BO16348 (HERA):

The primary endpoint was to investigate the potential predictive value of changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) for progression to symptomatic CHF in patients who experience a significant LVEF drop (as defined in the HERA protocol), in the HERA trial: in total, 18/1682 (1.07%) patients in the Herceptin 1-year arm and 17/1673 (1.02%) patients in the Herceptin 2-year arm had a primary cardiac endpoint.

Secondary cardiac endpoint was:

- To determine, if changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) correlate with outcome in patients experiencing congestive heart failure in the HERA trial.
- To investigate the potential predictive value of changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) for development of symptomatic CHF in all patients in the HERA trial (regardless of LVEF drop).
- To determine if changes in blood levels of NT-pro BNP (and/or other neuro-hormones or cardiac markers) correlate with LVEF changes in the HERA trial.
- To investigate the potential diagnostic value of NT-pro BNP (and/or other neuro-hormones or cardiac markers) in patients experiencing dyspnoea (of uncertain cause) in the HERA trial.

There was a higher incidence of secondary cardiac endpoints in the Herceptin 2-year arm (137/1673 [8.19%] patients) compared with the Herceptin 1-year arm (85/1682 [5.05%] patients). A total of 15/1744 (0.86%) patients in the Observation only arm had secondary cardiac endpoints.

MO28048 (SafeHER)

In the safety analysis for the whole study, cardiac AEs were reported by 529/2569 (20.6%) patients overall. The most frequently reported cardiac AE was decreased ejection fraction (139/2569 [5.4%] patients overall). Two other individual cardiac AEs reported in more than 2% of the overall population were palpitations in 2.8% (2.7% in Cohort A and 3.1% in Cohort B) and mitral valve incompetence in 2.3% [2.3% in Cohort A and 2.1% in Cohort B]).

During the follow-up period a total of 162 patients (6.3%) reported 203 cardiac events (7.0% of patients in Cohort A and 4.4% of patients in Cohort B). Overall, 165 of 203 cardiac events were coded under the Cardiac Disorders SOC and remaining 38 of 203 cardiac events were coded under the Investigations SOC. The most frequently reported cardiac event observed was ejection fraction decreased during the follow-up and whole study period (0.9% and 5.4% of patient, respectively).

Decreased ejection fraction led to treatment discontinuation in 48/2573 (1.9%) patients overall. Cardiac failure congestive was reported infrequently (0.4% of patients overall) and usually resulted in discontinuation of study treatment. In all cases except one which remained ongoing at the time of patient death, patients made a full recovery from CHF.

Overall, 60/2569 patients (2.3%) reported a serious cardiac AE during the whole study (2.9% in Cohort A and 0.8% in Cohort B).

Overall, 27 patients (1.1%) reported 28 serious cardiac AE during the follow-up period (1.3% in Cohort A and 0.4% in Cohort B). One patient reported a related SAE of CHF and one patient experienced a Grade 5 administration-related reactions (ARR) event of cardio-respiratory arrest.

Overall, 128/2573 (5.0%) patients had an AE that led to permanent study drug discontinuation. The AE most frequently leading to discontinuation was ejection fraction decreased (48/2573 [1.9%] patients overall), which accounted for all AEs reported in the Investigations SOC.

Joint Analysis of B-31 and N9831:

Most cardiac events occurred within 15 months from starting paclitaxel ± Herceptin. At 3 years, the cardiac event rate was estimated at 3.16% in the doxorubicin plus cyclophosphamide followed by docetaxel plus Herceptin (AC→T + H) group, 0.90% in the doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) group, and 1.72% in the doxorubicin plus cyclophosphamide followed by docetaxel followed by Herceptin (AC→T→H) group. Between 5 and 7 years of follow-up, an additional patient in each treatment group experienced a cardiac event; the cardiac event rate at 9 years follow-up was estimated at 3.22% in the AC→T + H group, 1.04% in the AC→T group, and 2.02% in the AC→T→H group.

In the joint safety population, 35.8% of patients in the AC→T + H group and 32.7% of patients in the AC→T→H group experienced an absolute drop in LVEF of 10% points to below 55% compared with 25.4% of patients in the AC→T group.

Also in the joint safety population, 25.3% of patients in the AC→T + H group and 22.0% of patients in the AC→T→H group experienced an absolute drop in LVEF of 5% points to below the institution's lower limit of normal (LLN) compared with 17.4% of patients in the AC→T group.

The rates of symptomatic CHF were 3.1% in the AC→T + H group, 1.6% in the AC→T→H group, and 1.0% in the AC→T group, which is comparable to the CHF rates observed in the other large adjuvant studies where Herceptin followed anthracycline chemotherapy. With further follow-up, the per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remains essentially unchanged. This updated

analysis also shows evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC→T + H group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

Neoadjuvant-adjuvant treatment in EBC

MO16432 (NOAH):

As expected, more patients in the HER2 positive + Herceptin + chemotherapy (TC) arm had a decline in LVEF during the chemotherapy period compared with patients in the other two arms who did not receive trastuzumab. Overall, only 13.3% of patients in the HER2 positive + TC arm showed no change or an increase in LVEF during chemotherapy compared with 27.5% of patients in the HER2 positive + C arm and 20.8% in the HER2 negative + C arm. However, most of the declines in LVEF were <10% points compared with baseline.

BO22227 (HannaH):

Please refer to Table 5 and Table 6 (Section 1.1 of Annex 7) or Table 40 below, which show the incidence of cardiac dysfunction-related AEs by severity for the Herceptin IV and Herceptin SC arms, respectively. In the new 5-year follow-up data, the overall incidence of cardiac dysfunction-related AEs was 19% in the IV arm and 16% in the SC arm.

The overall percentage of patients with at least one cardiac AE was similar in both study arms: 14.1% (42/298) of patients in the Herceptin IV arm and 14.8% (44/297) of patients in the Herceptin SC arm experienced 62 and 57 cardiac AEs (System Organ Class [SOC] Cardiac disorders and selected cardiac High Level Terms (HLTs) in the SOC Investigations), respectively Table 41.

Most AEs were from the SOC Cardiac disorders (a total of 41 patients in the Herceptin IV arm and 43 patients in the Herceptin SC arm experienced events in this SOC), with the remainder being abnormal cardiac function assessments reported as AEs under the SOC Investigation (experienced in 5 patients in the Herceptin IV arm and 2 patients in the Herceptin SC arm). In addition, as described in the Update Clinical Study Report (CSR) (Report No. 1057070, September 2013), an event of pleural effusion was reported in the Herceptin SC arm that coded primarily to the Respiratory, thoracic and mediastinal disorders SOC in which the contribution of underlying cardiac dysfunction could not be ruled out. This event is not included in the analyses of cardiac events.

The majority of cardiac AEs were Grade 1 or Grade 2 in intensity (59/62 events and 50/57 events in the Herceptin IV and Herceptin SC arms, respectively). A total of eight Grade 3 AEs were reported, two events in the Herceptin IV arm and six events in the Herceptin SC arm. No Grade 4 cardiac AEs were reported. For each of the treatment

arms, one Grade 5 event of MI was reported. There was no marked imbalance in incidence between the treatment arms in any individual type of cardiac event. The most frequently reported AEs were rhythm disorders and left ventricular dysfunction Table 41.

Clinically significant cardiac AEs (i.e., those that were serious, severe, led to withdrawal or death, or were symptomatic of left ventricular systolic dysfunction) that occurred during treatment were discussed in detail in the Update CSR (Report No. 1057070, September 2013). One cardiac AE was reported during the survival follow-up phase.

Table 40 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM

stae17cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	56 (19)	43 (14)	16 (5)	-	-	-
Total Number of AEs	63	47	16	-	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total Pts With at Least one AE	43 (14)	37 (12)	7 (2)	-	-	-
OEDEMA PERIPHERAL	30 (10)	27 (9)	3 (1)	-	-	-
OEDEMA	15 (5)	12 (4)	3 (1)	-	-	-
PERIPHERAL SWELLING	3 (1)	2 (<1)	1 (<1)	-	-	-
Total Number of AEs	48	41	7	-	-	-
CARDIAC DISORDERS						
Total Pts With at Least one AE	13 (4)	5 (2)	8 (3)	-	-	-
LEFT VENTRICULAR DYSFUNCTION	12 (4)	4 (1)	8 (3)	-	-	-
CARDIAC FAILURE	1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	13	5	8	-	-	-
INVESTIGATIONS						
Total Pts With at Least one AE	1 (<1)	-	1 (<1)	-	-	-
EJECTION FRACTION DECREASED	1 (<1)	-	1 (<1)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Table 40 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM (cont.)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	1 (<1)	1 (<1)	-	-	-	-
NOCTURNAL DYSPNOEA		1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
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Table 40 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM (cont.)

stae17cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	47 (16)	38 (13)	7 (2)	3 (1)	-	-
Total Number of AEs	52	41	7	4	-	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total Pts With at Least one AE	33 (11)	31 (10)	2 (<1)	-	-	-
OEDEMA PERIPHERAL	23 (8)	22 (7)	1 (<1)	-	-	-
OEDEMA	10 (3)	9 (3)	1 (<1)	-	-	-
PERIPHERAL SWELLING	3 (1)	3 (1)	-	-	-	-
Total Number of AEs	36	34	2	-	-	-
CARDIAC DISORDERS						
Total Pts With at Least one AE	15 (5)	7 (2)	5 (2)	3 (1)	-	-
LEFT VENTRICULAR DYSFUNCTION	10 (3)	4 (1)	5 (2)	1 (<1)	-	-
CARDIAC FAILURE CONGESTIVE	2 (<1)	-	-	2 (<1)	-	-
CARDIAC FAILURE	1 (<1)	-	-	1 (<1)	-	-
DIASTOLIC DYSFUNCTION	1 (<1)	1 (<1)	-	-	-	-
LEFT VENTRICULAR DILATATION	1 (<1)	1 (<1)	-	-	-	-
RIGHT VENTRICULAR FAILURE	1 (<1)	1 (<1)	-	-	-	-
Total Number of AEs	16	7	5	4	-	-

Table 40 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM (cont.)

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
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Table 41 Summary of Cardiac Events (SP)

stae11card_se Summary of Cardiac Adverse Events Including Selected HLTs (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	TRASTUZUMAB IV N = 298 No. (%)	TRASTUZUMAB SC N = 297 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	42 (14.1)	44 (14.8)
Total Number of AEs	62	57
CARDIAC DISORDERS		
Total Pts With at Least one AE	41 (13.8)	43 (14.5)
LEFT VENTRICULAR DYSFUNCTION	12 (4.0)	10 (3.4)
TACHYCARDIA	9 (3.0)	6 (2.0)
PALPITATIONS	4 (1.3)	6 (2.0)
SINUS TACHYCARDIA	3 (1.0)	3 (1.0)
BUNDLE BRANCH BLOCK RIGHT	1 (0.3)	2 (0.7)
DEFECT CONDUCTION INTRAVENTRICULAR	2 (0.7)	1 (0.3)
HEART VALVE INCOMPETENCE	2 (0.7)	1 (0.3)
ANGINA PECTORIS	1 (0.3)	1 (0.3)
AORTIC VALVE INCOMPETENCE	1 (0.3)	1 (0.3)
ARRHYTHMIA	-	2 (0.7)
ATRIAL FIBRILLATION	-	2 (0.7)
CARDIAC ANEURYSM	-	2 (0.7)
CARDIAC FAILURE	1 (0.3)	1 (0.3)
CARDIAC FAILURE CONGESTIVE	-	2 (0.7)
CARDIOMYOPATHY	1 (0.3)	1 (0.3)
CARDIOVASCULAR DISORDER	2 (0.7)	-
CORONARY ARTERY DISEASE	2 (0.7)	-
EXTRASYSTOLES	-	2 (0.7)
MYOCARDIAL INFARCTION	1 (0.3)	1 (0.3)
MYOCARDIAL ISCHAEMIA	1 (0.3)	1 (0.3)
PERICARDIAL EFFUSION	-	2 (0.7)
VENTRICULAR HYPOKINESIA	2 (0.7)	-
ARTERIOSCLEROSIS CORONARY ARTERY	-	1 (0.3)
ATRIAL FLUTTER	1 (0.3)	-
ATRIOVENTRICULAR BLOCK	1 (0.3)	-
ATRIOVENTRICULAR BLOCK FIRST DEGREE	-	1 (0.3)

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Selected from MedDRA SOC 'Cardiac disorders', HLTs
('CARDIAC FUNCTION DIAGNOSTIC PROCEDURES','CARDIAC IMAGING PROCEDURES','ECG INVESTIGATIONS','HEART RATE AND PULSE INVESTIGATIONS')
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Table 41 Summary of Cardiac Events (SP) (cont.)

stae11card_se Summary of Cardiac Adverse Events Including Selected HLTs (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	TRASTUZUMAB IV N = 298 No. (%)	TRASTUZUMAB SC N = 297 No. (%)
(... body system continuing)		
BRADYCARDIA	1 (0.3)	-
CARDIAC FLUTTER	-	1 (0.3)
CARDIOTOXICITY	-	1 (0.3)
DIASTOLIC DYSFUNCTION	-	1 (0.3)
DILATATION ATRIAL	1 (0.3)	-
LEFT ATRIAL ENLARGEMENT	1 (0.3)	-
LEFT VENTRICULAR DILATATION	-	1 (0.3)
LEFT VENTRICULAR HYPERTROPHY	-	1 (0.3)
MITRAL VALVE INCOMPETENCE	1 (0.3)	-
MITRAL VALVE PROLAPSE	1 (0.3)	-
MYOCARDIAL FIBROSIS	1 (0.3)	-
RIGHT VENTRICULAR FAILURE	-	1 (0.3)
SUPRAVENTRICULAR EXTRASYSTOLES	1 (0.3)	-
TRICUSPID VALVE INCOMPETENCE	1 (0.3)	-
VENTRICULAR ARRHYTHMIA	1 (0.3)	-
VENTRICULAR EXTRASYSTOLES	1 (0.3)	-
Total Number of AEs	57	55
INVESTIGATIONS		
Total Pts With at Least one AE	5 (1.7)	2 (0.7)
ELECTROCARDIOGRAM REPOLARISATION ABNORMALITY	2 (0.7)	-
EJECTION FRACTION	-	1 (0.3)
EJECTION FRACTION DECREASED	1 (0.3)	-
ELECTROCARDIOGRAM ABNORMAL	-	1 (0.3)
ELECTROCARDIOGRAM QRS COMPLEX ABNORMAL	1 (0.3)	-
HEART RATE INCREASED	1 (0.3)	-
Total Number of AEs	5	2

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Selected from MedDRA SOC 'Cardiac disorders', HLTs
('CARDIAC FUNCTION DIAGNOSTIC PROCEDURES','CARDIAC IMAGING PROCEDURES','ECG INVESTIGATIONS','HEART RATE AND PULSE INVESTIGATIONS')
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Observational study in EBC

BO20652 (OHERA)

Symptomatic CHF:

At the time of the final analysis, within the safety population, 106 of 3733 patients had developed symptomatic CHF (NYHA Class II-IV) prior to any recurrence of disease. This translates into a cumulative incidence of 2.8% (95% CI: 2.3%-3.4%) and an incidence rate of 690 per 100,000 person-years (95% CI 568-831).

Cardiac Death:

In the safety population, 6 of 3733 (0.2%) patients experienced a cardiac-related death without prior disease recurrence. The incidence of cardiac death, based on these 6 patients, was 0.2% (95% CI: 0.1% – 0.4%) and the incidence rate was 37 cardiac deaths per 100,000 person – years (95% CI: 14 – 80). Five patients (0.1%) experienced cardiac death after disease recurrence.

Seriousness/Outcomes

Clinical studies

- Metastatic Breast Cancer

In Study M77001 (CSR 1011941), There were a total of 12 possible cardiac related adverse events (mainly tachycardia and palpitations) reported in the Herceptin + docetaxel arm as compared with 3 in the docetaxel alone arm. Most of these events were non-serious (common toxicity criteria [CTC] grade 1 and 2). The majority of the AEs resolved. However, there were two fatal cases (2%) of CHF in the Herceptin + docetaxel arm.

In another study, BO16216, where trastuzumab along with anastrozole reported a total of four AEs (2 resolved) in anastrozole alone arm, 16 AEs (11 resolved) in anastrozole plus trastuzumab arm, and 10 AEs (3 resolved) in anastrozole alone after start of trastuzumab arm. No cardiac deaths were reported.

- Early Breast Cancer Adjuvant Treatment

In Study BCIRG-006, the most frequently occurring symptomatic cardiac event was Grade 3/4 cardiac left ventricular function (CLVF).

The incidence was highest in the AC→TH arm (1.9%) compared with AC→T (0.3%) and docetaxel plus carboplatin plus trastuzumab (TCH) arms (0.4%) arms.

In a 10-year median follow-up study, BO16348 (HERA), the most prominent cardiac SAE was cardiac failure congestive in Herceptin-1-year (reported in 19/1682 patients [1.1%]) and Herceptin-2- year arms (reported in 24/1673 patients [1.4%]). The 10-year median follow-up data reports death due to cardiac failure congestive occurred in seven patients at different follow-up intervals. In the trastuzumab containing arms, cardiac failure congestive and peripheral swelling were the serious cardiac AEs leading to dose interruption and cardiac failure congestive was the most common cardiac serious AE leading to drug discontinuation.

Similarly, Study MO28048 (SafeHER) reported that the most frequently related cardiac SAE was cardiac failure congestive in 11 patients. In 9 patients, the SAE of cardiac failure congestive led to drug discontinuation.

In Joint Analysis of NSABP B-31 and N9831, as of 10 March 2015, cardiac deaths were experienced by 2 patients (0.1%) in the AC→T + H group, 1 patient (0.3%) in the AC→T→H group, and 5 patients (0.3%) in the AC→T group. Sixty-four patients in AC→T + H group, 7 patients in the AC→T→H group, and 21 patients in the AC→T group reported cardiac left ventricular events. These AEs were not assessed as leading to study treatment withdrawal and/or discontinuation on the AE case report form (CRF) for either B-31 or N9831. The AEs leading to dose adjustment and outcomes of AEs were also not collected.

- Neoadjuvant-adjuvant Treatment in EBC

In Study MO16432 (NOAH), trastuzumab was administered concurrently with an anthracycline in neoadjuvant-adjuvant settings; the incidence of symptomatic cardiac dysfunction was low in the HER2+TC arm. Only 4 patients in the HER2+TC group had a decline in LVEF of ≥10% points to an LVEF of <50% and in only one of these patients (none in the other two groups) did the LVEF decline to <45%.

Study BO22227 compared Herceptin SC versus Herceptin IV in women with HER-2 positive early breast cancer. In the Herceptin IV arm, none of the events of cardiac dysfunction is reported serious and 56 of the 63 AEs resolved without sequelae. In Herceptin SC arm, two AEs (2 events of cardiac failure congestive) were assessed as serious. The most frequently reported Preferred Terms (PTs) were the same with the SC as for the IV formulation but with fewer AEs in the SC arm. There were no reports of fatal outcome from a cardiac dysfunction-related AE for both formulations.

In PrefHER Study (MO22982), the most frequently reported AEs in Herceptin IV (4 cycles) arm were left ventricular dysfunction (in 5/478 patients [1.05%]) and bradycardia (in 3/478 patients [0.63%]), palpitations, and ejection fraction abnormal (in 2/478 patients each [0.42%]). In Herceptin SC arm, the most frequently reported AEs were palpitations (in 3/479 patients [0.63%]), ejection fraction decreased (in 3/479 patients [0.63%]), and left ventricular dysfunction and cardiac failure congestive (each reported in 2/479 patients each [0.42%]). In Herceptin IV continuation period (Cohort 1,

226 patients) Cardiac AEs were reported for 7/226 patients (3.1%) and none of them were left ventricular systolic dysfunction or CHF events. None of the cardiac AEs were serious or Grade ≥3 events, or led to withdrawal from treatment. No Cardiac AEs were reported for SID self-administration for SC SID period. In Cohort 2, SC vial continuation, Cardiac AEs were reported for 8/208 patients (3.8%). Four patients experienced left ventricular dysfunction and 3 patients cardiac failure congestive. In Cohort 2, IV continuation, Cardiac AEs were reported for 1/10 (10.0%) patients (Grade 1 event) and no left ventricular systolic dysfunction events were reported during the IV continuation period.

Please refer to Section 1.2 of Annex 7 for detailed study wise data on seriousness and outcomes.

Global Safety Database

The information that was retrieved from the MAH's Global Safety Database, utilizing the MedDRA SMQ Cardiac failure (wide), is cumulative through 24 September 2020.

A total of 12,105 AEs (reported in 11,017 cases) were retrieved. Of these, 7,786 (64.3%) AEs were reported as serious by the reporter and/or the MAH. The most frequent SAEs were distributed as follows: ejection fraction decreased, n = 3,199 (41% of all SAEs in this identified risk group); cardiac failure, n 1,738 (22.3%); cardiac failure congestive, n = 822 (10.5%); left ventricular dysfunction, n = 531 (6.8%); and cardiac dysfunction, n = 389 (4.9%). The Summary Table of Adverse Events by SOC is presented in Table 12 (Annex 7).

A total of 199 AEs (1.6% of all AEs in this identified risk group) resulted in a fatal outcome. Of the fatal outcome AEs, the most frequently reported were as follows: cardiac failure (n = 78; 39.1 % of all fatal outcome AEs); cardiac failure congestive (n = 39; 19.5%); ejection fraction decreased (n = 15; 7.5%), pulmonary oedema (n = 13; 6.5%) cardiopulmonary failure and cardiac failure acute (n = 12; 6% each). A favorable outcome was reported in 4,141 (34.2%) of the 12,105 total AEs, having resolved/resolving/resolved with sequelae. For 5816 (48%) AEs, the outcome was either not reported or reported as unknown. The outcome was reported as not recovered/not resolved in 1852 (15.2%) AEs. The outcome for 54 (0.4%) AEs was reported as not applicable and 43 (0.3%) co-manifestations were reported as AEs. (Table 13 of Annex 7).

Herceptin treatment was maintained in response to the AE in 1,272 (10.4%) of the total reported drug events in the cardiac dysfunction risk group. It was withdrawn in 3,876 (31.7%) of the reported drug events, and the action taken in response to the event was unknown in 4,966 (40.6%) drug events. The dose was interrupted for 1,167 (9.5%) drug events and the dose was reduced for 30 (0.24%) AEs. The dose was increased in 1 (0.008%) drug events and modified in 3 (0.02%) drug events (Table 14 of Annex 7).

Severity and nature of risk

- Metastatic Breast Cancer

In Study M77001, eight Grade 3 AEs (8.5%) in the docetaxel alone arm and four (4.3%) in the trastuzumab + docetaxel arm were reported. No Grade 4 or 5 AEs were reported in either arm. In Herceptin containing arm, more Grade 1 AEs were reported in patients with age ≤50 years compared with patients with age >50 years (34.3% versus 21.1%); Grade 2 AEs were reported more frequently in the sub-group of patients >50 years (11.4% versus 22.8%). In the Herceptin containing arm, Grade 3 AEs were only reported in patients with age ≤50 years (5.7%). No Grade 4 or 5 AEs were reported in any arm. No discernible pattern seen in either of the age groups.

In Study BO16216, four Grade 3 AEs (3.8%) were reported in the anastrozole alone arm and two Grade 3 AEs (1.9%) were reported in the anastrozole plus Herceptin arm. In patients ≤50 years of age, cardiac AEs were 3.1% for anastrazole arm, 11.1% for anastrazole + Herceptin arm, and 16.7% for anastrazole alone after start of Herceptin arm compared to 1.4%, 11.8%, and 12.5% respectively in patients >50 years of age. Most cardiac events reported in age ≤50 years were of Grade 2, while those in age group >50 years were predominantly Grade 1 events. No Grade 4 or 5 events were reported in any of the age groups. A meaningful interpretation of the data is impacted by low event counts across both groups.

- Early Breast Cancer (Adjuvant Treatment)

BCIRG 006 (H2296s)/ GO00773:

The data were stratified for age and region. Across all the treatment arms, patients in age group >50 years reported higher percentage of "Any symptomatic or clinical significant asymptomatic cardiac events" (all assessment) compared with age group ≤50 years. In patients >50 years of age, cardiac AEs were 5.9% for AC—>T arm, 13.2% for AC—>TH arm, and 5.4% for and TCH arm, compared to 3.5%, 9.6%, and 4.6% respectively in patients ≤50 years of age. In AC—>T arm, the highest percentage of cardiac events were reported in North American patients, followed by Middle Eastern and European (Section 1.3 of Annex 7). In the AC—>TH arm, the highest percentage of cardiac events were observed in South African patients, followed by South American and North American patients. In the TCH arm, the highest percentages of cardiac events were observed in North American patients, followed by South Africa and South America. The number of Grade 3-4 events reported was low and precluded meaningful comparison between the sub groups. There was no discernible pattern observed in the Herceptin containing treatment arms across region.

BO16348 (HERA):

In a 10-year median follow-up Study, BO16348 (HERA), across the three study arms, AEs within the cardiac dysfunction risk were mainly mild-to-moderate in severity,

comprising Grades 1 and 2 of severity. In all of the clinical trial arms, the most commonly occurring Grade 1 and Grade 2 AEs were Oedema Peripheral, Cardiac Failure congestive and Ejection Fraction decreased. No Grade 3 AEs were reported in the Observation arm. Cardiac Failure congestive was the most common Grade 3 AE in all of the trastuzumab-containing arms: trastuzumab 1-year: 13/1682 (0.8%) patients; trastuzumab 2-year: 10/1673 (0.6%) patients. The other Grade 3 AEs in the trastuzumab-containing arms occurred at a frequency of < 0.1%. The most commonly occurring Grade 4 AE was Cardiac Failure congestive and it was observed in the trastuzumab 1-year and 2-year arms (4/1682 (0.2%) and 8/1673 (0.5%) patients , respectively), as well as the Observation only arm (1/1744 (0.1%) patients).

The AEs of cardiac dysfunction were stratified by the age and race (Section 1.3 of Annex 7). The >50 years subgroup reported higher percentage of patients with AEs compared with the <50 years subgroup in all the three arms. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs. Similarly, across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2. A meaningful interpretation of the data is impacted by low event counts across other race sub-groups.

MO28048 (SafeHER):

Overall, the cardiac dysfunction risks were mainly mild-to-moderate in severity, comprising of Grades 1 and 2 events. The most commonly occurring Grade 1 AEs were palpitations and mitral valve incompetence. The most commonly occurring Grade 2 AEs were left ventricular dysfunction and atrial fibrillation. Cardiac failure congestive was the most commonly occurring Grade 3 event. Myocardial infarction and atrial fibrillation were the Grade 4 events. Grade 5 fatal events were reported in four patients the events were acute myocardial infarction, arteriosclerosis coronary artery, cardiac hypertrophy, and cardio-respiratory arrest.

The AEs of cardiac dysfunction were stratified by the age and race (Section 1.3 of Annex 7). The >65 years sub-group reported higher percentage of patients with AEs compared with the ≤65 years sub-group. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs. Majority of the patients included in the trials were White. Across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2.

Overall, 27 patients (1.1%) reported 28 serious cardiac AE during the follow-up period and 60 patients (1.2%) reported 65 serious cardiac AEs during the whole study period.

There were a total of 7 patients who reported 7 related CHF SAEs during treatment period; all events were reported in Cohort A only; only one patient reported a related event of cardiac failure congestive during the follow-up period.

Joint Analysis of NSABP B-31 and N9831:

Of the Cardiac dysfunction AEs (as defined in this RMP), only severity data on Cardiac – left ventricular function and Oedema were collected for both Studies B-31 and N9831, i.e., no severity data was collected for CHF, decreased (LV)EF, or other Cardiac failure SMQ AEs. The distribution of AEs across all the arms are presented in Section 1.3 of Annex 7. A total of three cardiac deaths were observed in the trastuzumab-containing arms compared with five cardiac deaths in the control arm. These cardiac deaths did not necessarily include CHF (i.e., the category of cardiac death in the Joint Analysis included MI, arrhythmia, and sudden death).

The AEs of cardiac dysfunction were stratified by the presence of number of known risk factors (age >50 years, use of anti−hypertensive medications at baseline, and LVEF at paclitaxel baseline ≤55%), and by race (Section 1.3 of Annex 7). In this study, majority of patients were White. Other substantial groups included were Black and Hispanic. Most of these patients were in the AC –>T or AC –>T+H arm. The stratification by race, in patients with 0, 1, 2, or all the 3 of these risk factors is presented in Section 1.3 of Annex 7. A meaningful stratified comparison of cardiac dysfunction by race is impacted by low number of patients and AEs in most of the resulting subgroups.

- Neoadjuvant-adjuvant treatment in EBC

MO16432 (NOAH):

Cardiac events reported in at least two patients included: angina pectoris (5 patients in each of the HER2-positive arms), tachycardia (5 patients in each of the HER2-positive arms and one patient in the HER2-negative arm) and palpitations (3 patients in each of the HER2-positive arms and one patient in the HER2-negative arm). None of these cardiac events were reported as Grade 3 or 4 AEs. The myocardial ischemia in the HER2+TC arm was of Grade 2 intensity at worst and recovered on the same day without sequelae.

During the post-operative period, 16 patients experienced 22 cardiac AEs (8.9% [10/112] patients with 15 AEs in HER2 positive + TC, 10.0% [2/20] patients with two AEs in HER2 positive + C→T, 5.9% [4/68] patients with five AEs in HER2 positive + C). In the HER2 positive + C arm, patient [redacted] experienced a Grade 3 pericardial effusion and in the HER2 positive + TC arm, patient [redacted] had a Grade 3 decreased ejection fraction considered related to study medication and reported as an SAE.

- Neoadjuvant-adjuvant Treatment in EBC

BO22227 – (HannaH):

Severity per CTC Grading

In the IV arm, all AEs were either Grade 1 or Grade 2; there were no Grade 3 -5 AEs. In the Herceptin SC arm, 4 AEs in 3 patients were Grade 3 in severity; two of these were assessed as serious. One patient in each of the treatment arms experienced a Grade 5 event of myocardial infarction. The 5-year follow-up data with last patient last visit (LPLV) of 24 January 2017 did not show any change in the data presented.

The AEs of cardiac dysfunction were stratified by the age and race. No clear discernible pattern was observed in either of the age groups (age ≤50 and >50 years sub-groups) for cardiac dysfunction-related events. In Asian patients 30% and 27% of patients (IV, SC) had events, white 16% and 13%, other 17% and 15%.

MO22982 (PrefHER):

Results from crossover period SC-IV or IV-SC (479 patients for Herceptin SC period and 478 patients for Herceptin IV period).

Herceptin IV (4 cycles):

Two patients with grade 3 Left Ventricular Dysfunctions were reported. Three patients had three Cardiac AEs of Grade 2 severity and eleven had 12 Grade 1 AEs.

Herceptin SC (4 cycles):

One patient with grade 3 left ventricular dysfunction was reported. Two patients had two Cardiac AEs of a Grade 2 severity and nine patients had 12 Grade 1 AEs.

- Advanced Gastric Cancer

BO18255 (ToGA):

Across treatment arms, Fluoropyrimidine/Cisplatin arm and Trastuzumab/ Fluoropyrimidine/ Cisplatin arm, cardiac AEs were mostly mild-to-moderate in severity.

The AEs of cardiac dysfunction were stratified by the age, gender, race, and region (Section 1.3 of Annex 7). The stratified data from this study confirms that the age >50 years has an identified risk factor for cardiac dysfunction. The percentage of AEs was more in female patients. No Grade 3 or 4 AEs were reported in female patients. The Oriental patients reported higher numbers of AEs compared with the Caucasians; majority of them were Grade 1. The meaningful comparison of Grade 2, 3, and 4 events

is impacted by low numbers of events reported in each of these sub-groups. In the Herceptin containing arm, Asian patients reported the most number of Grade 1 AEs as compared with the European patients (25/164, 16.1% versus. 3/99, 3%). A relatively lower number of Grade 2 (Asia: 3, 1.9%; Europe: 3, 3%), Grade 3 (Asia: 1, 0.6%; Europe: 1, 1%), and Grade 4 (Asia: 2[1.3%], Europe: none) events were reported precluding a meaningful analysis.

Observational study in EBC

OHERA

The median age was 55 years (range: 21 – 86 years). Almost all the patients were female (3722 patients, 99.7%) and had Stage I or II breast cancer (3093 patients, 82.9%). Two-thirds of the patients were ER positive (62.6%).

Symptomatic CHF

Of the 106 patients with symptomatic CHF, (38 patients [1.0%]) were reported to have moderate to severe symptomatic CHF (NYHA Class III/IV), of which 1 patient died due to symptomatic CHF.

Please refer to Annex 7 for detailed study wise data on severity and nature of risk.

Impact on individual patient:

Cardiac failure may have a significant impact on the quality of life of individual patients. Treatment with trastuzumab should be suspended if LVEF percentage drops ≥ 10 points from baseline AND to below 50 %, and a repeat LVEF assessment should be performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of Herceptin should be strongly considered in order to avoid progression to CHF, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed-up. In the majority of patients, LVEF decrease is reversible.

Risk group or risk factors

Early Breast Cancer (EBC):

BCIRG 006 (H2296s)/GO00773:

Patient characteristics and clinical assessments specific to cardiac safety were analyzed to determine whether risk factors for a cardiac event could be identified. Variables that were evaluated include treatment received (AC→T versus. AC→TH), age, nodal status, prior or current use of cardiovascular medications at baseline, radiation to left side of the chest, baseline LVEF, on-study LVEF as characterized by LVEF at docetaxel baseline,

LVEF value at least 28 days prior to an event (continuous time-varying), and LVEF value <55 at least 28 days prior to an event (continuous dichotomous).

The risks of both symptomatic and asymptomatic LVEF events following initiation of treatment were increased with lower on-study LVEF values. Older patients (>50 years old) had an increased risk of both symptomatic cardiac and asymptomatic LVEF events regardless of treatment received.

No significant treatment-by-covariate interactions were detected.

The variables that remained significant in the multivariate model were treatment with AC→TH, age >50, and an LVEF value of <55% at least 28 days prior to the event. All covariates were associated with an increased risk of a cardiac event. Refer to Table 17 (Annex 7).

Risk Factor Modelling

BCIRG 006 (H2296s)/ GO00773

Asymptomatic LVEF events were defined as an absolute decrease of >15% in LVEF from baseline and to a value below an institution's law of large numbers (LLN). The analyses herein are of time to first symptomatic cardiac event per the individual case report form (ICRF) and/or asymptomatic LVEF events.

Patients who had an absolute LVEF decline of >15% from baseline during AC therapy had an approximately 6-fold increased risk of developing a cardiac event after initiation of T, TH, or TCH (p 0.0018; 95% CI: 1.9, 18.8). However, caution must be exercised in the interpretation of this association, as the decline in LVEF during AC treatment may be a factor used by the Independent Cardiac Review Panel (ICRP) to subsequently confirm a symptomatic cardiac event.

A 10-percentage point lower LVEF at the initiation of T, TH, or TCH at baseline resulted in a 1.5-fold increase risk of developing an event. Refer to Table 18 (Annex 7).

BO16348 (HERA):

Among the variables evaluated in univariate and multivariate Cox models to identify factors associated with an increased risk of a primary or secondary cardiac endpoint, Herceptin treatment, screening LVEF <60 EF points and, to a lesser extent, prior or current use of cardiovascular disease medication at baseline were significant risk factors[2].

[2] BO16348 (HERA) CSR Report 1044055.

Joint Analysis of B-31 and N9831:

Clinically meaningful cardiac event risk factors identified by subgroup included age and LVEF values at paclitaxel baseline as shown in Table 17 (Annex 7). The use of anti-hypertensive medications at baseline or during study was no longer a significant factor.

Table 19 (Annex 7) presents the incidence of cardiac events by the number of risk factors following initiation of paclitaxel or Herceptin + paclitaxel Therapy. The risk factors considered were age >50 years, the use of anti-hypertensive medication, and LVEF ≤55%.

Herceptin therapy, enrolment in Study B-31, and age >50 years were associated with an increased risk of a cardiac event in the AC→T + H group compared with the AC→T group. A lower LVEF, whether at baseline or ≥28 days prior to an event, was associated with an increased risk of CHF.

Patients in the AC→T + H group had an estimated 3.4-fold higher risk ($p< 0.001$, 95% CI 1.8, 6.1) of a cardiac event compared with patients in the AC→T group.

Patients >50 years of age had a 2.21-fold increased risk ($p=0.0011$, 95% CI 1.4-3.6) of a cardiac event compared with women ≤50 years of age. While the results suggest a large relative risk, the incidence of these events was relatively low.

A patient whose LVEF value (≥28 days prior to event) was 10-percentage points lower than another patient (everything else being equal) resulted in a 2.87-fold—$(1/0.90)^{10}$—increase in the risk of an event.

H4613g:

Trastuzumab did not prolong the QTc interval duration, and there was no apparent relationship between serum trastuzumab concentrations and the change in QTcF interval durations over time.

Trastuzumab had no clinically relevant effect on heart rate, uncorrected QT, PR, or QRS interval duration, and no cases of clinically significant abnormal U-wave or T-wave changes from baseline were observed.

Concomitant medication with carboplatin did not influence the pharmacokinetics of trastuzumab and vice versa.

MO28048 (SafeHER)

A greater proportion of patients in the highest weight quartile experienced cardiac AEs (21.3%) compared with other weight quartiles (proportions ranged from 12.3% to 18.9%). Of note, these upper weight quartile patients had a higher proportion of active

medical conditions at baseline, with a marked imbalance for vascular disorders (44.6% in the highest weight quartile and between 17.6% and 29.8% for other weight quartiles) as well as for cardiac disorders (9.6% of patients in the highest weight quartile and between 5.3% and 9.4% for other weight quartiles).

BO20652 (OHERA)

Risk Factors for Symptomatic CHF:

Patients who experienced symptomatic CHF had more risk factors than non-CHF patients. More than half of the patients who experienced CHF (66.0%) had at least one medical condition representing a risk for symptomatic CHF compared to non-CHF patients (41.5%). At baseline, a higher proportion of patients who had symptomatic CHF were reported to have high blood pressure, diabetes mellitus, arrhythmias, cardiac valvular disorders, and other major cardiac/non-cardiac diseases or conditions (e.g., asthma, Chronic Obstructive Pulmonary Disease (COPD), aortic aneurysm, diastolic dysfunction, embolism, etc.) compared to non-CHF patients. In addition, patients with symptomatic CHF were older compared to patients without CHF (median age 63 years versus. 55 years) and more were overweight/obese (body mass index [BMI]≥25 kg/m^2) (61.3% versus. 51.7%). Patients with symptomatic CHF also had more often a diagnosis of asymptomatic CHF (NYHA Class I) at study entry compared to non-CHF patients (3.8% versus. 0.9%).

The incidence of symptomatic CHF was higher in patients with the following baseline characteristics; pre-existing cardiac condition, use of cardiovascular medications at study entry, hypertension or high blood pressure, baseline LVEF ≤ 55%, overweight/obese (i.e., BMI≥ 25 kg/m^2), age ≥ 65 years, and history of cardiac failure or active cardiac failure at study entry.

Risk Factors for Cardiac Death:

When restricting to patients without disease recurrence, of the 6 patients that died due to a cardiac-related event, these patients were in the age range of 46-74 years, and 5 out of 6 patients had a previous cardiovascular medical condition.

Preventability:

In the prescribing information, the MAH describes the need for cardiac function assessment, periodic LVEF monitoring, and management of cardiac dysfunction.

Impact on the benefit-risk balance of the product:

The review of the latest available data did not lead to any change in the benefit-risk profile of Herceptin.

Public health impact

The safety concern of cardiac dysfunction does not have a potential public health impact.

1.5 ADMINISTRATION-RELATED REACTIONS (ARRS)

MedDRA terms:

'Modified Anaphylactic Reaction basket' which consists of the Anaphylactic Reaction SMQ plus the individual PTs: Infusion-Related Reaction; and Injection Site Hypersensitivity, Hypersensitivity and drug hypersensitivity.

Potential mechanism:

The potential mechanism of administration-related reactions have not been clearly established. However, Calogiuri et al. 2009 hypothesize that such reactions (to monoclonal antibodies in general) are attributable to Beta-type reactions: immediate and delayed hypersensitivity; Gamma-type reactions: over-reactions or depression of the immune functions like the immunodeficit, autoimmune or allergic phenomena; but that other mechanisms such as a specific release of cytokines, might be also involved.

Evidence source(s) and strength of evidence:

- EBC: Studies BO16348, BO22227, MO22982, and MO28048.
- Global Safety Database.
- Drug Safety Reports (DSR): DSR 1036301 dated 12 December 2009, DSR 1056779 dated 27 June 2013 and DSR 1060413 dated 15 May 2014

Characterization of the risk:

Frequency with 95% CI

Adjuvant Treatment in EBC

- BO16348 (HERA)

The frequency for corresponding grades of AEs under ARR is presented in Table 42. The most frequently occurring AEs were cough (n=62; in observation only arm, n=117; in Herceptin 1 Year arm and n=147 in Herceptin 2 Year arm) and dyspnoea (n=46; in observation only arm, n=83; in Herceptin 1 Year arm and n=117; in Herceptin 2 Year arm).

Table 42 HERA (BO16348) Infusion-Related Reactions (IRR)/ARR Frequency and Severity

Arm	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Observation only N =1744	217	149 (68.7)	63 (29.0)	3 (1.4)	1 (0.5)
Herceptin 1 Year N = 1682	569	405 (71.2)	146 (25.7)	15 (2.6)	2 (0.4)
Herceptin 2 Year N = 1673	736	521 (70.8)	191 (26.0)	17 (2.3)	1 (0.0)
MedDRA The Modified Anaphylactic Reaction SMQ consists of the Anaphylactic Reaction SMQ plus the individual PTs: Infusion-Related Reactions; and Injection-Site Hypersensitivity, Hypersensitivity and drug hypersensitivity. Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual. Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.					

- MO28048 (SafeHER)

During the whole study, 1053 patients (41.4% in Cohort A and 39.9% in Cohort B) reported a total of 1937 ARR events. These events were mainly (≥15% of patients) skin and subcutaneous tissue disorders (609 patients overall [23.7%] with 973 events) and respiratory, thoracic and mediastinal disorders (455 patients overall [17.7%] with 578 events). The most frequently reported (≥5% of patients) individual ARRs events overall were cough (281 patients [10.9%] with 331 events), rash (265 patients [10.3%] with 383 events), erythema (247 patients [9.6%] with 339 events), dyspnoea (185 patients [7.2%] with 208 events), and pruritus (158 patients [6.2%] with 189 events)

Neoadjuvant-adjuvant Treatment in EBC

- BO22227 (HannaH)

In the IV arm, the most frequently reported AEs were Rash (44); Pruritus (27); Cough (24), and Dyspnoea (22);

The overall incidence (all AEs, all grades) was 37.2% in the IV arm and 47.8% in the SC arm. The incidence of patients with grade 1 events was 31.5% in the IV arm compared to 40.7% in the SC arm, while the incidence of patients with grade 2 events was 11.4% in the IV arm compared to 16.8% in the SC arm thus difference in overall incidence was largely driven by more non-severe grade 1 and 2 events in the SC arm compared to the IV arm.

In the subcutaneous arm, five AEs were reported as NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 3) grade 3, and six respectively in the IV arm. The most frequently reported AEs were the same with the SC formulation as for the IV formulation and were in similar order of frequency: Rash (48); Cough (35); Pruritus (26), and Dyspnoea (21).

Table 22 and Table 23 in Annex 7 show the incidence of ARR events according to severity.

No additional data on ARRs was available in the final CSR (based on the 5-year follow-up data, LPLV 24 January 2017) as ARRs are events which occur, during the treatment phase and as such, full information on these events was presented in the primary updated CSR (Report number 1057070).

Seriousness and outcomes

Early Breast Cancer (EBC)

Adjuvant Treatment:

- BO16348 (HERA)

Administration-related reaction was defined under the basket of modified anaphylactic reactions. Across all treatment arms, 25 patients reported SAEs of ARR. Observation Only (n=1744): 11/1744 (0.6%) patients; Herceptin 1-year (n=1682): 7/1682 (0.4%) patients and Herceptin-2-year (n=1673): 7/1673 (0.4%) patients, the reported SAEs in the 1-year Herceptin arm included 2 events of hypotension reported in 2 patients and one event each reporting urticaria, anaphylactic shock, cardiac arrest, cough, rash generalized and throat tightness. The 2-year treatment arm included 3 events of dyspnea reported in 3 patients, and one event each reporting erythema, urticaria, asthma, hypotension and anaphylactic reaction. No case of ARRs with fatal outcome was reported.

Hypotension, rash generalized, throat tightness, erythema and anaphylactic reaction were the ARRs leading to dose interruption in the trastuzumab-containing arms: Herceptin-1-year: 3 patients in1682 (0.2%) and Herceptin-2-year: 2 patients in 1673 (0.1%).

Hypotension and dyspnoea were the cardiac AEs leading to drug discontinuation in the trastuzumab-containing arms: Herceptin 2-year: 2/1673 (0.1%) patients.

- MO28048 (SafeHER)

In the overall safety population, 51 Grade ≥3 ARRs were reported in 46 [1.8%] of 2569 patients (34 patients [1.8%] with 39 events in Cohort A and 12 patients [1.7%] with 12 events in Cohort B). The SOC with the most number of Grade ≥3 ARRs was respiratory, thoracic and mediastinal disorders (20 patients [0.7%] with 21 events overall). The most frequently reported (≥0.2% of patients, overall) individual Grade ≥3 ARRs were dyspnoea (12 patients [0.5%] followed by erythema (5 patients [0.2%]).

Two patients experienced life-threatening (Grade 4) event: asthma (Cohort A) reported by one patient during treatment period and anaphylactic shock (Cohort B) reported by one patient during the follow-up period. One patient experienced a Grade 5 ARR event of cardio-respiratory arrest reported during the follow-up period.

Neoadjuvant-adjuvant Treatment in EBC

- BO22227 (HannaH)

The data presented below take into account the most severe intensity reported for multiple occurrences of the same adverse event in a given individual patient. For each AE Preferred Term and patient, the event is counted only once per patient and the worst outcome is counted.

Herceptin IV (n=298)

A total of 200 events were reported in 111 patients falling under the definition of Administration-related reaction. Six AEs were reported as NCI CTCAE (version 3) Grade 3, thereof 2 AEs were also reported as SAEs (PT: Hypersensitivity). Both events of Hypersensitivity were related to use of docetaxel leading to its discontinuation in 1 event. In 1 event, there was no docetaxel modification. Both events lasted ≤ 1 day and no action was taken with regards to Herceptin administration. 199 AEs were reported to have resolved. One AE was reported as unresolved.

Herceptin SC (n=297)

A total of 234 events were reported in 142 patients. None of the events was reported as serious. 230 AEs were reported to have resolved. One AE resolved with sequelae. Three AEs were reported as unresolved.

- MO22982 (PrefHER[3])

Results from crossover period SC-IV or IV-SC

Herceptin IV (4 cycles):

A total of 38 events in 31 out of 478 patients were reported falling under the definition of Administration-related reaction. The most frequently reported AEs were erythema, rash and cough (in 6 patients each), dyspnoea (in 5 patients) and pruritus (in 3 patients).

Herceptin SC (4 cycles):

A total of 90 events in 61 out of 479 patients were reported falling under the definition of Administration-related reaction.
The most frequently reported AEs were erythema (in 17 patients), cough and dyspnoea

[3] Data has been presented as per PrefHER CSR

(in 9 patients each), rash (in 8 patients), flushing (in 7 patients), Dyspnoea (n=12 in 9 patients), Refer to Table 24 (Annex 7).

Results from Herceptin continuation period

Cohort 1: A total of 226 patients in Cohort 1 received 1239 Herceptin IV cycles during the IV continuation period and 43 patients received 98 cycles administered with the SC SID during the SID self-administration period. All ARRs reported during the continuation period of Cohort 1 were Grade 1 or 2 in severity

IV continuation: ARRs AEs were reported for 12/226 (5.3%) patients during IV continuation period.

SID self-administration: ARRs were reported for 1/43 (2.3%) patients (erythema). There were no AEs leading to discontinuation of trial drug during the SID self-administration period.

Cohort 2

Patients in Cohort 2 (SC Vial) continued to receive Herceptin SC via handheld syringe to complete their remaining cycles after the crossover period. A total of 208 patients in Cohort 2 received 1152 cycles with SC Vial during the SC continuation period and 10 patients received 34 cycles with IV during the IV continuation period. All ARRs reported during the continuation period of Cohort 2 were Grade 1 or 2 in severity.

IV continuation: No ARRs were reported for IV continuation in Cohort 2.

SC vial continuation: 28 ARRs were reported for 22 out of 208 patients. The most frequently reported AEs were erythema and cough (in 6 patients each) and rash (in 3 patients).

Global Safety Database

The information retrieved from the MAH's Global Safety Database, utilizing the Modified Anaphylactic Reaction MedDRA basket, is cumulative through 31 August 2017 (Table 26 in Annex 7).

A total of 16,654 AEs (reported in 12,840 cases) were retrieved (Table 26; Annex 7). Of these, 5,316 (32.1%) AEs were assessed as serious by the reporter and/or the MAH. The most frequent serious PTs were as follows: dyspnoea (n=1,348; 25.4%), infusion related reaction (n=471; 8.9%) and rash (n=335; 6.3%). Based on the exposure of

Herceptin (upto 24 September 2020, the data-lock point of the 2020 PBRER report number 1103351) in 2,935,329 patients, the crude reporting rate of ARRs is 0.4%

A total of 391 AEs (2.4% of all AEs) had a fatal outcome. Of these, the most frequently reported PTs were as follows: respiratory failure (n=110, 28.1% of all fatal outcomes); cardiac arrest and dyspnoea (n=63; 16.1%each); and cardio-respiratory arrest (n=35; 9. 0%).

A favorable outcome was reported in 6,798 AEs (40.8% of the 16,654 total AEs), having resolved/resolving/resolved with sequelae. There were 6,678 AEs (41.0%) that had an unknown or unreported outcome. The overall AE outcomes are shown in Table 27 of Annex 7.

Trastuzumab treatment was maintained (i.e., dose not changed) in response to the drug event in 3,441 (20.4%) of the reported drug events. It was withdrawn in 2,521(15.0%) of the reported drug events, and the action taken in response to the event was unknown in 8.398 (50.0%) of the reported drug events. Please refer to Table 28 of Annex 7 for the tabulation of the other actions taken with trastuzumab.

Severity and Nature of Risk

Early breast cancer

Adjuvant treatment:

- BO16348 (HERA)

An overview of the AEs reported under Modified anaphylactic reactions MedDRA basket Version 18.0, based on the reported grades in this study is presented in Table 42

The majority of AEs reported were of Grade 1 or 2 intensity across all arms (69.1% grade 1 and 29.0% grade 2 in observation arm; 71.0% grade 1 and 25.8% grade 2 in 1-year treatment arm; and 71.0% grade 1 and 26.2% grade 2 in 2-year treatment arm. The majority of the cases reporting Grade 3 under the one year and two-year Herceptin arm were with PT: dyspnea. No other skewed pattern was observed in reporting of Grade 3 and Grade 4 events. Grade 4 cases in Herceptin containing arm consisted of one event each of cardiac arrest (1-year treatment arm) and anaphylactic reaction (2-year treatment arm). One event of hypotension was reported in observation only arm.

Stratified Data

Age ≤ 50 years:

- Observation only arm: 9.1% (87 out of 959 patients reported a total of 101 AEs). Only Grade 1 (n=80 in 70 patients) and Grade 2 (n=21 in 20 patients) events were reported.

- Herceptin 1-year arm: 23.1% (219/947 patients reported a total of 297 AEs). Majority were Grade 1 (n=211 in 166 patients) and, followed by Grade 2 (n=80 in 72 patients), and six Grade 3 events in 6 patients (dyspnoea [n=2] and one event each of asthma, rash generalized, hypersensitivity and drug hypersensitivity (n=6). No Grade 4 events were reported.
- Herceptin 2-year arm: 28.4% (263/926 patients reported a total of 373 AEs). Majority were Grade 1 (n=270 in 199 patients), followed by Grade 2 (n=92 in 79 patients), Nine Grade 3 events in 8 patients (dyspnoea [n=3] and one event each of cough, hyperventilation, urticaria, chest discomfort, flushing and infusion related reaction, and one Grade 4 event (anaphylactic reaction) were reported.

Age >50 years:

- Observation only arm: 11.8% (93 out of 785 patients reported a total of 116 AEs). Majority were reported as Grade 1 (n=70 in 61 patients) and Grade 2 (n=42 in 38 patients), Three Grade 3 events in 3 patients (asthma [n=2] and one dyspnoea and one Grade 4 event (hypotension) were reported.
- Herceptin 1-year arm: 27.5% (202/735 patients reported a total of 276 events). Majority were Grade 1 (n=196 in 153 patients) and Grade 2 (n=68 in 62 patients). Nine Grade 3 events (in 9 patients (dyspnoea [n=4], hypotension and cough [n=2] each and circulatory collapse [n=1]) and two Grade 4 events (in 2 patients (anaphylactic shock and cardiac arrest) events.
- Herceptin 2-year arm: 32.0% (239/747 patients reported a total of 368 events). Majority were Grade 1 (n=255 in 171 patients) and Grade 2 (n=102 in 90 patients). Eight Grade 3 events in 8 patients (dyspnoea [n=4], asthma [n=2], rash and anaphylactic reaction). There were no Grade 4 events reported.

Summary: The patients in sub-group >50 years reported higher percentage of patients with AEs compared with the sub-group ≤50 years in all the three arms. For all age groups, majority of the AEs were either Grade 1 or 2 and in line with the unstratified outputs.

Age ≤ 65 years

- Observation only arm: 9.74% (160 out of 1642 patients reported a total of 191 AEs). Majority were reported as Grade 1 (n=133 in 177 patients) and Grade 2 (n=57 in 52 patients), followed by one Grade 3 (asthma) events. There was no Grade 4 event reported.
- Herceptin 1-year arm: 24.7% (393/1588 patients reported a total of 539 events). Majority were Grade 1 (n=385 in 298 patients) and Grade 2 (n=138 in 125 patients). Thirteen Grade 3 events in 13 patients (dyspnoea [n=5], cough, hypotension [n=2 each], asthma, rash generalized, hypersensitivity and drug hypersensitivity [n=1 each] and two Grade 4 events in two patients (anaphylactic shock and cardiac arrest) were reported.
- Herceptin 2-year arm: 30.1% (477/1583 patients reported a total of 705 events). Majority were Grade 1 (n=502 in 354 patients) and Grade 2 (n=182 in 157 patients). Sixteen Grade 3 events in 15 patients (dyspnoea [n=7], cough, asthma,

hyperventilation, rash, urticaria, chest discomfort, flushing, anaphylactic reaction and infusion related reaction [n=1each]) and one Grade 4 (anaphylactic shock) were reported.

Age >65 years

- Observation only arm: 19.6% (20 out of 102 patients reported a total of 26 AEs). Majority were reported as Grade 1 (n=17) and Grade 2 (n=6), followed by Grade 3 (n=2) and Grade 4 (n=1) events.
- Herceptin 1-year arm: 29.8% (28/94 patients reported a total of 34 events). Majority were Grade 1 (n=22) and Grade 2 (n=10), followed by Grade 3 (n=2) events. There was no Grade 4 event reported.
- Herceptin 2-year arm: 27.8% (25/90 patients reported a total of 36 events). Majority were Grade 1 (n=23) and Grade 2 (n=12), followed by Grade 3 (n=1) events. There was no Grade 4 event reported.

Summary: The data for the patients in sub-groups ≤65 years and >65 years do not show a difference compared with the age groups ≤50 years and >50 years; most AEs were reported in the 2-year arm and the majority of the AEs were either Grade 1 or 2. A meaningful interpretation of the data is impacted by low event counts in the sub-group >65 years.

Race:

Observation arm

- Black: 1/6 patients reported 2 events; Caucasian: 144/1453 reported 172 events (Grade 3: 3 events; Grade 4: 1 event); Oriental: 25/218 patients reported 31 events (neither Grade 3 nor Grade 4 events); other: 10/67 patients reported 12 events (neither Grade 3 nor Grade 4 events).

Herceptin 1-year arm

- Black: 3/8 patients reported 3 events (Grade 1:2 events and grade 2: 1 event); Caucasian: 339/1404 patients reported 456 events (Grade 3: 15 events, Grade 4: 2 events); Oriental: 63/213 patients reported 95 events (neither Grade 3 nor Grade 4 events); Other: 16/57 patients reported 19 events (neither Grade 3 nor Grade 4 events).

Herceptin 2-year arm

- Black: 3/5 patients reported 6 events (neither Grade 3 nor Grade 4 events); Caucasian: 395/1397 patients reported 578 events (Grade 3: 16 events, Grade 4: 1 event); Oriental: 82/213 patients reported 127 events (neither Grade 3 nor Grade 4 events); Other: 22/58 patients reported 30 events (Grade 3: 1 event; no Grade 4 event).

Summary: The majority of the patients included in the trials were Caucasian. Across all the race sub-groups, the majority of the events reported were Grade 1 and Grade 2. A

meaningful interpretation of the data is impacted by low event counts across other race sub-groups

Neoadjuvant-adjuvant treatment:

- BO22227 (HannaH):

- Table 22 (Annex 7) (IV arm) and Table 23 (Annex 7) (SC arm) show the incidence of ARR events according to severity.
- The severities of the administration-related AEs were similar for both study arms and were distributed amongst Grade 1 through 3. There were no Grade 4 or 5 administration-related AEs for either the Herceptin IV or Herceptin SC treatment arms. The overall incidence of ARRs in the Herceptin IV arm was 37.2% compared with 47.8% in the Herceptin SC arm, i.e., a difference of 10.6%. Following modification of the search parameters (removal of the preferred terms "hypersensitivity" and "drug hypersensitivity") the overall incidence changes to 29.8% versus 41.1% (IV versus SC, respectively), a difference of 11.3%. This difference in overall incidence was driven by events in the *Skin and subcutaneous tissue disorders* SOC, specifically by erythema (which occurred in 2.7% of patients in the IV arm compared with 7.1% of patients in the SC arm); and by events in the *Respiratory, thoracic and mediastinal disorders* SOC, specifically by cough (which occurred in 8.1% of patients in the IV arm compared with 11.8% of patients in the SC arm). There were six Grade 3 events reported in the Herceptin IV arm (Hypersensitivity/ Drug hypersensitivity (4) and Hypotension (2)) and five Grade 3 events in the Herceptin SC arm (one each for Erythema, Cough, Hypersensitivity, and 2 events for Drug hypersensitivity).

Stratified Data

Events of ARRs in the HannaH trial have been stratified by the following parameters: Age (by categories), Region, and Race.

No stratification by gender: almost exclusively women were included.

Age:

All Body Systems, percentage of patients with at least one AE (and total number of AEs) per age group:

- Age ≤ 50 years, IV treatment: 45.2% (70 patients, total number of AEs 130).
- Age >50 years, IV treatment: 28.7% (41 patients, total number of AEs 70).
- Age ≤ 50 years, SC treatment: 51.0% (80 patients, total number of AEs 128).
- Age >50 years, SC treatment: 44.3% (62 patients, total number of AEs 106).

Summary: The patients in sub-group >50 years reported a lower number of AEs compared with the sub-group ≤50 years in both IV and SC arms. For all age-groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Stratification for age-group ≤65 years versus >65 years was not meaningful due to the small number of patients in sub-group >65 years.

Region:

Asia Pacific

- IV: 61.0% (36 patients, total number of AEs 86). All AEs Grade 1 and 2.
- SC: 90.5% (57 patients, total number of AEs 115). All AEs reported as Grade 1 and 2.

Western E.U. incl Canada

- IV: 60.7% (34 patients, total number of AEs 54). All AEs from Grade 1 to 3, most frequently Grade 1 AEs reported (50.0%), Grade 3 minor (3.6%).
- SC: 69.2% (36 patients, total number of AEs 56). All AEs from Grade 1 to 3, most frequently Grade 1 (63.5%), least Grade 3 (5.8%) AEs reported.

South Africa

- IV: 53.3% (8 patients, total number of AEs 14), AEs from Grade 1 to 3, most frequently Grade 1 (53.3), Grade 3 least (6.7%).
- SC: 58.8% (10 patients, total number of AEs 15). All AEs reported as Grade 1 and 2.

South America

- IV: 26.7% (12 patients, total number of AEs 16), all AEs Grade 1 and 2.
- SC: 39.2% (20 patients, total number of AEs 25). All AEs reported as Grade 1 and 2.

Eastern European Area

- IV: 17.1% (21 patients, total number of AEs 30). All AEs from Grade 1 to 3, most frequently Grade 1 (13.8%), Grade 3 least (2.4%).
- SC: 16.7% (19 patients, total number of AEs 23). All AEs from Grade 1 to 3, most frequently Grade 1 (12.3%), Grade 3 least (1.8%).

Summary: Overall, most of the reported events across all sub-groups were Grade 1 and Grade 2. The patients in Asia-Pacific sub-group (both Herceptin IV and Herceptin SC) reported a relatively higher percentage of IRRs.

Race:

Asian:

- IV: 60.7% reported Grade 1 and 2 AEs. No Grade 3 AEs reported.

- SC: 89.1% reported Grade 1 and 2 AEs. No Grade 3 AEs reported.

White:

- IV: 32.7% reported Grade 1 to 3 AEs (2.9% Grade 3 AEs).
- SC: 35.0% reported Grade 1 to 3 AEs (2.5% Grade 3 AEs).

Other:

- IV: 20.7% reported Grade 1 and 2 AEs. No Grade 3 AEs reported.
- SC: 45.5 % reported Grade 1 and 2 AEs. No Grade 3 AEs reported.

Summary: The Asian patients reported a higher number of AEs compared with White and 'Other' race. However, no Grade 3 or greater AE was reported in Asian patients. This finding is consistent with the finding in the regional stratification.

The 5 year follow-up data (last patient last visit 24 January 2017) from this study has now been analyzed and is presented above. No new safety concerns were identified.

- MO22982 (PrefHER)

Results from crossover period SC-IV or IV-SC (N=479 for SC period)

Both Herceptin IV and Herceptin SC:

Most patients reported maximum CTCAE grades during the crossover period of Grade 1 or 2. Mild AEs: 45/479 (9.4%) patients reported 66 events for Herceptin SC period, 20/478 (4.2%) patients reported 25 events for IV period. Moderate AEs: 14/479 (2.9%) patients reported 19 events for Herceptin SC period, 11/478 (2.3%) patients reported 11 events for IV period. Maximum CTCAE Grade 3 events during the crossover period were reported for 5/479 (1.0%) patients (n=5 events) during the Herceptin SC treatment and for 2/478 (0.4%) patients (n=2 events) during IV treatment.

The observed difference between the two formulations results from more mild AEs reported in patients treated with the SC formulation; the AEs primarily contributing to the difference were mild erythema, dyspnoea, and flushing.

There was no meaningful difference between the SC or IV treatment periods in the proportion of patients reporting Grade 3 AEs. A summary of all AEs by maximum CTC Grade is shown in Table 25 of Annex 7.

Continuation period: All ARRs reported during the continuation period were Grade 1 or 2 in severity.

- Study MO28048 (SafeHER)

Overall, the administration-related risks were mainly mild-to-moderate in severity, comprising of Grades 1 and 2 events. The most commonly occurring Grade 1 and

Grade 2 AEs were rash cough and erythema. Dyspnoea was the most commonly occurring Grade 3 events. One event each of Anaphylactic shock, asthma were reported as Grade 4 event. One event of cardio-respiratory arrest was reported as the Grade 5 event.

Age ≤65 years

- 39.9% (881 out of 2137) patients reported a total of 1626 AEs. Majority were Grade 1 events (n = 1259 in 736 patients) and Grade 2 (n = 329 in 267 patients). There were 36 Grade 3 events in 32 patients, most frequently occurring were dyspnoea (n = 5), cough (n = 3), asthma, hyperventilation and respiratory distress (n = 1 each). Anaphylactic shock and cardio-respiratory arrest were reported as Grade 4 and Grade 5 events, respectively.

Age >65 years

- 38.2% (172 out of 432) patients reported a total of 311 AEs. Majority were Grade 1 events (n = 237 in 140 patients) and Grade 2 (n = 61 in 50 patients). There were 12 Grade 3 events in 11 patients (dyspnoea [n = 8], rash, erythema, respiratory failure and drug hypersensitivity [n = 1 each]) and one Grade 4 event of asthma was reported. No Grade 5 events were reported.

Summary: The patients in the sub-group ≤65 years reported more AEs compared with the sub-group >65 years. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Race

White: 766/1973 (38.82%) patients reported 1411 events (Grade 3: 37 events in 42 patients, Grade 4: two events in two patients and no Grade 5 events were reported).

Black: 19/31 (61.3%) patients reported 33 events (Grade 3: one event, no Grade 4 or 5 events).

Asian: 176/378 (46.6%) patients reported 315 events (Grade 3: 3 events reported in 3 patients, no Grade 4 and Grade 5 events).

Other: 36/89 (40.4%) patients reported 91 events (two Grade 3 event in two patients, one Grade 5 event, and no Grade 4 events).

N/A (per local regulation): 52/89 (58.42%) patients reported 81 events (no Grade 3, 4 or 5 events).

Unknown: 4/9 (44.4%) patients reported 6 events (no Grade 3, 4 or 5 events).

Summary: The majority of the patients included in the trials were White. Across all the race sub-groups, the majority of the events reported were Grade 1 and Grade 2. A

meaningful interpretation of the data is impacted by low event counts across other race sub-groups.

Impact on individual patient:

The ARRs are known to occur with the trastuzumab. Serious ARRs to Herceptin IV and Herceptin SC including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress have been reported. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin.

Since patients are essentially treated in clinical settings under controlled environment equipped to monitor and treat individual patients, the majority of ARRs are identifiable and are clinically manageable.

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not be susceptible to administration related reactions to Herceptin. However, the Summary of Product Characteristics (SPC) indicates that patients, who are experiencing dyspnea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.

Preventability:

Pre-medication may be used to reduce risk of occurrence of ARRs. The MAH describes how ARRs can be managed in the SmPC. For the Herceptin IV administration, these reactions can usually be managed by slowing the infusion or temporarily stopping the infusion until resolution of the symptoms. It should also be noted that Herceptin is also given in combination with chemotherapy on the same (+/- one) day that may also instigate such infusion reactions.

Impact on the benefit-risk balance of the product:

ARRs are clinically manageable with standard therapeutic interventions. The safety profile of Herceptin is well characterized and based on the evaluation of the latest available data the cumulative benefit-risk profile of Herceptin is considered positive and unchanged in all indications.

Public health impact:

No additional public health impact in view of the population treated is anticipated, as monitoring and treatment of ARRs is a routine part of oncology clinical practice. Use outside of controlled environments by non- healthcare professionals (HCPs) is not anticipated.

1.6 OLIGOHYDRAMNIOS

MedDRA Terms:

MedDRA High Level Group Term (HLGT): Neonatal and perinatal conditions; and, MedDRA HLT: Amniotic fluid and cavity disorders of pregnancy NEC and following PTs: Amniotic fluid index, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid index increased, Amniotic fluid volume, Amniotic fluid volume decreased, Amniotic fluid volume increased, Intra-amniotic injection, Vesicoamniotic shunt.

Potential mechanisms:

Bader et al. 2007 hypothesized that Herceptin may have a direct effect on the function of HER2 receptors in the fetal kidney, leading to reduce cell proliferation and restriction of fetal kidney function in vivo. Hypothesis was confirmed in pharmacovigilance surveillance (Drug Safety Report (DSR) 1040470).

Evidence source(s) and strength of evidence:

- Global Safety Database,
- Drug safety reports: DSR #1030381, DSR #1040470 and DSR #10156279.
- Pregnancy registry MotHER [H4621g/GE28099].

Characterization of the risk:

Frequency with 95% CI: Not applicable

Severity and Nature of Risk: Not applicable

Seriousness/ Outcomes:

Oligohydramnios has not been observed in any clinical trials thus far.

<u>Global Safety Database</u>

The information was retrieved cumulatively through August 2018 from the MAH's Global Safety Database, utilizing the MedDRA HLGT 'Neonatal and perinatal conditions' and HLT 'Amniotic fluid and cavity disorders of pregnancy NEC' and following 9 PTs -

> Amniotic fluid index, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid index increased, Amniotic fluid volume, Amniotic fluid volume

decreased, Amniotic fluid volume increased, Intra-amniotic injection, Vesicoamniotic shunt MedDRA groupings..

A total of 104 AEs (reported in 92 cases) were retrieved (Table 29; Annex 7). Of these, 83(79.8%) AEs were assessed as serious by the reporter and/or the MAH and were distributed amongst 15MedDRA PTs: oligohydramnios n=41 (49.4% of all SAEs in this identified risk group); premature baby n=8 (9.6%), failure to thrive n=10 (12.0%);; neonatal respiratory distress syndrome n=5 6.0%); amniotic fluid volume decreased n=4 (4.8%) each; transient tachypnea of the newborn and death neonatal n=2 (2.4%) each; and thrombocytopenia neonatal, agitation neonatal, meconium aspiration syndrome, neonatal anoxia, neonatal disorder, small for dates baby thrombocytopenia neonatal and umbilical cord abnormality n=1 (1.24%) each. Based on the exposure of Herceptin (until 24 September 2020, the DLP of the latest PBRER of the 2020 PBRER report number 1103351) in 2,935,329 patients, the crude reporting rate of AEs (reported under the risk of oligohydramnios) is 0.003%.

Five AEs (premature baby (n=2), death neonatal, failure to thrive and umbilical cord abnormality), which was 4.8 % of all AEs in this identified risk group, had a fatal outcome. The majority of AEs (n=40) had an unknown or not reported outcome. In six AE reports the event was reported as persisting. A favorable outcome was reported in 36 AEs (34.6% of the 104 total AEs), having recovered/resolved, recovered/resolved with sequelae, or having been recovering/resolving as listed in Table 30 (Annex 7).

Herceptin treatment was withdrawn in response to the AE in 24 (23.1%) of the reported AEs; the action taken in response to the event was unknown in 28 (26.9%) AEs; and the dose was not changed in4 (3.8%) of the AEs, the dose was interrupted for 6 (5.8%) AEs. Further details are illustrated in Table 31 (Annex 7).

A search of the Global Safety Database using the same methodology as described in DSR 1056279 to retrieve any additional cases with the PT 'oligohydramnios' and cases with events within 'Congenital, familial and genetic disorders' SOC, received in the bridging period between the cut-off date of DSR 1056279 (24 April 2013) and 24 September 2014. In the DSR 1056279, four cases of renal impairment co-reported with oligohydraminos had been mentioned. After the cut-off date of the DSR, there was one additional case that reported fetal renal impairment with oligohydramnios.

The five reports of renal impairment co-reported with oligohydraminos are not considered excessive given the total cumulative exposure of Herceptin.

Impact on Individual Patient

Oligohydramnios is associated with risks to fetal development and therefore may have a significant impact on an individual patient. In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in

pregnant women receiving Herceptin. The need to avoid pregnancy during and for 7 months after Herceptin treatment may affect patients' quality of life.

However, patients are likely to face the same restrictions even if Herceptin were not given, since most treatments for breast cancer (chemotherapy, Herceptin, hormone therapy, and radiotherapy) are associated with significant risks to the developing fetus.

Risk factors and risk groups:

There are no reliable indicators of patients who may or may not be at risk.

Preventability:

Current SmPC indicates that treatment with Herceptin only be considered during pregnancy when the potential benefits to the mother outweigh the potential risks to the fetus. Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 7 months after treatment has concluded.

Impact on the benefit-risk balance of the product:

The current labeling documents adequately describe both the risk of oligohydramnios and appropriate risk minimization measures. The MAH has implemented the global enhanced pharmacovigilance (PV) pregnancy program with a purpose to ask for follow-up information at pre-specified time points to collect additional maternal and fetal/infant information on all reports of women exposed to trastuzumab during pregnancy, or within seven months prior to conception, received by the MAH. The review of the latest available data did not lead to any change in the benefit-risk profile for Herceptin.

Public health impact:

Cumulative patient exposure data to Herceptin as of 30 September 2017 was more than 2.6 million. At this time, the number of pregnancies recorded on the Global Safety Database was approximately 467 (given the potential for duplication attributable to the complications of spontaneous reporting). The percentage of pregnancies complicated by oligohydramnios in patients exposed to Herceptin is higher than that seen in the population unexposed to Herceptin; however this does not take into account previous or concurrent chemotherapy or radiotherapy and given the small number of pregnancies reported in the Herceptin exposed population, there is only a very limited, if at all, potential public health impact.

- Pregnancy Registry MotHER [H4621g/GE28099].

MotHER Pregnancy Registry (H4621g/GE28099) was an observational registry sponsored by Roche/Genentech to obtain prospective data on adverse pregnancy complications, including oligohydramnios, as well as pregnancy outcomes, and infant outcomes from pregnancies of women in the United States that have been exposed to a Herceptin-, Perjeta-, or Kadcyla-containing regimen during pregnancy or within 7 months

prior to conception. Obstetric and oncologic data are prospectively collected in pregnant women until completion of pregnancy, followed by data related to the infants born to enrolled mothers for 12 months after birth.

As of 31 January 2018 (clinical cut-off date for ADS for 2018), 20 mothers were enrolled in the MotHER Registry (17 mothers exposed to Herceptin-only and 3 mothers exposed to Perjeta plus Herceptin; no mothers exposed to Kadcyla were enrolled). Fifteen mothers have completed Registry follow-up, 4 mothers discontinued early (including 1 mother who was deemed ineligible for the Registry), and 1 mother (Patient [redacted]) is completed for infant follow-up. Among the 4 mothers who discontinued early, 1 mother discontinued after 6 months of post-delivery follow-up (Patient [redacted]), 1 mother discontinued after 2 months of post-delivery follow-up (Patient [redacted]), 1 mother discontinued after delivery with no additional follow-up (Patient [redacted]), and 1 mother was deemed ineligible for the Registry due to lack of further detail subsequent to self-enrolling into the Registry (Patient [redacted]). This mother was lost to follow-up following self-enrollment.

During pregnancy, 3 mothers experienced oligohydramnios (Patients [redacted] and [redacted]), and 3 mothers experienced polyhydramnios (Patients [redacted] and [redacted]). Oligohydramnios is a recognized and important risk of Herceptin exposure and is listed as an adverse drug reaction in the core data sheet (CDS) for Herceptin and in the boxed warnings of the Herceptin U.S. prescribing information (USPI) as a risk associated with Herceptin use during pregnancy.

The incidence of oligohydramnios observed in this small number of pregnancies is consistent with observations from published literature. However, the rate of polyhydramnios is higher than expected when compared to the literature (1%–2%). Polyhydramnios may be associated with increased perinatal morbidity and mortality (Hamza et al. 2013). Some of the known common causes for polyhydramnios include gestational diabetes, fetal anomalies, smoking, drug exposures (e.g., lithium), and other rare causes (Myhra et al. 1992; Oyebode et al. 2012; Hamza et al. 2013).

In the MotHER Registry, 1 of 3 mothers with polyhydramnios had gestational diabetes (Patient [redacted]). Two remaining mothers with polyhydramnios had exposure to risk factors during their pregnancy that might be associated with the incidence of polyhydramnios (Patient [redacted] had exposure to lithium treatment and smoking, and Patient [redacted] had exposure to smoking during pregnancy). One of the infants of the mothers with polyhydramnios was reported to have the targeted adverse event (TAE) (these TAEs should be reported regardless of seriousness or severity and include: Oligohydramnios , Hypertensive disorders of pregnancy [e.g., pre-eclampsia, gestational hypertension], Gestational diabetes, intrauterine growth restriction [IUGR], Birth weight below the 10th percentile [i.e., small for gestational age], Delayed renal development) of "small for gestational age" (Patient [redacted]), and one other infant had events of congenital umbilical hernia and congenital skin dimples (Patient [redacted]) that were initially

reported as non-serious AE but corrected to SAE after additional queries to HCPs regarding these congenital abnormalities. Among the 3 mothers reported with polyhydramnios, Patient [redacted] had an estimated date of conception (EDC) on [redacted] 2012, and her last dose of Herceptin was given on [redacted] 2012; polyhydramnios was reported with onset on [redacted] 2012, early in the third trimester of pregnancy and nearly 7 months after the last dose of Herceptin. Patient [redacted] had an EDC on [redacted] 2013, and her last dose of Herceptin was given on [redacted] 2013; polyhydramnios was reported with onset date of [redacted] 2013, late in the third trimester of pregnancy and nearly 8 months after the last dose of Herceptin. For the remaining mother (Patient [redacted]), despite repeated requests, lack of detail regarding the mother's anticancer treatment and lack of information about the event of polyhydramnios, including sonographic assessments and the polyhydramnios diagnosis date, limit the ability to assess its relationship to Herceptin treatment.

Confounding factors with reported risk for polyhydramnios, such as exposure to lithium treatment (Patient [redacted]), smoking (Patients [redacted] and [redacted]), and concomitant gestational diabetes (Patient [redacted]), have been reported in these mothers (Myhra et al. 1992; Oyebode et al. 2012; Hamza et al. 2013). Thus, the higher relative rate of polyhydramnios is interpreted with caution given the confounding risk factors and overall small number of pregnancies in the MotHER Registry. Nevertheless, these events will continue to be monitored per routine pharmacovigilance activities as well as in the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Perjeta, and Kadcyla.

Among the three Perjeta plus Herceptin-exposed mothers in the MotHER Registry (Patients [redacted] and [redacted]), one mother (Patient [redacted]) was deemed ineligible for the registry as mentioned previously. The two other mothers each had a live birth (Patients [redacted] and [redacted]), and no specific SAE or TAE has been reported for these mothers during their pregnancy or post-delivery follow-up provided by the HCP. One mother (Patient [redacted]) has completed the follow-up in the Registry with 2-and 6-month scheduled pediatric visits and an unscheduled pediatric visit at around [redacted] months of [redacted] for the infant (the birth date was missing for this infant). In addition to the infant's weight, no other information is reported at the pediatric visits, and multiple case report forms have not been reported to the Registry for this mother despite repeated requests. The second Perjeta plus Herceptin-exposed mother (Patient [redacted]) had a live birth and all infant follow-up visits were completed with no reports of congenital defects, life-threatening conditions or serious complications. The third Perjeta plus Herceptin-exposed mother (Patient [redacted]) self-enrolled into the Registry, however lack of further detail resulted in ineligibility of this mother for the Registry and she was lost to follow-up.

As of 31 January 2018, there were known outcomes for 19 pregnancies among 20 mothers enrolled into the Registry, including 18 live birth outcomes (19 infants as one pregnancy was a [redacted]) and an [redacted] due to [redacted] in a

Herceptin-(only) exposed mother; follow-up is ongoing for an infant of a mother (Patient [redacted]). Overall, gestational age at birth ranged from 33 to 41 weeks. There were three preterm deliveries, one of which was a [redacted] that was likely preterm because of [redacted] (Patient [redacted]), one preterm delivery was in a mother with oligohydramnios (Patient [redacted]), and the third preterm delivery was in a mother who experienced pregnancy-induced hypertension (PIH)/preeclampsia (Patient [redacted]). There was a case of Herceptin-(only) exposed mother (Patient [redacted]) who underwent [redacted] detected through detailed ultrasound imaging at 15.1 weeks of gestation. No information on specific exposure to Herceptin was reported to the Registry for Patient [redacted] despite multiple repeated attempts to obtain data from the HCPs. Patient narratives are provided as part of ADS for 2018.

No unexpected or new safety findings were identified during the evaluation of patients enrolled in the Registry.

The MotHER Registry ADS for 2017 (reporting interval: 1 February 2016 through 31 January 2017) was provided with the application.

Pursuant to the General Advice Letter received from United States Food and Drug Administration (FDA) on 10 August 2017 where the Agency stated that it planned to grant Genentech early fulfillment of the post-marketing commitment for Herceptin only, the MotHER Registry has stopped enrollment for women exposed only to Herceptin during pregnancy or within 7 months prior to conception as of 30 November 2017. The MotHER Registry is closed for eligible women exposed to Perjeta (in combination with Herceptin) or Kadcyla during pregnancy or within 7 months prior to conception. As of 31 January 2018, three mothers exposed to Perjeta plus Herceptin (currently not ongoing in the Registry) and no mothers exposed to Kadcyla have been enrolled in the Registry.

The MAH considers the release of Herceptin from the existing post-marketing commitment appropriate as no new or unexpected safety findings were identified during the latest or any of the previous interim analyses of the Registry. Additionally, maternal and fetal/infant information on all reports of women exposed to Herceptin only (or in combination with Perjeta) including risks of oligohydramnios continues to be monitored per routine pharmacovigilance activities as part of the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Perjeta, and Kadcyla.

Information on Important Potential Risks

1.7 IMMUNOGENICITY/ HYPERSENSITIVITY AND ANAPHYLAXIS OF HERCEPTIN SC

MedDRA term:

Brighton collaboration criteria for anaphylaxis and MedDRA SMQ "Anaphylactic reaction (broad scope)".

Potential mechanisms:

Immune response to the administration of a protein (IgG). In regard to hypersensitivity, Calogiuri et al. 2009 hypothesize that such reactions (to monoclonal antibodies in general) are attributable to Beta-type reactions: immediate and delayed hypersensitivity; Gamma-type reactions: over-reactions or depression of the immune functions like the immunodeficient, autoimmune or allergic phenomena; but that other mechanisms such as a specific release of cytokines, might be also involved.

Trastuzumab consists of two antigen-specific sites that bind to the juxtamembrane portion of the extracellular domain of the HER2 receptor and that prevent the activation of its intracellular tyrosine kinase. The remainder of the antibody is human IgG with a conserved fragment crystallizable (Fc) portion that can activate the complement system. Therefore, trastuzumab may cause systemic reactions, which includes hypersensitivity.

Evidence source(s) and strength of evidence:

BO22227 (HannaH), MO22982 (PrefHER), MO28048 (SafeHER) and Halozyme clinical trials.

Characterization of the risk:

Frequency with 95 % CI

<u>Neoadjuvant-adjuvant Treatment in EBC:</u>

- BO22227 (HannaH)

At the time of the final analysis and last patient last visit of 24 January 2017, the overall immunogenicity rate for anti- trastuzumab antibodies is 11.1% and 18.0% for patients in the IV and SC arms, respectively. The overall anti-trastuzumab antibody rate at baseline was 5.9 %.

Using the new definition which includes only treatment-induced in the determination of ADA incidence, the overall incidence of anti-trastuzumab antibodies was 10.1% in the Herceptin IV arm and 15.9% in the Herceptin SC arm.

The overall immunogenicity rate for anti-rHuPH20 antibodies is 23.7% for patients in the SC arm. The overall anti-rHuPH20 antibody rate at baseline was 7.46%.

Using the new definition which includes only treatment-induced in the determination of anti-rHuPH20 antibody incidence, the overall incidence of anti-rHuPH20 antibodies was 21.0%. The difference in the overall incidence is due to the exclusion of 9 treatment-unaffected patients that did not have a 4-fold increase in titer post-baseline from their baseline titer or where all post-baseline results were negative, irrespective of the response at baseline.

- MO22982 (PrefHER)

Patients in Cohort 1 (SC SID) only: At baseline and pre-dose Cycle 5, blood samples for rHuPH20 and trastuzumab antibody analyses, respectively, were taken. Serum trastuzumab concentrations were analyzed for these patients to aid in the assessment of immunogenicity.

Of the patients in the safety population with baseline samples available for trastuzumab anti-drug antibody (ADA) testing, 120 patients in the SC SID/IV arm (27 patients de Novo, 93 patients non de Novo) and 121 patients in the IV/SC SID arm (29 patients de Novo, 92 patients non de Novo) were included in the calculation of the baseline trastuzumab ADA rates.

The overall baseline trastuzumab ADA rates were 2.5% (3/120) in the SC SID/IV arm (2 de novo patients and 1 non de novo patient) and 4.1% (5/121) in the IV/SC SID arm (3 de novo patients and 2 non de novo patients). ADA-positive results at baseline among de novo patients were not unexpected as ADA assays utilized statistically derived cut-points designed to result in a small percentage of "false-positives".

Of the patients in the safety population who received trastuzumab treatment and had post-baseline samples available for trastuzumab anti-drug antibody (ADA) testing, 114 patients in the SC SID/IV arm (25 patients de Novo, 89 patients non de Novo) and 119 patients in the IV/SC SID arm (28 patients de Novo, 91 patients non de Novo) were considered evaluable for an ADA response to trastuzumab.

The overall post-baseline trastuzumab ADA rates were 0% (0/114) in the SC SID/IV arm and 3.4% (4/119) in the IV/SC SID arm. In the IV/SC SID arm, the patients were split 1 de-novo patient and 3 non de-novo patients. The rates were determined using a conservative approach, which considers all patients who were trastuzumab ADA-positive post-baseline regardless of the trastuzumab ADA results at baseline.

Of the 4 patients who were trastuzumab ADA-positive post-baseline, 2 non de-novo patients were trastuzumab ADA-positive at baseline and at Cycle 5 with titers ranging from <1 to 4. The remaining 2 patients (1 de-novo and 1 non de-novo) were trastuzumab ADA-positive at Cycle 5 only with similar titers ranging from <1 to 4. Neutralizing antibodies were not detected in any patients at any time point.

Trastuzumab concentrations > 50 µg/mL may interfere with the detection of neutralizing anti-trastuzumab antibodies which may result in an under-reporting of neutralizing antibodies while patients are receiving trastuzumab. In both treatment arms, the trastuzumab ADA rates at baseline were higher than the post-baseline rate, which may be due to the increased interference from trastuzumab post-baseline.

ADAs and Injection site reaction (ISRs):

No patients in the SC SID/IV arm were classified as trastuzumab ADA positive. No patients classified as anti-trastuzumab antibody positive post-baseline in the IV/SC SID arm were associated with an ISR. One de Novo patient classified as anti-trastuzumab antibody positive post-baseline in the IV/SC SID arm had an ARR (Table 36 Annex 7). The reported ARR events were AEs of mild local flushing of the skin after SC administration and resolved after 6 to 8 days.

Anti-rHuPH20 Antibodies

Of the patients in the safety population with baseline samples available for rHuPH20 antibody testing, 120 patients in the SC SID/IV arm (27 patients de-novo, 93 patients non de-novo) and 121 patients in the IV/SC SID arm (29 patients de-novo, 92 patients non de-novo) were included in the calculation of the baseline rHuPH20 antibody rates.

The overall baseline rHuPH20 antibody rates were 5.8% (7/120) in the SC SID/IV arm (2 de-novo and 5 non de-novo) and 7.4% (9/121) in the IV/SC SID arm (2 de-novo and 7 non de-novo patients). Three of the patients in the SC SID/IV arm (1 de-novo and 2 non de-novo) were rHuPh20 antibody positive at baseline and predose Cycle 5. The remaining 4 patients (1 de-novo and 3 non de-novo) were rHuPH20 antibody positive only at baseline. Of the 9 patients in the IV/SC SID arm, 7 patients (2 de novo, 5 non de-novo) were rHuPh20 antibody positive at baseline and predose Cycle 5. The remaining 2 non de-novo patients were rHuPH20 antibody positive only at baseline.

Of the safety population who received trastuzumab treatment and had post baseline samples available for rHuPH20 antibody testing, 115 patients in the SC SID/IV arm (26 de novo patients, 89 non de novo patients) and 119 IV/SC SID arm (28 de-novo patients, 91 non de-novo patients) were considered evaluable for an antibody response to rHuPH20 (Table 35; Annex 7).

The overall post baseline rHuPH20 antibody rates were 2.6% (3/115) in the SC SID/IV arm and 7.6% (9/119) in the IV/SC SID arm (Table 37; Annex 7). The rates were determined using a conservative approach, which considers all patients who were rHuPH20 antibody positive post baseline regardless of the rHuPH20 antibody results at baseline.

No additional PK samples for immunogenicity analyses were collected following the Primary analysis.

- MO28048 (SafeHER)

As per the primary CSR, there was no discernable impact of trastuzumab ADA or anti-rHuPH20 antibodies on pharmacokinetics or safety (based on ISR or ARR).

The prevalence and treatment emergent incidence of anti-trastuzumab ADA was 3.3% (6/181) and 10.7% (19/178), respectively, with one patient testing positive for neutralizing antibodies at baseline only which is unchanged from the Primary CSR. For anti-rHuPH20 antibodies, the prevalence at baseline was 14.4% (26/181). The incidence of treatment emergent anti-rHuPH20 antibodies using the new definition (**Ref: Section 3.8.1 of final CSR**[4]) was 6.2% (11/178) which is lower than the incidence of 14.6% (26/178) reported in the Primary CSR. The lower difference is due to the exclusion of the 23 treatment-unaffected patients from the calculation of incidence.

There is no change from the Primary CSR on the potential impact of treatment emergent trastuzumab ADA or anti-rHuPH20 antibodies on trastuzumab pharmacokinetics or safety. There remains no discernable impact on pharmacokinetics or safety based on injection site reactions or ARRs.

Severity and nature of risk

Neoadjuvant-adjuvant Treatment in EBC:

- BO22227 (HannaH)

Presented in the Table 22 in Annex 7, are listings of terms from the SC arm of BO22227 that have met Brighton collaboration criteria. There were no Herceptin discontinuations or chemotherapy dosage modifications/discontinuations in response to these events.

rHuPH20

There have been very few potential allergic reactions to hyaluronidase, and none that met the Brighton Collaboration Criteria for an anaphylactic reaction with any diagnostic certainty:

One clinical study has been performed to evaluate the sensitivity of healthy volunteer subjects to a single intradermal dose of HYLENEX versus saline (Yocum 2007). Study R04-0851 was a single-center, double-blind, placebo - and within-subject-controlled study. A total of 100 subjects were injected with 0.1 mL (15 U) of HYLENEX intradermally in the forearm and with 0.1 mL of 0.9% sodium chloride injection USP

[4] MO28048 (SafeHER) CSR Report 1102524

(saline) in the contralateral forearm (control arm). The study population was 75% female and 79% White, and the mean age was 37 ± 13 years (range 18 to 70 years).

No positive allergic reactions (defined as the occurrence of a wheal with pseudopods within 5 minutes of injection that persisted for at least 20 minutes and was accompanied by localized itching) were observed after the HYLENEX product injection.

In addition, in study HZ2-05-04 AEs representing a possible allergic reaction to HYLENEX/rHuPH20 occurred in a single subject following SC injection of 150 U HYLENEX; the subject experienced erythematous rash on the chest and upper back reported to represent a possible allergic reaction to HYLENEX. The AEs resolved within 10 minutes without intervention. There was no dyspnea, wheezing or pruritus, and no change in vital signs. These data suggest that the subject may have experienced a self-limited allergic reaction to HYLENEX, without anaphylaxis or anaphylactoid reaction. Serological evaluation was not performed.

In two studies involving hyaluronidase/insulin formulations, the following two adverse reactions were reported:

HALO-117-205: An allergic reaction related to aspart-PH20 occurred in a single subject. The subject experienced mild urticaria at the site of the prandial injection.

HALO-117-206: A possible allergic reaction to lispro-PH20 occurred in a single subject and led to premature withdrawal from the study AEs (moderate increased appetite and flushing). Both subjects were tested for rHuPH20 antibodies and were negative at all time points tested. No allergic reactions to HYLENEX have been reported in the post-marketing database (refer to PBRER 2020 report number 1103351).

Seriousness/ outcomes

Neoadjuvant-adjuvant Treatment in EBC

- BO22227 (HannaH)

At the time of final analysis, all patients in the safety population who received Herceptin treatment and had post-baseline samples available for trastuzumab anti-drug antibody (ADA) testing (296 patients in the Herceptin IV arm and 295 patients in the Herceptin SC arm) were considered evaluable for an ADA response to trastuzumab (Table 33; Annex 7).

Of these evaluable patients, a total of 33 patients in the Herceptin IV arm and 53 patients in the Herceptin SC arm had at least one anti-trastuzumab ADA positive post-baseline result (during treatment or in the treatment-free follow-up phase). Using a conservative approach, which considers all patients who were ADA positive post-baseline regardless of the trastuzumab ADA result at baseline, the overall trastuzumab ADA rate was 11.1% (33/296) in the Herceptin IV arm and 18.0% (53/295)

in the Herceptin SC arm (Table 33; Annex 7). Neutralizing anti-trastuzumab antibodies (Nabs) were detected in post-baseline (treatment-free) samples from 2 patients in the IV arm and 4 patients in the SC arm.

Using the new definition which includes only treatment-induced and treatment-enhanced patients in the determination of ADA incidence, the overall incidence of anti-trastuzumab antibodies was 10.1% (30/296) in the Herceptin IV arm and 15.9% (47/295) in the Herceptin SC arm (Table 34, Annex 7). Neutralizing anti-trastuzumab antibodies (NAbs) were detected in post-baseline (treatment-free) samples from 2 patients (1 treatment-induced ADA and 1 treatment-enhanced ADA) in the Herceptin IV arm and 3 treatment-induced ADA patients in the Herceptin SC arm. One patient in the SC arm tested positive for NAbs according to the previous definition but was classified as treatment-unaffected ADA, thus reducing the number of patients with NAbs by 1.

In the SC arm, the mean trastuzumab concentrations at both Cycles 8 and 13 were comparable between Nab-negative and Nab-positive patients. In the IV arm, the mean trastuzumab concentration in Nab-positive patients was numerically lower than the mean concentration in Nab-negative patients. However, the concentrations were within the range of concentrations observed in Nab-negative patients. Given the very low number of Nab-positive samples, a definitive conclusion on the effect of neutralizing anti-trastuzumab antibodies on pharmacokinetics cannot be drawn.

The overall immunogenicity rate for anti-rHuPH20 antibodies was 23.7 % (70/295 patients) in the Herceptin SC arm had at least one anti-rHuPH20 antibody positive post-baseline result (during treatment or in the treatment free follow-up phase).

Using a conservative approach, which considers all patients who were anti-rHuPH20 antibody positive post-baseline regardless of the anti rHuPH20 antibody result at baseline, the overall anti-rHuPH20 antibody rate in the Herceptin SC arm was 23.7% (70/295). Neutralizing anti-rHuPH20 antibodies were not detected in any of the patients in the SC arm at any time during the study.

Using the new definition which includes only treatment-induced and treatment-enhanced patients in the determination of anti-rHuPH20 antibody incidence, the overall incidence of anti-rHuPH20 antibodies was 21.0% (62/295) (Table 36, Annex 7). The difference in the overall incidence is due to the exclusion of 9 treatment-unaffected patients that did not have a 4-fold increase in titer post-baseline from their baseline titer or where all post-baseline results were negative, irrespective of the response at baseline.

Nine of 295 evaluable patients (3.1%) treated with Herceptin SC had antibodies to both trastuzumab and rHuPH20.

Neutralizing anti-trastuzumab antibodies (NAbs) were detected in post-baseline samples from 2 patients in the Herceptin IV arm and 4 patients in the Herceptin SC arm.

Impact on individual patient

Exploratory analyses from the HannaH study showed that the occurrence of anti-trastuzumab or anti-rHuPH20 antibodies did not appear to have any clinical consequences with respect to efficacy, safety, or pharmacokinetics.

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not develop anti-therapeutic antibodies. However, current professional labeling indicates that patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions. These patients should not be treated with Herceptin.

Preventability:

Not applicable

Impact on the benefit-risk balance of the product:

The final analysis from study BO22227 (HannaH) confirmed that no correlation has been identified between the trastuzumab ADA status and trastuzumab pharmacokinetics, efficacy, or safety. The benefit-risk profile of Herceptin remains unchanged.

Public health impact:

None

1.8 SHORT-TERM SAFETY OF HERCEPTIN SC COMPARED TO HERCEPTIN IV

MedDRA terms:

Comparison of all AEs from post-marketing source with a latency of onset ≤1 year from first dose of Herceptin at the level of SOC was performed.

Potential mechanisms:

Higher absolute dose intensity of Herceptin SC versus Herceptin IV.

Evidence source(s) and strength of evidence:

Studies BO22227 (HannaH), MO22982 (PrefHER), MO28048 (SafeHER) and Global Safety Database.

Characterization of the risk:

Frequency with 95% CI: Not available

Severity and nature of risk

- BO22227 (HannaH)

At the time of final analysis, the incidence of severe (Grade ≥3) AEs was comparable between treatment arms (53.7% [160/298] in the Herceptin IV arm and 53.2% [158/297] in the Herceptin SC arm).

- MO22982 (PrefHER)

Results from crossover period SC-IV or IV-SC (N=479).

All SAEs were considered unrelated to the treatment with Herceptin and the majority for both Herceptin IV and SC were Grade 3 AE's.

Any differences in AE rates between Herceptin IV and Herceptin SC were due to Grade 1 or 2 AEs – primarily ISRs - and were not clinically relevant.

- MO28048 (SafeHER)

Five Grade 5 AEs (death) were reported during the treatment period in Cohort A.

Overall, 67 patients (2.6%) reported 74 Grade 4 (life-threatening) AEs (52 patients [2.8%] with 59 events in Cohort A (Herceptin SC Vial applied with a handheld syringe) and 15 [2.1%] with 15 events in Cohort B (Herceptin SC applied with an SID)). Most of the Grade 4 AEs were blood and lymphatic system disorders (reported in 46 patients [1.8%], with neutropenia in 24 patients [0.9%] and febrile neutropenia in 18 [0.7%]).

A similar pattern was observed in the case of Grade 3 AEs (severe), with 21.5% patients overall (22.3% in Cohort A and 19.2% in Cohort B) reporting this grade of AE. Thus, the most frequently reported SOC was blood and lymphatic system disorders (145 patients [5.6%] with 203 events). Other frequently reported SOCs with Grade 3 AEs were gastrointestinal disorders (74 patients [2.9%] with 96 events), vascular disorders (69 patients [2.7%] with 88 events), and infections and infestations (69 patients [2.7%] with 81 events). The most frequently reported individual Grade 3 events were neutropenia and febrile neutropenia (69 patients [2.7%] and 43 patients [1.7%], respectively).

Seriousness/outcomes:

<u>Neoadjuvant-adjuvant Treatment in Early Breast Cancer:</u>

- BO22227 (HannaH)

Overall, there were 15.1% (45/298) of patients in the Herceptin IV arm who experienced an SAE compared with 21.9% (65/297) in the Herceptin SC arm. During the treatment-free follow-up phase, the SAE incidence rates were low in both treatment arms (5/298 patients [1.7%] in the Herceptin IV arm and 2/297 patients [0.7%] in the

Herceptin SC arm had experienced seven SAEs in total). The difference between treatment arms driven by an imbalance during the treatment period is described in the Update CSR (Report No. 1057070, September 2013). No other pattern in types of events, affected SOCs, or latency accounted for the imbalance.

Nine fatal AEs were reported and four occurred during the neoadjuvant treatment phase (acute pneumonia in the Herceptin IV arm and myocardial infarction, sudden death, and septic shock in the Herceptin SC arm). The remaining 5 patients died due to reportable AEs that occurred during the treatment-free follow-up phase (4 in the Herceptin IV treatment arm 1 with Grade 3 myeloid leukemia leading to death of patient, death due to an unknown cause, Grade 5 myocardial infarction leading to death on the same day and emphysema leading to the death of the patient on the same day; in the Herceptin SC treatment arm there was 1 case due to Grade 3 endometrial cancer). Refer to Section 1.7 for immunogenicity data from Study BO22227.

- MO22982 (PrefHER)

Results from crossover period SC-IV or IV-SC (479 patients Herceptin SC and 478 patients received Herceptin IV). The total number of AEs was higher with Herceptin SC (300/479 [62.6%] of patients reported 913 AEs) compared with Herceptin IV (258/478 [54.0%] of patients reported 581 AEs). The difference is mainly due to the occurrence of Injection Site Reactions which is specific for the SC phase. After excluding the 186 ISRs the rate of AE's is similar for both Herceptin IV and SC (57.4% versus. 54.0%). Refer to Table 39 (Annex 7).

The number of SAE during the crossover period was low and balanced between Herceptin IV and Herceptin SC: 4 for SC and 5 for IV were reported. All SAEs were considered unrelated to the treatment with Herceptin and the majority were grade 3 AEs. No deaths occurred. Refer to Table 40 (Annex 7).

- MO28048 (SafeHER)

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for Herceptin IV and SC. Please refer to Table 42 (Annex 7).

Global Safety Database

The following assessment is based on the number of AEs, SAEs, and fatal events, reported in the global safety database (cut-off date of 31 August 2017) as a proportion of the total events reported (Refer to Table 43 (Annex 7).

For the majority of SOCs, the number of AEs for Herceptin SC is less than the number of AEs for Herceptin IV. A higher percentage (≤ 1%) of AEs, SAEs, or both, were reported for the following SOCs for Herceptin SC compared to Herceptin IV:

General disorders and administration site conditions:

A comparable percentage of overall AEs with trastuzumab SC versus trastuzumab IV (19.8% versus. 17.3%), however, SAEs were reported with similar frequency with both trastuzumab SC and trastuzumab IV (13.3% versus. 13.8%).

Infections and Infestations:

A comparable percentage of overall AEs and SAEs, respectively with trastuzumab SC versus. trastuzumab IV (6.1% versus. 4.5%) and (7.6% versus. 5.6%).

Musculoskeletal and connective tissue disorders:

A higher percentage of overall AEs and SAEs, respectively with trastuzumab SC versus. trastuzumab IV (11.9% versus. 6.4%) and (6.1% versus. 2.8%).

Skin and subcutaneous tissue disorders:

A comparable percentage of overall AEs with trastuzumab SC versus trastuzumab IV (9.9% versus. 8.9%), however, SAEs were reported less frequently with trastuzumab SC versus trastuzumab IV (3.3% versus. 4.6%).

Impact on individual patient:

Herceptin SC is injected as a fixed dose formulation (600 mg), this may potentially lead to relative overdose in patients with low body mass index and may thence have propensity for increased adverse effects. Currently, the data suggesting direct impact on individual patient is limited.

Risk factors and risk groups:

Patients receiving the higher absolute dose intensity of Herceptin SC

Preventability:

Not applicable

Impact on the benefit-risk balance of the product:

The review of the latest available data did not lead to any change in the benefit-risk profile of Herceptin.

Public health impact:

None

SVII.3.2. Presentation of the Missing Information

1 Long-term safety of Herceptin SC compared to Herceptin IV

Evidence source:

Patient treated with the Herceptin SC receive a higher cumulative dose of Herceptin compared to Herceptin IV. At the time of Herceptin SC extension application, the

evidence if this higher cumulative dose could lead to more adverse effects was limited and was expected to be observed with longer follow-up.

Long-term safety of Herceptin SC compared to Herceptin IV was evaluated from the long-term safety follow-up for Study BO22227 (HannaH) and Study MO28048 (SafeHER). Patients were followed for 5 years post treatment and underwent echocardiogram (ECHO) or multi gated acquisition scan (MUGA) scans every 6 months until the 2-year timepoint, then yearly until the 5-year timepoint. Study BO22227 and Study MO28048 (SafeHER) 5 year follow up data and final CSRs are now available.

The overall safety profile of Herceptin SC continues to be consistent with the known safety profile for Herceptin IV. A limited number of new AEs/SAEs/Cardiac AEs were observed during the 5-year follow-up period and no new safety signals were observed. During the follow up phase, although a greater proportion of patients in the highest weight quartile experienced SAEs compared to patients in the lower weight quartiles, these patients in the highest weight quartile also had greater proportions of active medical conditions at baseline compared to patients in the lower weight quartiles.

- BO22227 (HannaH)

Long-term safety of Herceptin SC and the safety profile of the proportionally higher dose of Herceptin SC in lower weight patients (fixed dose of 600 mg Herceptin SC irrespective of the patient's body weight) was considered to be important missing information.

This was evaluated from the long-term safety follow-up for Study BO22227 (HannaH). Patients were followed for 5 years post treatment and underwent ECHO or MUGA scans every 6 months until the 2-year time-point, then yearly until the 5 year time-point. The 5-year follow-up data as presented in the Final CSR provided the long-term data (data collected after median follow-up of 71 months). The overall safety profile of Herceptin SC continues to be consistent with the known safety profile for Herceptin IV. No new safety signals were observed, and similar incidences of all AEs were observed in the lower weight patient quartiles in the Herceptin SC treatment arm compared with the Herceptin IV treatment arm.

2 Safety of Docetaxel 75 mg/m^2 versus 100 mg/m^2

Evidence source:

In trials with Herceptin SC in early breast cancer, concomitant docetaxel was administered at 75 mg/m^2 compared to 100 mg/m^2 with Herceptin IV.

Study BO22227 included concomitant usage of Herceptin with docetaxel 75 mg/m^2; therefore, the concomitant use of Herceptin with docetaxel 100 mg/m^2 is considered to be missing information. The MAH committed to present an annual analysis of the safety profile of Herceptin when used concomitantly with docetaxel 75 mg/m^2 versus usage

with docetaxel 100 mg/m^2 within scheduled PSURs. The first analysis was submitted to regulatory authorities in 2014.

The Study BO22227 (HannaH) was completed and the data from final study results concluded that the overall safety profile of Herceptin in combination with docetaxel 75 mg/m^2 continues to be consistent with the known safety profile. No new safety signals were observed.

The data from the Roche Global safety database was reviewed to compare the safety of Herceptin + docetaxel 75 mg/m^2 and Herceptin+docetaxel 100 mg/m^2. A meaningful comparison between the two dosing regimens of docetaxel with the SC Herceptin formulation for breast cancer is impacted by the small number of reported cases, especially with the 100 mg/m^2 regimen.

The MAH does not have access to the data regarding exposure to the two different docetaxel regimens: the increase in docetaxel dosage from 75 mg/m^2 to 100 mg/m^2 is at prescribers' discretion and may vary across clinical practice. The lower reporting proportion of cases with the 100mg/m^2 regimen is suggestive that the use of this regimen is too limited to support further analysis or provide any conclusive evidence.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 43 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Administration-Related Reactions • Oligohydramnios
Important potential risks	• Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC • Short term safety of Herceptin SC compared to Herceptin IV
Missing information	• Long term safety of Herceptin SC compared to Herceptin IV • Safety of 75mg/m^2 vs 100mg/m^2 docetaxel dose

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires (guided questionnaires):

- Pregnancy related adverse events (Oligohydramnios):

  The purpose of these guided questionnaire is to collect information on pregnancies and pregnancy outcomes. Please see Annex 4 of the RMP for details.

  The global enhanced PV pregnancy program is effective and being implemented globally including the E.U., since 1 January 2015 for the identified risk of oligohydramnios.

- Medication Error

  For Herceptin: IV administration of SC formulation or SC administration of IV formulation

  It is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not another trastuzumab-containing product (e.g., trastuzumab emtansine or trastuzumab deruxtecan). Please see Annex 4 of the RMP for details.

Other forms of routine pharmacovigilance activities:

Safety of 75 mg/m^2 versus 100 mg/m^2 docetaxel dose: Annual review and analysis of data from the global safety database for submission with the PBRER/PSUR.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 44 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance				
NA	NA	NA	NA	NA

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

IV.1 PLANNED AND ONGOING POST-AUTHORIZATION IMPOSED EFFICACY STUDIES THAT ARE CONDITIONS OF THE MARKETING AUTHORISATION OR THAT ARE SPECIFIC OBLIGATIONS

Not applicable. Herceptin is advanced in clinical development. No post authorization efficacy studies are planned or needed to investigate efficacy in the target population.

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

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 45 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Administration-related reactions	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.

Safety concern	Routine risk minimization activities
Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Short term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
Long term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.

Safety concern	Routine risk minimization activities
Safety of docetaxel 75 mg/m^2 versus 100 mg/m^2	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine.
LVEF=left ventricular ejection fraction; SmPC=summary of product characteristics;	

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

None

Rationale for proposing to remove additional risk minimization measures

Direct Health Care Professional Communication (DHCP) for increased risk of cardiac dysfunction has been removed as additional risk minimization measure considering a report of the survey findings was submitted to the EMA in January 2018 and was assessed by PRAC under PAM procedure EMEA/H/C/000278/LEG100. Confirmation of CHMP adoption of PAM fulfilment was issued on 29 April 2018.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 46 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. **Additional risk minimization measures:** None	
Administration-Related Reactions (ARRs)	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information**: Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** (Guided questionnaire for pregnancy related adverse events)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	specific clinical measures to address the risk: If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None	Please see Annex 4 of the RMP for details Global enhanced PV pregnancy program is effective and being implemented globally including the EU, since 1 January 2015 for the identified risk of oligohydramnios **Additional pharmacovigilance activities:** None
Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous (SC vial) E.U. SmPC) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial **Legal Status:** Herceptin is a prescription only medicine. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Short term safety of Herceptin SC	**Routine risk communication:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimization measures	Pharmacovigilance activities
compared to Herceptin IV	SmPC Section 4.8 Undesirable effects (Subcutaneous (SC vial) E.U. SmPC) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial **Legal Status:** Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**signal detection:** None **Additional pharmacovigilance activities:** None
Long term safety of Herceptin SC compared to Herceptin IV	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous (SC vial) E.U. SmPC) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial **Legal Status:** Herceptin is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety of 75mg/m^2 v 100mg/m^2 docetaxel dose	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration **Routine risk minimization activities recommending**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None	

ADA=anti-drug antibody; ADS=annual data summary; EMA= European Medicines Agency; FDA=Food and Drug Administration; LVEF=left ventricular ejection fraction; rHuPH20= recombinant human hyaluronidase PH20; RMP=risk management plan; SC= subcutaneous; SmPC=summary of product characteristics.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR HERCEPTIN

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

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

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

Important new concerns or changes to the current ones will be included in updates of Herceptin® RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Herceptin® is authorized for metastatic breast cancer (MBC), early breast cancer (EBC) and metastatic gastric cancer (MGC) (see SmPC for the full indication). It contains trastuzumab as the active substance and it is given by intravenous and subcutaneous.

Further information about the evaluation of Herceptin® benefits can be found in Herceptin® EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000278/human_med_000818.jsp&mid=WC0b01ac058001d124

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

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

In the case of Herceptin®, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed: including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

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

List of important risks and missing information	
Important identified risks	Cardiac dysfunction Administration-Related Reactions (ARRs) Oligohydramnios
Important potential risks	Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC Short term safety of Herceptin SC compared to Herceptin IV
Missing information	Long term safety of Herceptin SC compared to Herceptin IV Safety of 75mg/m^2 vs 100mg/m^2 docetaxel dose

II.B Summary of Important Risks

Important Identified Risk	
Cardiac dysfunction	
Evidence for linking the risk to the medicine	MBC: M77001 and BO16216. EBC: Joint Analysis (NSABP B-31 and NCCTG N9831), BCIRG 006 (H2296s)/GO00773, BO16348, MO16432, BO22227, MO22982, MO28048 GC: BO18255. QTc-study H4613g (HerQLes). Global Safety Database
Risk factors and risk groups	Patient with Early Breast Cancer (EBC)
Risk minimization measures	**Routine risk communication:** SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Identified Risk	
Administration-Related Reactions (ARRs)	
Evidence for linking the risk to the medicine	EBC: Studies BO16348, BO22227, MO22982, and MO28048. Global Safety Database. Drug Safety Reports, DSR 1036301 dated 12 December 2009, DSR 1056779 dated 27 June 2013 and DSR 1060413 dated 15 May 2014
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to administration related reactions to Herceptin. However, the SPC indicates that patients, who are experiencing dyspnea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimization measures beyond the Product Information**: Pack Size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. *Additional risk minimization measures:* No risk minimization measures
Additional pharmacovigilance activities	There are no additional pharmacovigilance activities

Important Identified Risk	
Oligohydramnios	
Evidence for linking the risk to the medicine	Global Safety Database, Drug safety reports #1030381, 1040470 and 10156279. Pregnancy registry MotHER [H4621g/GE28099 is closed].
Risk factors and risk groups	There are no reliable indicators of patients who may or may not be at risk
Risk minimization measures	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Herceptin or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of E.U. SmPC. **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine *Additional risk minimization measures:* No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Potential Risk	
Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC	
Evidence for linking the risk to the medicine	BO22227 (HannaH), MO22982 (PrefHER) and Halozyme clinical trials.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not develop anti-therapeutic antibodies. However, current professional labelling indicates that patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions. These patients should not be treated with Herceptin.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. *Additional risk minimization measures:* No risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Potential Risk	
Short term safety of Herceptin SC compared to Herceptin IV	
Evidence for linking the risk to the medicine	Studies BO22227, MO22982,MO28048 (SafeHER) and Global Safety Database
Risk factors and risk groups	Patients receiving the higher absolute dose intensity of Herceptin SC.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. Additional risk minimization measures: No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Missing Information	
Long term safety of Herceptin SC compared to Herceptin IV	
Evidence for linking the risk to the medicine	Patient treated with the Herceptin SC receive a higher cumulative dose of Herceptin compared to Herceptin IV. It is not yet known whether this higher cumulative dose may lead to more adverse effects which can only be observed after a longer follow-up.
Risk factors and risk groups	As above
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 Undesirable effects (Subcutaneous vial) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. Additional risk minimization measures: No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Missing Information	
Safety of 75mg/m^2 v 100mg/m^2 docetaxel dose	
Evidence for linking the risk to the medicine	In trials with Herceptin SC in early breast cancer, concomitant docetaxel was administered at 75 mg/m^2 compared to 100 mg/m^2 with Herceptin IV.
Risk factors and risk groups	As above
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Pack size:** Each carton contains one vial Legal Status: Herceptin is a prescription only medicine. Additional risk minimization measures: No risk minimization measures
Additional pharmacovigilance activities	None

II.C Post-Authorization Development Plan

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

Not applicable.

II.C.2 Other Studies in Post-Authorization Development Plan

Not Applicable

ANNEX 1:

EUDRAVIGILANCE INTERFACE

ANNEX 1 – EUDRAVIGILANCE INTERFACE

Available in electronic format only

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

1. Guided Questionnaire for pregnancy related adverse events
2. Guided Questionnaire for Medication Errors

Guided Questionnaire
Pregnancy-Related Adverse Events

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Other Patient Identifiers	
Patient Gender:	❑ M ❑ F		

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with Herceptin in the post-marketing setting. Oligohydramnios has been identified as an important identified risk for Herceptin, while for Perjeta and Kadcyla, oligohydramnios has been classified as an important potential risk.

By filling out this questionnaire, you will help us to understand more fully the risk factors for this condition and associated abnormalities, to communicate potential adverse pregnancy complications and fetal/infant outcomes to Health Authorities, Healthcare Professionals and patients.

Reporter Information	
Name of reporter completing this form ***(if other than addressee, please provide contact information below)*:**	
Health Care Provider? ❑ Yes ❑ No - Please Specify:	
Phone number:	Fax number:
Email address:	

☐ Drug: **Herceptin** Lot Number(s):_____
☐ Drug: **Perjeta** Lot Number(s):_____
☐ Drug: **Kadcyla** Lot Number(s):_____

Maternal Information

	Selected Medical History			Comment
☐	None	☐	Unknown	
☐	Hypertension			
☐	Diabetes; if yes, specify type			
☐	Seizure disorders			
☐	Thyroid disorder			
☐	Smoking / use of alcohol; specify			
☐	Family history of diabetes mellitus			
☐	Family history of congenital renal anomalies; if yes, specify			
☐	Other; specify			

	Selected Obstetric History (*previous pregnancies*)			Please, provide specifics including contributing factors
☐	None	☐	Unknown	
☐	Gestational hypertension/preeclampsia/eclampsia			
☐	Gestational diabetes			
☐	Spontaneous or induced abortions; if yes/known, specify cause			

☐	Oligohydramnios	
☐	History of other pregnancy complications; specify	
☐	Other; specify	
	Fetal Abnormalities in Previous Pregnancies	Please, provide specifics including contributing factors
☐	None ☐ Unknown	
☐	Delayed renal development	
☐	Death in utero; if yes/known, specify reason	
☐	Birth defects; if yes, specify	
☐	Family history of birth defects; if yes, specify	
☐	Other; specify	

Current Pregnancy

Pre-pregnancy weight and height	**Weight:**	Height:
Blood pressure prior to conception	Date:	BP:

Prenatal Imaging and Anauploidy Screening/tasting (e.g., ultrasound, amniocentesis, etc.)

Was a prenatal test performed? ☐ Yes ☐ No

If yes, Prenatal Test Type	Date	Indication for test	Was a defect noted?	Specify

Ultrasound Assessment Log

Date	Gestational Age	Amniotic Fluid (AF) Measurement	Provider's Assessment of AF	Estimated Fetal Weight	Reported Percentile Growth	Provider's Assessment of Growth
	_____ weeks	AF Index _____ cm Maximum Vertical Pocket _____ cm Other _____ □ AF not measured	1 Normal 2 Abnormal 3 Oligohydramnios 4 Anhydramnios 5 Polyhydramnios 6 Delayed renal development 7 Other: _____ 8 Not assessed	_____ grams ☐ Not estimated	_____ ☐ Not reported ☐ Growth not measured	☐ Normal ☐ Abnormal ☐ IUGR* (< 10%ile) ☐ Severe IUGR (< 3%ile) ☐ Large for Gestational Age (> 90%ile) ☐ Growth not measured

* IUGR=Intrauterine growth retardation

Concomitant Medications, including ACE inhibitors and prostaglandin synthase inhibitors and all known teratogens up to 6 months prior to conception or during pregnancy:				
Product Name	**Indication**	**Total daily dose**	**Start date**	**Stop date/Ongoing**

	Maternal Medical Conditions During Current Pregnancy *Please check all that apply and provide detailed information on pregnancy-related complications on last page*			
☐	Gestational Hypertension/ Preeclampsia/Eclampsia ☐ chronic hypertension ☐ pregnancy-induced hypertension ☐ Preeclampsia-eclampsia ☐ Preeclampsia superimposed on chronic hypertension	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Gestational Diabetes	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Spontaneous or induced abortions; if yes/known, specify cause	Pathology results:	Start date / Gestational age	Contributing factors
☐	Chronic leakage of amniotic fluid	Start date / Gestational age		Contributing factors
☐	Other; specify	Pathology results:	Start date / Gestational age	Contributing factors
	Fetal Conditions During Current Pregnancy *Please check all that apply and provide detailed information on fetal complications on last page*			
☐	Renal abnormalities in fetus ☐ Normal fetal kidneys and fluid filled bladder ☐ Delayed renal development ☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction	Diagnostic tests: ☐ Ultrasonography	Start date / Gestational age	Contributing factors
☐	Fetal abnormalities, including genetic disorders; if yes, specify	Diagnostic tests: ☐ Ultrasound ☐ Alpha-fetoprotein ☐ Amniocentesis ☐ Aneuploidy screening ☐ Other	Date / Gest. age	Specify
☐	Post-maturity syndrome	Evidence:	Start date / Gestational age	Contributing factors
☐	Death in utero; if yes/known, specify reason	Pathology results:	Date / Gestational age	Contributing factors
☐	Other; specify			

Infant information

Mode of birth	☐ Spontaneous vaginal delivery ☐ Forceps / vacuum ☐ Cesarean section	Date	
Gestational age at birth		Apgar score	

Please check all that apply and provide detailed information on complications in infants on last page

	Date of Assessment			Contributing factors
☐	Birth outcome	☐ Live birth ☐ Neonatal death	Cause	
☐	Small for gestational age at birth (SGA)	☐ Gestational age ☐ Weight/length	Date of assessment	
☐	Congenital anomalies	☐ Major malformation A defect that has either cosmetic or functional significance to the child	Specify	
		☐ Minor malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify	
		☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify	
		☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify	
☐	Abnormal renal function	☐ Proteinuria ☐ Electrolyte imbalance ☐ Other	Lab results	
☐	Other; specify			

FOR INTERNAL USE ONLY
Company Awareness Date:
MCN:

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

Contact name for further information on pregnancy and/or on the infant:

.....

Function ..... Tel. No.: .....

Contact Address: ..... Fax No.: .....

..... Email: .....

.....

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

Herceptin Guided Questionnaire
Medication Errors

Patient ID/Initials:	
Patient Gender:	❑ M ❑ F
Patient Date of Birth (dd-MMM-yyyy):	
Patient Weight	Kg Lb

AER:	
Site No:	
Local Case ID:	

With the introduction of the Herceptin subcutaneous (SC) formulation and other trastuzumab-containing products, medication errors may occur. It is important to check the drug being prepared and administered is Herceptin (trastuzumab) and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).
By filling in this questionnaire, you will help us to gain an understanding of the types of errors that occur, which would enable preventative measures to be put into place.

Reporter Information	
Name of reporter completing this form **(if other than addressee, provide contact information below):**	
Health Care Provider? ❑ Yes ❑ No-Specify:	
Phone number:	Fax number:
Email address:	

Details of medication error:	
Date of medication error (dd-mmm-yyyy):	Herceptin Start Date (dd-mmm-yyyy):
Herceptin Indication:	Dosage administered:
Product Administered: ❑ Herceptin IV ❑ Herceptin SC ❑ Trastuzumab emtamsine ❑ Trastuzumab deruxtecan Route of Administration: ❑ Intravenous (IV) ❑ Subcutaneous (SC)	

Description of the error (e.g. incorrect route, incorrect dose or overdose, accidental exposure, wrong technique in drug usage process, drug administration error etc.)

Herceptin (trastuzumab) Treatment Details

Please provide details of the prescribed or intended treatment details for Herceptin	
Herceptin Indication:	
Start Date (dd-mmm-yyyy):	End Date (if applicable: dd-mmm-yyyy):
Treatment dosage:	❑ 3-weekly ❑ weekly
Formulation prescribed: ❑ Herceptin IV	❑ Herceptin SC

Adverse Events (as a result of the medication error)

Adverse Event	Onset Date (dd-mmm-yyyy)	Event Outcome (date if applicable: dd-mmm-yyyy)
1.		
2.		
3.		
4.		

Relevant Medical History and Clinical Conditions

Concurrent/Previous Anti-neoplastic Drug Information

Drug name Generic/Trade	Start Date (dd-mmm-yyyy):	Stop Date (dd-mmm-yyyy):	On going
			❑ Yes
			❑ Yes
			❑ Yes

Other Concomitant Medications			
Drug name Generic/Trade	Start Date (dd-mmm-yyyy):	Stop Date (dd-mmm-yyyy):	On going
			❑ Yes
			❑ Yes
			❑ Yes

Relevant Laboratory Tests/Diagnostic Data						
Test	Baseline (pre-event onset)		At Event Onset		Following Event Resolution	
	Date (dd-mmm-yyyy):	Results	Date (dd-mmm-yyyy):	Results	Date (dd-mmm-yyyy):	Results

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

NOT APPLICABLE

ANNEX 7:

OTHER SUPPORTING DATA

(INCLUDING REFERENCED MATERIAL)

ANNEX 7: OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

LIST OF PTS FOR IMPORTANT IDENTIFIED RISKS

1) CARDIAC DYSFUNCTION

Cardiac Failure (SMQ)-Wide

Acute left ventricular failure
Acute pulmonary oedema
Acute right ventricular failure
Artificial heart implant
Atrial natriuretic peptide abnormal
Atrial natriuretic peptide increased
Bendopnoea
Brain natriuretic peptide abnormal
Brain natriuretic peptide increased
Cardiac asthma
Cardiac cirrhosis
Cardiac contractility modulation therapy
Cardiac dysfunction
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output
Cardiac index decreased
Cardiac output decreased
Cardiac resynchronisation therapy
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal
Cardiac ventriculogram right abnormal
Cardio-respiratory distress

Cardiogenic shock
Cardiomegaly
Cardiopulmonary failure
Cardiorenal syndrome
Cardiothoracic ratio increased
Central venous pressure increased
Chronic left ventricular failure
Chronic right ventricular failure
Cor pulmonale
Cor pulmonale acute
Cor pulmonale chronic
Diastolic dysfunction
Dilatation ventricular
Dyspnoea paroxysmal nocturnal
Ejection fraction decreased
Heart transplant
Hepatic congestion
Hepatic vein dilatation
Hepatojugular reflux
Intracardiac pressure increased
Jugular vein distension
Left ventricular diastolic collapse
Left ventricular dilatation
Left ventricular dysfunction
Left ventricular enlargement

Left ventricular failure

Low cardiac output syndrome

Lower respiratory tract congestion

Myocardial depression

N-terminal prohormone brain natriuretic peptide abnormal

N-terminal prohormone brain natriuretic peptide increased

Neonatal cardiac failure

Nocturnal dyspnoea

Obstructive shock

Oedema

Oedema blister

Oedema due to cardiac disease

Oedema neonatal

Oedema peripheral

Orthopnoea

Peripheral oedema neonatal

Peripheral swelling

Post cardiac arrest syndrome

Prohormone brain natriuretic peptide abnormal

Prohormone brain natriuretic peptide increased

Pulmonary congestion

Pulmonary oedema

Pulmonary oedema neonatal

Radiation associated cardiac failure
Right ventricular diastolic collapse
Right ventricular dilatation
Right ventricular dysfunction
Right ventricular ejection fraction decreased
Right ventricular enlargement
Right ventricular failure
Scan myocardial perfusion abnormal
Stroke volume decreased
Surgical ventricular restoration
Systolic dysfunction
Venous pressure increased
Venous pressure jugular abnormal
Venous pressure jugular increased
Ventricular assist device insertion
Ventricular compliance decreased
Ventricular dysfunction
Ventricular dyssynchrony
Ventricular failure
Wall motion score index abnormal

2) ADMINISTRATION-RELATED REACTIONS

MedDRA terms: 'Modified Anaphylactic Reaction basket', which consists of the Anaphylactic Reaction SMQ plus the individual PTs:

Infusion-Related Reaction; and Injection Site Hypersensitivity, Hypersensitivity and drug hypersensitivity.

Herceptin-Specific AEGT-Anaphylaxis+IRR

Acquired C1 inhibitor deficiency
Acute respiratory failure
Allergic oedema
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Asthma
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Bronchial oedema
Bronchospasm
Cardiac arrest
Cardio-respiratory arrest
Cardio-respiratory distress
Cardiovascular insufficiency
Chest discomfort
Choking
Choking sensation
Circulatory collapse
Circumoral oedema
Cough

Cyanosis
Dialysis membrane reaction
Diastolic hypotension
Dyspnoea
Erythema
Eye oedema
Eye pruritus
Eye swelling
Eyelid oedema
Face oedema
Fixed eruption
Flushing
Generalised erythema
Hereditary angioedema with C1 esterase inhibitor deficiency
Hyperventilation
Hypotension
Injection site urticaria
Irregular breathing
Kounis syndrome
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Lip oedema
Lip swelling

Mouth swelling
Nasal obstruction
Nodular rash
Ocular hyperaemia
Oedema
Oedema blister
Oedema mouth
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Periorbital oedema
Pharyngeal oedema
Procedural shock
Pruritus
Pruritus allergic
Pruritus generalised
Rash
Rash erythematous
Rash generalised
Rash pruritic
Respiratory arrest
Respiratory distress
Respiratory dyskinesia
Respiratory failure
Reversible airways obstruction

Sensation of foreign body
Shock
Shock symptom
Skin swelling
Sneezing
Stridor
Swelling
Swelling face
Swollen tongue
Tachypnoea
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Type I hypersensitivity
Upper airway obstruction
Urticaria
Urticaria papular
Wheezing
Hypersensitivity
Drug hypersensitivity
Infusion Related Reaction
Injection Site hypersensitivity

3) OLIGOHYDRAMNIOS

MedDRA Terms: MedDRA High Level Group Term (HLGT): Neonatal and perinatal conditions; and, MedDRA HLT: Amniotic fluid and cavity disorders of pregnancy NEC and following PTs: Amniotic fluid index, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid

index increased, Amniotic fluid volume, Amniotic fluid volume decreased, Amniotic fluid volume increased, Intra-amniotic injection, Vesicoamniotic shunt.

HLGT - Neonatal and perinatal conditions

Abnormal organ growth
Abnormal organ maturation
ABO haemolytic disease of newborn
ABO incompatibility
Adrenal insufficiency neonatal
Adrenocortical insufficiency neonatal
Agitation neonatal
Alloimmunisation
Alveolar capillary dysplasia
Anaemia neonatal
Anaesthetic complication neonatal
Apparent life threatening event
Arrhythmia neonatal
Asymmetric gluteal fold
Atelectasis neonatal
Atrioventricular node dispersion
Benign familial neonatal convulsions
Birth trauma
Blood incompatibility haemolytic anaemia of newborn
Blood loss anaemia neonatal
Blood type incompatibility
Bradycardia neonatal
Breast milk substitute intolerance
Bronchopulmonary dysplasia
Caput succedaneum

Cardiac arrest neonatal
Cardiomyopathy neonatal
Cardio-respiratory arrest neonatal
Central nervous system lymphoma
Cephalhaematoma
Cerebral haemorrhage neonatal
Cerebral palsy
Circulatory failure neonatal
Coagulation disorder neonatal
Collodion baby
Coma neonatal
Congenital chylothorax
Congenital condyloma
Congenital cytomegalovirus infection
Congenital floppy infant
Congenital hepatitis B infection
Congenital herpes simplex infection
Congenital HIV infection
Congenital infection
Congenital malaria
Congenital pneumonia
Congenital pulmonary hypertension
Congenital rubella infection
Congenital syphilis
Congenital syphilitic encephalitis

Congenital syphilitic meningitis
Congenital toxoplasmosis
Congenital tuberculosis
Congenital varicella infection
Congenital Zika syndrome
Conjunctivitis gonococcal neonatal
Convulsion neonatal
Coxsackie viral disease of the newborn
Cranial nerve injury secondary to birth trauma
Cranial sutures widening
Craniotabes
Cronobacter necrotising enterocolitis
Cutaneous extramedullary haemopoiesis
Cyanosis neonatal
Death neonatal
Delayed visual maturation
Diarrhoea infectious neonatal
Diarrhoea neonatal
Disseminated intravascular coagulation in newborn
Disturbance of thermoregulation of newborn
Drug withdrawal syndrome neonatal
Dry lung syndrome
Ductus arteriosus premature closure
Ductus venosus agenesis
Dyskinesia neonatal

Encephalopathy neonatal
Erythema toxicum neonatorum
Erythroblastosis foetalis
Facial nerve injury due to birth trauma
Failure to thrive
Feeding intolerance
Fever neonatal
Fixed bowel loop
Floppy infant
Fontanelle bulging
Fontanelle depressed
Fracture of clavicle due to birth trauma
Funisitis
Gangrene neonatal
Gasping syndrome
Granulocytopenia neonatal
Grey syndrome neonatal
Group B streptococcus neonatal sepsis
Haemolysis neonatal
Haemorrhage neonatal
Haemorrhagic disease of newborn
Harlequin foetus
Harlequin skin reaction
Hepatitis neonatal
Hepatocellular damage neonatal

Hepatosplenomegaly neonatal
Herpes simplex virus conjunctivitis neonatal
Hyperbilirubinaemia neonatal
Hyperglycinaemia
Hyperkinesia neonatal
Hypertension neonatal
Hypertonia neonatal
Hypoglycaemia neonatal
Hypokinesia neonatal
Hypothermia neonatal
Hypotonia neonatal
Hypoventilation neonatal
Immature larynx
Immature respiratory system
Inclusion conjunctivitis neonatal
Infantile apnoea
Infantile back arching
Infantile colic
Infantile spitting up
Infantile vomiting
Injury to brachial plexus due to birth trauma
Injury to spinal cord secondary to birth trauma
Intoxication by breast feeding
Intraventricular haemorrhage neonatal
Isoimmune haemolytic disease

Jaundice neonatal

Junctional ectopic tachycardia

Kernicterus

Large for dates baby

Late metabolic acidosis of newborn

Lenticulostriatal vasculopathy

Leukopenia neonatal

Low birth weight baby

Lymphocytopenia neonatal

Meconium abnormal

Meconium aspiration syndrome

Meconium cyst

Meconium ileus

Meconium increased

Meconium peritonitis

Meconium plug syndrome

Melaena neonatal

Meningitis neonatal

Meningoencephalitis herpes simplex neonatal

Myasthenia gravis neonatal

Necrotising enterocolitis neonatal

Neonatal alloimmune thrombocytopenia

Neonatal alveolar aeration excessive

Neonatal anoxia

Neonatal anuria

Neonatal asphyxia
Neonatal aspiration
Neonatal behavioural syndrome
Neonatal candida infection
Neonatal cardiac failure
Neonatal cholestasis
Neonatal complications of substance abuse
Neonatal deafness
Neonatal diabetes mellitus
Neonatal disorder
Neonatal gastrointestinal disorder
Neonatal gastrointestinal haemorrhage
Neonatal haemochromatosis
Neonatal hepatomegaly
Neonatal hypoacusis
Neonatal hypocalcaemia
Neonatal hyponatraemia
Neonatal hypoparathyroidism
Neonatal hypotension
Neonatal hypoxia
Neonatal infection
Neonatal infective mastitis
Neonatal insufficient breast milk syndrome
Neonatal intestinal dilatation
Neonatal intestinal obstruction

Neonatal intestinal perforation
Neonatal leukaemia
Neonatal lupus erythematosus
Neonatal mucocutaneous herpes simplex
Neonatal multi-organ failure
Neonatal oversedation
Neonatal pneumonia
Neonatal respiratory acidosis
Neonatal respiratory alkalosis
Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory distress
Neonatal respiratory distress syndrome
Neonatal respiratory failure
Neonatal tachycardia
Neonatal tachypnoea
Neonatal testicular torsion
Neonatal tetany
Neonatal thyrotoxicosis
Neonatal toxicity
Netherton's syndrome
Neuroendocrine cell hyperplasia of infancy
Neutropenia neonatal
Newborn head moulding
Oedema neonatal

Omphalitis
Omphalorrhexis
Ophthalmia neonatorum
Overfeeding of infant
Perinatal brain damage
Perinatal HBV infection
Perinatal HIV infection
Perinatal stroke
Peripheral oedema neonatal
Periventricular haemorrhage neonatal
Periventricular leukomalacia
Persistent foetal circulation
Polycythaemia neonatorum
Poor feeding infant
Poor sucking reflex
Poor weight gain neonatal
Posthaemorrhagic hydrocephalus
Postmature baby
Premature baby
Premature baby death
Primary familial hypomagnesaemia
Pulmonary air leakage
Pulmonary dysmaturity syndrome
Pulmonary lymphangiectasia
Pulmonary oedema neonatal

Purpura neonatal
Rash neonatal
Renal failure neonatal
Renal impairment neonatal
Respiratory disorder neonatal
Respiratory tract haemorrhage neonatal
Retinopathy of prematurity
Rhesus haemolytic disease of newborn
Rhesus incompatibility
Sepsis neonatal
Single umbilical artery
Small for dates baby
Somnolence neonatal
Subarachnoid haemorrhage neonatal
Subdural haemorrhage neonatal
Subgaleal haematoma
Subgaleal haemorrhage
Sudden infant death syndrome
Term baby
Tetanus neonatorum
Thrombocytopenia neonatal
Thrombophlebitis neonatal
Transient hypogammaglobulinaemia of infancy
Transient hypothyroxinaemia of prematurity
Transient neonatal pustular melanosis

Transient tachypnoea of the newborn
Tremor neonatal
Umbilical artery hypoplasia
Umbilical cord abnormality
Umbilical cord around neck
Umbilical cord compression
Umbilical cord cyst
Umbilical cord haemorrhage
Umbilical cord occlusion
Umbilical cord prolapse
Umbilical cord short
Umbilical cord thrombosis
Umbilical cord vascular disorder
Umbilical discharge
Umbilical granuloma
Umbilical malformation
Umbilical sepsis
Urinary tract infection neonatal
Venous thrombosis neonatal
Virilism foetal
Vision abnormal neonatal
Weight decrease neonatal
Zika virus associated birth defect
Zika virus associated ocular birth defect

HLT - Amniotic fluid and cavity disorders of pregnancy NEC

Amniorrhexis

Amniorrhoea

Amniotic band syndrome

Amniotic cavity disorder

Amniotic cavity infection

Amniotic infection syndrome of Blane

Meconium in amniotic fluid

Meconium stain

Oligohydramnios

Polyhydramnios

1. CARDIAC DYSFUNCTION

1.1 FREQUENCY WITH 95% CI:

Table 1 Cardiac Dysfunction, Severity, and Frequency – M77001

Treatment: Docetaxel Alone1; N=94					
CTC Grade	**1**	**2**	**3**	**4**	**5**
Cardiotoxicity *	18 (19.1%)	15 (16.0%)	4 (4.3%)	0 (0.0%)	0 (0.0%)
Oedema	2 (2.1%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	16 (17.0%)	15 (16.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Treatment: Docetaxel plus Trastuzumab; N=92					
CTC Grade	**1**	**2**	**3**	**4**	**5**
Cardiotoxicity *	24 (26.1%)	17 (18.5%)	2 (2.2%)	0 (0.0%)	0 (0.0%)
Ejection Fraction Decreased	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Left Ventricular Failure	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema	4 (4.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	21 (22.8%)	15 (16.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pitting Oedema	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1] There were 41 patients originally randomised in docetaxel alone and who switched during the study and received trastuzumab. AEs for these patients were not recorded, therefore the summary is not provided.

* Number of highest CTC grade per patient, estimated on the subset of patients with at least one Cardiac dysfunction related term.

Percentages are based on the total number of patients in treatment group.

Table 2 Cardiac Dysfunction, Severity & Frequency: BO16216

[1]Anastrozole alone; N=104					
CTC Grade	1	2	3	4	5
Cardiotoxicity*	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Anastrozole + Trastuzumab; N=103					
CTC Grade	1	2	3	4	5
Cardiotoxicity*	6 (5.8%)	5 (4.9%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Cardiac Failure	0 (0.0%)	2 (1.9%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Oedema	2 (1.9%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	5 (4.9%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
[2]Anastrozole alone after start of Trastuzumab; N=58					
CTC Grade	1	2	3	4	5
Cardiotoxicity*	3 (5.2%)	5 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac Failure	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ejection Fraction Decreased	2 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oedema Peripheral	1 (1.7%)	3 (5.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

(1) For patients originally randomized in anastrozole alone arm and who switched to trastuzumab, only AEs before the first trastuzumab administration are summarised.

(2) Cross-over patients: anastrozole + trastuzumab after having anastrozole alone until progression of disease.

(*) Number of highest CTC grade per patient, estimated on the subset of patients with at least one Cardiac dysfunction related term.

Note: Percentages are based on the total number of patients in treatment group.

[1]Anastrozole alone; N=104					
CTC Grade	**1**	**2**	**3**	**4**	**5**

Table 3 Cardiac Dysfunction, Severity: BO18255 (Gastric Cancer)

Cardiac Dysfunction , Severity
Safety Evaluable Patients

	Fluoropyrimidine/Cisplatin (n=290)				Trastuzumab/Fluoropyrimidine/Cisplatin (n=294)			
CTC GRADE	1	2	3	4	1	2	3	4
CARDIAC FAILURE	0	0	1	1	0	0	0	1
CARDIAC FAILURE CONGESTIVE	0	0	0	0	0	0	0	1
EJECTION FRACTION DECREASED	0	0	0	0	1	0	1	0
LEFT VENTRICULAR DYSFUNCTION	0	0	0	0	0	1	0	0
OEDEMA	22	4	0	0	22	3	0	0
OEDEMA PERIPHERAL	8	4	1	0	13	4	1	0

Table 4 Cardiac Dysfunction, Frequency: AEs by Patient-Years– BO18255 (Gastric Cancer)

Cardiac Dysfunction, Frequency: AEs by Patient-Years
Safety Evaluable Patients

	Fluoropyrimidine/Cisplatin (n=290)	Trastuzumab/Fluoropyrimidine/Cisplatin (n=294)
Total Patient Years	201.39	287.26
Oedema		
Number of Patients with an Event	26	25
Total Number of Events	28	28
Events per Patient Year	0.14	0.10
Events per 100 Patients Years	13.90	9.75
Oedema Peripheral		
Number of Patients with an Event	13	18
Total Number of Events	15	25
Events per Patient Year	0.07	0.09
Events per 100 Patients Years	7.45	8.70
Cardiac Failure		
Number of Patients with an Event	2	1
Total Number of Events	2	1
Events per Patient Year	0.01	0.00
Events per 100 Patients Years	0.99	0.35
Cardiac Failure Congestive		
Number of Patients with an Event		1
Total Number of Events		1
Events per Patient Year		0.00
Events per 100 Patients Years		0.35
Ejection Fraction Decreased		
Number of Patients with an Event		2
Total Number of Events		2
Events per Patient Year		0.01
Events per 100 Patients Years		0.70

Left Ventricular Dysfunction	
Number of Patients with an Event	1
Total Number of Events	1
Events per Patient Year	0.00
Events per 100 Patients Years	0.35

Table 5 Cardiac Dysfunction, Severity & Frequency: BO22227 IV ARM

stael7cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	56	(19)	43	(14)	16	(5)	-		-		-	
Total Number of AEs	63		47		16		-		-		-	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Total Pts With at Least one AE	43	(14)	37	(12)	7	(2)	-		-		-	
OEDEMA PERIPHERAL	30	(10)	27	(9)	3	(1)	-		-		-	
OEDEMA	15	(5)	12	(4)	3	(1)	-		-		-	
PERIPHERAL SWELLING	3	(1)	2	(<1)	1	(<1)	-		-		-	
Total Number of AEs	48		41		7		-		-		-	
CARDIAC DISORDERS												
Total Pts With at Least one AE	13	(4)	5	(2)	8	(3)	-		-		-	
LEFT VENTRICULAR DYSFUNCTION	12	(4)	4	(1)	8	(3)	-		-		-	
CARDIAC FAILURE	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	13		5		8		-		-		-	
INVESTIGATIONS												
Total Pts With at Least one AE	1	(<1)	-		1	(<1)	-		-		-	
EJECTION FRACTION DECREASED	1	(<1)	-		1	(<1)	-		-		-	
Total Number of AEs	1		-		1		-		-		-	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS												
Total Pts With at Least one AE	1	(<1)	1	(<1)	-		-		-		-	
NOCTURNAL DYSPNOEA	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	1		1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE17 03MAY2017:22:22:16 (1 of 2)

Table 6 Cardiac Dysfunction, Severity & Frequency: BO22227 SC ARM

stael7cf_se Summary of CTC Grading (Worst Case) for Cardiac Failure - SMQ Broad (SMQ) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS											
Total Pts with at Least one AE	47	(16)	38	(13)	7	(2)	3	(1)	-		-	
Total Number of AEs	52		41		7		4		-		-	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS											
Total Pts With at Least one AE	33	(11)	31	(10)	2	(<1)	-		-		-	
OEDEMA PERIPHERAL	23	(8)	22	(7)	1	(<1)	-		-		-	
OEDEMA	10	(3)	9	(3)	1	(<1)	-		-		-	
PERIPHERAL SWELLING	3	(1)	3	(1)	-		-		-		-	
Total Number of AEs	36		34		2		-		-		-	
CARDIAC DISORDERS											
Total Pts With at Least one AE	15	(5)	7	(2)	5	(2)	3	(1)	-		-	
LEFT VENTRICULAR DYSFUNCTION	10	(3)	4	(1)	5	(2)	1	(<1)	-		-	
CARDIAC FAILURE CONGESTIVE	2	(<1)	-		-		2	(<1)	-		-	
CARDIAC FAILURE	1	(<1)	-		-		1	(<1)	-		-	
DIASTOLIC DYSFUNCTION	1	(<1)	1	(<1)	-		-		-		-	
LEFT VENTRICULAR DILATATION	1	(<1)	1	(<1)	-		-		-		-	
RIGHT VENTRICULAR FAILURE	1	(<1)	1	(<1)	-		-		-		-	
Total Number of AEs	16		7		5		4		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE17 03MAY2017:22:22:16 (2 of 2)

1.2 SERIOUSNESS/ OUTCOMES:

Clinical Studies: Metastatic Breast Cancer:

- **M77001**

The action taken with study medications docetaxel and trastuzumab in response to each AE in both study arms were as follows: docetaxel alone arm (total AEs 53); none taken (43), dosage modified (2) and discontinued (8); docetaxel plus trastuzumab arm (total AEs 63); none taken (57), dosage modified (2) and discontinued (4). The dose of docetaxel used in this study was 100 mg/m^2 IV on study Day 2; followed by docetaxel 100 mg/m^2 IV every 3 weeks.

Across the two treatment arms, cardiac AEs were mainly mild to moderate in severity: docetaxel alone arm – mild 18, moderate 15, and severe 4; docetaxel plus trastuzumab arm – mild 24, moderate 18, and severe 2 (NB; individual patients may have experienced the same cardiac AE on more than one occasion and captured here is the worst case intensity occurrence, therefore the number of AEs assigned severity values does not necessarily match the total number of AEs).

Outcomes at AE level by treatment arm

Overall, in each of the treatment arms, the percentage of outcomes expressed as a total of the number of AEs were as follows: docetaxel alone arm (total AEs 53) – resolved 36, persisting 16, and fatal 1; docetaxel plus trastuzumab arm (total AEs 63) – resolved 51, resolved with sequelae 1, and persisting 11.

- **BO16216**

The action taken with study medications anastrozole and trastuzumab in response to each AE in all three study arms were as follows: anastrozole alone arm (total AEs 4) – none taken; anastrozole plus trastuzumab arm (total AEs 16) – none taken (11), dosage modified (3) and discontinued (2); anastrozole alone after start of trastuzumab arm (total AEs 10) – none taken (4), dosage modified (2) and discontinued (4). No cardiac deaths were reported.

Outcomes at AE level by treatment arm

Overall, in each of the treatment arms, the outcomes at AE level were as follows: anastrozole alone arm (total AEs 4) – resolved 2 and persisting 2; anastrozole plus trastuzumab arm (total AEs 16) – resolved 11 and persisting 5; anastrozole alone after start of trastuzumab arm (total AEs 10) – resolved 3 and persisting 7.

Early Breast Cancer (EBC)

Adjuvant Treatment in EBC

- **BCIRG-006 (H2296s)/GO00773)**

Please refer to Table 7, which summarizes symptomatic cardiac events reported at any time during the study. The most frequently occurring symptomatic cardiac event was Grade 3/4 CLVF

(cardiac left ventricular function) which corresponds to symptomatic CHF. The incidence was highest in the AC→TH arm (1.9%) and increased relative to both AC→T (0.3%) and TCH arms (0.4%). The overall incidence was highest in the AC→TH arm largely due to the incidence of Grade 3/4 CLVF. Please refer to Table 7 to Table 10 in for further information.

Table 7 Symptomatic Cardiac Events per Independent Cardiac Review Panel (ICRP) Occurring at Any Time during the Study: Safety Population - BCIRG 006 (H2296s/GO00773)

Event Type	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
CHF (Grade 3/4 CLVF)	3 (0.3%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0 (0.0%)	2 (0.2%)	2 (0.2%)
Grade 3/4 arrhythmia	3 (0.3%)	2 (0.2%)	6 (0.6%)
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any symptomatic cardiac event [a]	6 (0.6%)	23 (2.2%)	12 (1.1%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; CHF=congestive heart failure; CLVF=cardiac left ventricular function; SD=standard deviation; TCH=docetaxel, carboplatin, and Herceptin.

[a] A patient could be included in more than one event type category; therefore, the "any symptomatic cardiac event row" is less the sum of number of events in a given column.

Asymptomatic LVEF Declines

Per the protocol, seven left ventricular ejection fraction (LVEF) evaluations were to be performed during treatment and follow-up. Overall, compliance with the protocol-specified LVEF assessment schedule was high for patients in all three arms (AC→T: 80.6%, AC→TH: 84.7%, and TCH: 83.6%).

Table 8 Asymptomatic and Symptomatic LVEF Declines by Baseline Events BCIRG 006 (H2296s/GO00773)

Event Type	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Absolute decline of > 15% from baseline and to a value below the LLN	43 (4.1%)	109 (10.2%)	36 (3.4%)
Absolute decline of > 10% from baseline and to a value below 50%	60 (5.7%)	130 (12.2%)	48 (4.5%)
Symptomatic and/or asymptomatic decline of > 15%, below the LLN	45 (4.3%)	115 (10.8%)	47 (4.5%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; ANC=absolute neutrophil count; LLN=lower limit of normal; TCH=docetaxel, carboplatin, and Herceptin.

Timing of Symptomatic Cardiac and LVEF Events

The timing of symptomatic cardiac and LVEF events is presented in Table 9. The majority of all events occurred during trastuzumab monotherapy or follow-up.

Table 9 Timing of First Symptomatic and LVEF Events: Safety Population BCIRG 006 (H2296s/GO00773)

Type and Timing of Event	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Symptomatic cardiac event			
All periods	6 (0.6%)	23 (2.2%)	12 (1.1%)
During AC	0 (0.0%)	0 (0.0%)	—
During T, TH, and TCH	1 (0.1%)	3 (0.3%)	4 (0.4%)
During Herceptin monotherapy or follow-up	5 (0.5%)	20 (1.9%)	8 (0.8%)
Absolute decline of > 15% in LVEF from baseline and to a value below the LLN			
All periods	43 (4.1%)	109 (10.2%)	36 (3.4%)
During AC	2 (0.2%)	5 (0.5%)	—
During T, TH, and TCH	12 (1.1%)	27 (2.5%)	14 (1.3%)
During Herceptin monotherapy or follow-up	29 (4.1%)	77 (7.2%)	22 (2.1%)
Symptomatic and/or LVEF event			
All periods	45 (4.3%)	115 (10.8%)	47 (4.5%)
During AC	2 (0.2%)	5 (0.5%)	—
During T, TH, and TCH	12 (1.1%)	29 (2.7%)	18 (1.7%)
During Herceptin monotherapy or follow-up	31 (3.0%)	81 (7.6%)	29 (2.7%)

A=doxorubicin; AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; C=cyclophosphamide in AC arms and carboplatin or cisplatin in TCH arm; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; T=docetaxel; TCH=docetaxel, carboplatin, and Herceptin; TH=docetaxel and Herceptin.

At 3 years, the rate of symptomatic cardiac events was 0.5%, 2.4%, and 1.16% in the AC→T, AC→TH, and TCH arms, respectively. For symptomatic CHF (Grade 3/4 CLVF), the 3-year rate was 0.3%, 2.1%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.

An overall summary of cardiac adverse events is presented in Table 10 (Annex 7). The overall incidence of cardiac AEs was increased by 10.6% in the AC→TH arm relative to the AC→T arm. The overall incidence of cardiac AEs was increased by 7.5% in the TCH arm relative to the AC→T arm. The overall incidence of cardiac AEs was slightly higher in the AC→TH arm relative to the TCH arm; however, the incidence of serious and Grade 3/4 cardiac AEs is similar for the two arms. Cardiac AEs resulting in study treatment discontinuation or hospitalization were infrequent. Approximately, 9% of patients in the AC→TH and TCH arms experienced cardiac AEs classified as possibly- or probably-related to trastuzumab.

The most frequently reported (in ≥4% of all patients) cardiac AEs included hypertension (18.6%), palpitations (8.3%), sinus tachycardia (4.7%), and CLVF (4.0%). The overall incidence of CLVF AEs was increased by ≥2% in the AC→TH arm relative to both the AC→T and TCH arms.

The overall incidence of hypertension was increased by more than 2% in both trastuzumab-containing arms compared with AC→T. Of note, the incidence of Grade 3 or 4 hypertension was highest in the TCH arm and was increased by ≥2% relative to the AC→T arm. No additional notable differences were present in the occurrence of cardiac AEs.

Table 10 Cardiac Adverse Events Occurring at Any Time during the Study: Safety Population BCIRG 006 (H2296s/GO00773)

Genentech Inc., F. Hoffmann-La Roche Ltd & Sanofi-Aventis Group — Phase III Study: BCIRG006 (H2996s, TAX GMA 302)
10-year follow-up Analysis Update — Adjuvant Herceptin Therapy in Breast Cancer

Table S.3/5

Overview of Cardiac Adverse Events Occurring at Any Time during the Study
Safety Population

Type of Cardiac Adverse Event	AC -> T (n=1018)	AC -> TH (n=1100)	TCH (n=1056)	All Patients (n=3174)
Any cardiac adverse events	373 (36.6%)	527 (47.9%)	471 (44.6%)	1371 (43.2%)
Grade 3-4	50 (4.9%)	90 (8.2%)	92 (8.7%)	232 (7.3%)
Characterized as serious	18 (1.8%)	49 (4.5%)	35 (3.3%)	102 (3.2%)
Deemed possibly or probably related to study drug	91 (8.9%)	162 (14.7%)	136 (12.9%)	389 (12.3%)
Related to chemotherapy	90 (8.8%)	138 (12.5%)	106 (10.0%)	334 (10.5%)
Related to Herceptin	2 (0.2%)	98 (8.9%)	96 (9.1%)	196 (6.2%)
Resulting in study drug discontinuation	4 (0.4%)	16 (1.5%)	17 (1.6%)	37 (1.2%)
Discontinuation of chemotherapy	4 (0.4%)	2 (0.2%)	8 (0.8%)	14 (0.4%)
Discontinuation of Herceptin	(0.0%)	16 (1.5%)	16 (1.5%)	32 (1.0%)
With hospitalization as a consequence	18 (1.8%)	48 (4.4%)	40 (3.8%)	106 (3.3%)
With death as a consequence	2 (0.2%)	2 (0.2%)	3 (0.3%)	7 (0.2%)

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.

Source: Biostatistics/[redacted] pgm(/immuno/her2/bcirg006/pmc10yr/programs/t_cae_overall) output (t_cae_overall_rel)
Database (Cutoff 30DEC2014) Datasets (patsaf)

The most frequently reported (in ≥4% of all patients) cardiac AEs included hypertension (18.6%), palpitations (8.3%), sinus tachycardia (4.7%), and CLVF (4.0%). The overall incidence of CLVF AEs was increased by ≥2% in the AC→TH arm relative to both the AC→T and TCH arms.

The overall incidence of hypertension was increased by more than 2% in both trastuzumab-containing arms compared with AC→T. Of note, the incidence of Grade 3 or 4 hypertension was highest in the TCH arm and was increased by ≥2% relative to the AC→T arm. No additional notable differences were present in the occurrence of cardiac AEs.

- **BO16348 (HERA)**

Based on a 10-year median follow-up of HERA data, the SAE of Cardiac dysfunction was reported in 53 patients and were distributed amongst the three study arms as follows: Observation Only arm (n=1744): 4/1744 (0.2%) patients; Herceptin-1-year arm (n=1682): 23/1682 (1.4%) patients; Herceptin-2-year arm (n=1673): 26/1673 (1.6%) patients. The most prominent cardiac SAE was cardiac failure congestive reported in 19/1682 (1.1%) patients (17 being assessed as related to trial treatment) in the Herceptin-1-year arm and 24/1673 (1.4%) patients (21 being assessed as related to trial treatment) in the Herceptin 2-year arm.

The 10-year median follow-up data reports death due to cardiac failure congestive occurred as follows during the study arms: Observation Only arm: 1/1744 (0.1%) patients; Herceptin-1-year: 2/1682 (0.1%) patients; Herceptin-2-year arm: 4/1673 (0.2%) patients. Of these seven cardiac failure congestive related fatal outcomes, three occurred during the first year of the study, one occurred in the 2-year treatment arm during the second year of the study and three deaths (two in the 1-year Herceptin arm and one in the 2-year Herceptin arm) occurred after the third year of the study during follow-up phase.

Cardiac failure congestive and peripheral swelling were the serious cardiac AEs leading to dose interruption- in the trastuzumab-containing arms: Herceptin-1-year arm: 1/1682 (0.06%) patient for each of the two events.

Cardiac Failure congestive was the most common cardiac serious AE leading to drug discontinuation in the trastuzumab-containing arms: Herceptin-1-year arm: 14/1682 (0.8%) patients; Herceptin-2-year arm: 21/1673 (1.3%) patients.

- **MO28048 (SafeHER)**

As of 12 October 2020, the most frequently reported cardiac SAE was cardiac failure congestive reported as related in 11 patients. In 9 patients, the SAE of cardiac failure congestive led to drug discontinuation.

– **Joint Analysis of NSABP B-31 and N9831**

Serious adverse events were not collected or reported in these two clinical trials. Grades 3-5 were reported; however, National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 (which did not contain Grade 5 coding) was utilized. Fatal outcomes, not necessarily designated as Grade 5, were captured and reported. Additionally, NCI-CTC version 2.0 (instead of MedDRA) coding of adverse events was utilized in clinical trial data collection or analysis.

Cardiac deaths were experienced by 2 patients (0.1%) in the AC→T + H group, 1 patient (0.3%) in the AC→T→H group, and 5 patients (0.3%) in the AC→T group.

In the AC→T + H group of the joint safety population, left ventricular events (i.e., symptomatic CHF [non-death] or cardiac death) were reported for 64 patients (3.2%). Events were reported for 12 patients during Herceptin + paclitaxel treatment (Period 2), 13 patients during Herceptin monotherapy (Period 3), and 32 patients during follow-up (Period 4). Events that could not be classified into any time period, because of uncertainty in the dosing records, were reported for 7 patients.

In the AC→T→H group, cardiac left ventricular events were reported for 7 patients. Events were reported for 2/984 of these patients during Herceptin monotherapy (Period 3) and 4/1023 during follow-up (Period 4). For 1 patient, an event was reported that could not be classified into any time period, because of uncertainty in the dosing records.

In the AC→T group, cardiac left ventricular events were reported for 21 patients. Events were reported for 2/887 of these patients during AC chemotherapy (Period 1), 2/823 during paclitaxel treatment (Period 2), and 16/734 during follow-up (Period 4). For 1 patient, an event was reported that could not be classified into any time period, because of uncertainty in the dosing records.

The AEs were not assessed as leading to study treatment withdrawal and/or discontinuation on the AE case report form (CRF) for either B-31 or N9831. The AEs leading to dose adjustment and outcomes of AEs were also not collected.

Neoadjuvant-adjuvant Treatment in EBC

- **MO16432 (NOAH)**

In the neoadjuvant-adjuvant setting trastuzumab was administered concurrently with an anthracycline the incidence of symptomatic cardiac dysfunction was low in the HER2+TC arm (patients with HER2-positive disease randomized to treatment with trastuzumab plus chemotherapy). More trastuzumab-treated patients had a decline in LVEF during the neoadjuvant part of the study but these were mostly declines of <10% points compared to baseline. Only 4 patients in the HER2+TC group (vs. one in the HER2+C group [Patients with HER2-positive disease randomized to treatment with chemotherapy alone] and none in the HER2–C group) [Parallel control group of patients with HER2-negative disease treated with

chemotherapy alone]) had a decline in LVEF of ≥10% points to an LVEF of <50%. From these 4 patients in the HER2+TC group only in one did the LVEF decline to <45%. The incidence of cardiac AEs during neoadjuvant therapy was similar in the two HER2-positive arms. During the follow-up period from 30 March 2009 to 14 July 2012, one Grade 3 cardiac AE of atrial fibrillation was reported in the HER2–C arm.

- **BO22227 (HannaH)**

Herceptin IV (n=298)

A total of 63 events were reported in 56 patients in the cardiac dysfunction risk grouping (SMQ: Cardiac failure Broad). None of these events were reported as serious. The most frequently reported AEs were peripheral oedema (30); oedema (15); left ventricular dysfunction (12), peripheral swelling (3) and one case each of ejection fraction decreased, cardiac failure and nocturnal dyspnea. A total of 56of the 63 AEs resolved without sequelae, while 6 AEs were unresolved and 1 AE of left ventricular dysfunction was resolved with sequelae at the time of the AE reports.

Herceptin SC (n=297)

A total of 52 events in 47 patients were reported in the cardiac dysfunction risk grouping (SMQ: Cardiac failure Broad). A total of 2 AEs (2 events of cardiac failure congestive) were assessed as serious.

The most frequently reported PTs were the same with the SC as for the IV formulation but with fewer AEs in the SC arm: peripheral edema (23); oedema (10); left ventricular dysfunction (10), peripheral swelling (3) and 2 events of cardiac failure congestive, one event each reporting diastolic dysfunction, cardiac failure and right ventricular failure. A total of 47 of the 52 total AEs resolved without sequelae; 2 resolved with sequelae; and 3 were unresolved at the time of the AE reports. There were no reports of fatal outcome from a cardiac dysfunction-related AE for both formulations.

- **MO22982 (PrefHER)**

Results from crossover period SC-IV or IV-SC (N=483 overall)

Herceptin IV (4 cycles)

15 patients (out of 478 patients) reported 17 cardiac events..

The most frequently reported AEs were Left ventricular dysfunction (in 5/478 patients [1.05%]) and bradycardia (in 3/478 patients [0.63%]) and palpitations and ejection fraction abnormal (in 2/479 patients each [0.442%])

Herceptin SC (4 cycles)

12 patients (out of 479 patients) reported 15 cardiac events.

The most frequently reported AEs were palpitations (in 3/479 patients [0.63%[), ejection fraction decreased (in 3/479 patients [0.63%]) and left ventricular dysfunction and cardiac failure congestive (each reported in 2/479 patients each [0.42%]).

Results from Herceptin continuation period

Cohort 1

A total of 226 patients in Cohort 1 received 1239 Herceptin IV cycles during the IV continuation period and 43 patients received 98 cycles administered with the SC SID during the SID self-administration period.

IV continuation: Cardiac AEs were reported for 7/226 (3.1%) patients during IV continuation period, none of which were left ventricular systolic dysfunction or congestive heart failure events. None of the cardiac AEs were serious or Grade ≥3 events, or led to withdrawal from treatment.

SID self-administration: No cardiac AEs were reported for SID self-administration for SC SID period.

Cohort 2

Patients in Cohort 2 (SC Vial) continued to receive Herceptin SC via handheld syringe to complete their remaining cycles after the crossover period. A total of 208 patients in Cohort 2 received 1152 cycles with SC Vial during the SC continuation period and 10 patients received 34 cycles with IV during the IV continuation period.

SC vial continuation: Cardiac AEs were reported for 8/208 (3.8%) patients during the continuation period. Four patients experienced left ventricular dysfunction and 3 patients cardiac failure congestive.

IV continuation: Cardiac AEs were reported for 1/10 (10.0%) patients (Grade 1 event) and no left ventricular systolic dysfunction events were reported during the IV continuation period.

Table 11 Cardiac Dysfunction Summary MO22982 (Crossover SC-IV / IV-SC, EBC)

Cohort 1 and 2

System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Number of Cardiac Adverse Events	12	(2.5)	15	15	(3.1)	17
Cardiac Disorders	8	(1.7)	11	14	(2.9)	14
Left Ventricular Dysfunction	2	(0.4)	2	5	(1.0)	5
Palpitations	3	(0.6)	5	2	(0.4)	2
Cardiac Failure Congestive	2	(0.4)	2	0		
Bradycardia	1	(0.2)	1	3	(0.6)	3
Extrasystoles	1	(0.2)	1	0		
Angina Pectoris	0			1	(0.2)	1
Cardiomyopathy	0			0		
Diastolic Dysfunction	0			1	(0.2)	1
Heart Valve Incompetence	0			1	(0.2)	1
Left Ventricular Hypertrophy	0			0		
Mitral Valve Incompetence	0			1	(0.2)	1
Sinus Bradycardia	0			0		
Tachycardia	0			0		
Investigations	4	(0.8)	4	3	(0.6)	3
Ejection Fraction Decreased	3	(0.6)	3	2	(0.4)	2
Ejection Fraction Abnormal	1	(0.2)	1	0		
Electrocardiogram Change	0			1	(0.2)	1

Roche: MO22982/CIL-TS/FINAL/AEC01P.SAS
Produced: 16 March 2016, 11:26 Page 3 of 3
Source: Listing 16.2.7.1
Notes: [1] All Cardiac Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Global Safety Database

Table 12 Cardiac Dysfunction, Global Safety Database: Summary Tabulation of Adverse Events by SOC

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	Preferred Term					
Cardiac disorders	Acute left ventricular failure	5	5	0.1	5	0.0
	Cardiac dysfunction	471	389	5.0	472	3.9
	Cardiac failure	1772	1738	22.3	1790	14.8
	Cardiac failure acute	55	55	0.7	55	0.5
	Cardiac failure chronic	43	43	0.6	43	0.4
	Cardiac failure congestive	815	822	10.6	822	6.8
	Cardio-respiratory distress	1	1	0.0	1	0.0
	Cardiogenic shock	28	27	0.3	28	0.2
	Cardiomegaly	70	33	0.4	70	0.6
	Cardiopulmonary failure	19	19	0.2	19	0.2
	Chronic left ventricular failure	1	1	0.0	1	0.0
	Cor pulmonale	1	1	0.0	1	0.0
	Cor pulmonale acute	1	1	0.0	1	0.0
	Diastolic dysfunction	57	23	0.3	57	0.5

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
	Dilatation ventricular	9	8	0.1	9	0.1
	Left ventricular dilatation	24	15	0.2	24	0.2
	Left ventricular dysfunction	686	531	6.8	697	5.8
	Left ventricular enlargement	12	5	0.1	12	0.1
	Left ventricular failure	72	70	0.9	72	0.6
	Right ventricular dilatation	2	2	0.0	2	0.0
	Right ventricular dysfunction	4	2	0.0	4	0.0
	Right ventricular enlargement	2	1	0.0	2	0.0
	Right ventricular failure	25	24	0.3	25	0.2
	Systolic dysfunction	21	17	0.2	21	0.2
	Ventricular compliance decreased	3	0	0.0	3	0.0
	Ventricular dysfunction	53	46	0.6	53	0.4
	Ventricular failure	1	1	0.0	1	0.0
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	41	39	0.5	41	0.3
	Dyspnoea paroxysmal nocturnal	7	2	0.0	7	0.1
	Lower respiratory tract congestion	11	2	0.0	11	0.1
	Nocturnal dyspnoea	7	4	0.1	7	0.1
	Orthopnoea	18	7	0.1	18	0.1
	Pulmonary congestion	14	7	0.1	14	0.1
	Pulmonary oedema	246	219	2.8	246	2.0

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Hepatobiliary disorders	Congestive hepatopathy	3	2	0.0	3	0.0
General disorders and administration site conditions	Oedema	526	117	1.5	532	4.4
	Oedema due to cardiac disease	2	0	0.0	2	0.0
	Oedema peripheral	875	164	2.1	899	7.4
	Peripheral swelling	880	111	1.4	919	7.6
Investigations	Brain natriuretic peptide increased	13	2	0.0	13	0.1
	Cardiac index decreased	2	0	0.0	2	0.0
	Cardiac output decreased	31	20	0.3	31	0.3
	Cardiac ventriculogram abnormal	3	2	0.0	3	0.0
	Cardiothoracic ratio increased	1	0	0.0	1	0.0
	Ejection fraction decreased	4985	3199	41.1	5053	41.7
	N-terminal prohormone brain natriuretic peptide increased	4	2	0.0	4	0.0
	Right ventricular ejection fraction decreased	5	3	0.0	5	0.0
	Stroke volume decreased	2	2	0.0	2	0.0
	Venous pressure jugular increased	2	2	0.0	2	0.0
Total		**N/A**	**7786**	**100.0**	**12105**	**100.0**
Data cutoff: 24 September 2020. Exposure cut-off: 24 September 2020. Comanifestations are counted as AEs						

Table 13 Cardiac Dysfunction, Global Safety Database: Summary Tabulation of Adverse Event by Outcome

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Acute left ventricular failure	0	0	0	1	0	1	0	2	1	5
Acute pulmonary oedema	2	3	0	5	2	19	0	4	6	41
Brain natriuretic peptide increased	0	0	0	1	4	1	0	2	5	13
Cardiac dysfunction	0	0	0	71	235	40	2	53	71	472
Cardiac failure	2	78	0	269	372	404	51	319	295	1790
Cardiac failure acute	0	12	0	3	4	17	1	16	2	55
Cardiac failure chronic	0	1	0	7	7	7	3	10	8	43
Cardiac failure congestive	6	39	10	90	230	165	32	153	97	822
Cardiac index decreased	0	0	0	0	0	0	0	1	1	2
Cardiac output decreased	1	0	0	2	16	3	0	3	6	31

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Cardiac ventriculogram abnormal	0	0	0	0	0	2	0	0	1	3
Cardio-respiratory distress	0	0	0	0	0	0	0	1	0	1
Cardiogenic shock	1	10	0	3	1	5	2	3	3	28
Cardiomegaly	1	0	1	16	26	4	1	4	17	70
Cardiopulmonary failure	0	12	0	1	1	3	0	2	0	19
Cardiothoracic ratio increased	0	0	0	1	0	0	0	0	0	1
Chronic left ventricular failure	0	0	0	0	0	0	0	0	1	1
Congestive hepatopathy	0	0	0	1	0	0	0	0	2	3
Cor pulmonale	0	0	0	0	1	0	0	0	0	1
Cor pulmonale acute	0	0	0	0	1	0	0	0	0	1
Diastolic dysfunction	0	0	0	11	26	10	0	2	8	57
Dilatation ventricular	0	0	1	2	3	0	0	0	3	9

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Dyspnoea paroxysmal nocturnal	1	0	0	0	4	0	0	1	1	7
Ejection fraction decreased	6	15	13	676	1579	1120	31	425	1188	5053
Left ventricular dilatation	0	1	0	6	10	4	0	1	2	24
Left ventricular dysfunction	3	3	2	107	220	236	12	55	59	697
Left ventricular enlargement	0	0	0	2	5	1	0	1	3	12
Left ventricular failure	0	2	1	15	7	12	2	23	10	72
Lower respiratory tract congestion	0	0	0	0	8	0	0	1	2	11
N-terminal prohormone brain natriuretic peptide increased	0	0	0	0	2	0	1	0	1	4
Nocturnal dyspnoea	0	0	0	1	2	2	0	1	1	7
Oedema	1	2	2	117	163	110	1	71	65	532

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Oedema due to cardiac disease	0	0	0	0	2	0	0	0	0	2
Oedema peripheral	6	0	12	188	259	211	1	140	82	899
Orthopnoea	3	0	0	0	6	4	1	2	2	18
Peripheral swelling	3	2	8	195	452	106	3	67	83	919
Pulmonary congestion	0	0	0	2	3	4	0	1	4	14
Pulmonary oedema	7	13	4	36	55	59	2	34	36	246
Right ventricular dilatation	0	0	0	2	0	0	0	0	0	2
Right ventricular dysfunction	0	0	0	0	2	1	0	1	0	4
Right ventricular ejection fraction decreased	0	0	0	2	2	1	0	0	0	5
Right ventricular enlargement	0	0	0	0	2	0	0	0	0	2
Right ventricular failure	0	5	0	1	4	5	0	7	3	25

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Stroke volume decreased	0	0	0	0	1	0	0	0	1	2
Systolic dysfunction	0	0	0	6	9	2	1	1	2	21
Venous pressure jugular increased	0	0	0	2	0	0	0	0	0	2
Ventricular compliance decreased	0	0	0	0	1	0	0	1	1	3
Ventricular dysfunction	0	1	0	10	10	19	2	5	6	53
Ventricular failure	0	0	0	0	0	0	0	1	0	1
Total	**43**	**199**	**54**	**1852**	**3737**	**2578**	**149**	**1414**	**2079**	**12105**
Data cutoff: 24 September 2020. Exposure cut-off: 24 September 2020. Comanifestations are counted as AEs										

Table 14 Cardiac Dysfunction, Global Safety Database: Summary Tabulation of Event Outcome by Action Taken

Outcome	Drug continuation										Total No. Drug Events
	Coman	Dose Increased	Dose Interrupted	Dose Modified NOS	Dose Not Changed	Dose Reduced	Drug Withdrawn	Infusion Rate Decreased	Not Applicable	Unknown	
Coman	43	0	0	0	0	0	0	0	0	0	43
Fatal	0	0	3	0	7	0	36	0	112	41	199
Not Applicable	0	0	0	0	1	0	0	0	51	2	54
Not Recovered/Not Resolved	0	0	164	0	344	3	696	2	168	498	1875
Not Reported	0	1	305	1	160	5	639	0	90	2575	3776
Recovered/Resolved	0	0	424	1	412	11	994	1	176	597	2616
Recovered/Resolved With Sequelae	0	0	15	0	14	1	73	0	31	17	151
Recovering/Resolving	0	0	156	0	190	5	600	0	127	345	1423
Unknown	0	0	100	1	144	5	838	0	105	891	2084
Total	**43**	**1**	**1167**	**3**	**1272**	**30**	**3876**	**3**	**860**	**4966**	**12221**
Data cutoff: 24 September 2020. Exposure cut-off: 24 September 2020. Comanifestations are counted as AEs											

1.3 SEVERITY AND NATURE OF RISK

Metastatic Breast Cancer

- **M77001**

Eight Grade 3 AEs (8.5%) in the docetaxel alone arm and four (4.3%) in the trastuzumab + docetaxel arm were reported. No Grade 4 or 5 AEs were reported in either arm (Table 1).

Stratified data:

Age: In the Herceptin containing arm, more Grade 1 AEs were reported in patients with age ≤50 years compared with an age >50 years (34.3% vs. 21.1%); Grade 2 AEs were reported more frequently in the sub-group of patients >50 years (11.4% vs. 22.8%). In the Herceptin containing arm, Grade 3 AEs were only reported in patients with age ≤50 years (2, 5.7%). No Grade 4 or 5 AEs were reported in any arm.

Summary: No discernible pattern seen in either of the age groups

- BO16216

Across the two treatment arms of anastrozole alone and anastrozole + trastuzumab, cardiac AEs were mainly mild-to-moderate in severity (23/29). Four Grade 3 AEs (3.8%) were reported in the anastrozole alone arm and two Grade 3 AEs (1.9%) were reported in the anastrozole plus trastuzumab arm (Table 2).

Stratified data:

Age:

In patients ≤50 years of age the cardiac events of any grade were reported as follows:

Arimidex arm: 1/32 (3.1%)

Arimidex + Herceptin: 3/27 (11.1%)

Arimidex alone after start of Herceptin: 3/18 (16.7%).

In patients >50 years of age:

Arimidex: 1/72 (1.4%)

Arimidex + Herceptin: 9/76 (11.8%)

Arimidex alone after start of Herceptin: 5/40 (12.5%).

Most cardiac events reported in age ≤50 years were of Grade 2, while those in age group >50 years were predominantly Grade 1 events. No Grade 4 or 5 events were reported in any of the age groups.

A meaningful interpretation of the data is impacted by low event counts across both groups.

Early Breast Cancer (EBC)

Adjuvant Treatment in EBC

- **(BCIRG 006) (H2296s)/GO00773**

Please refer to Table 6 to Table 10.

Stratified data:

Age: The data was stratified for Age with subgroup ≤50 years and >50 years.

Across all the treatment arms, patients in age group >50 years reported higher percentage of " Any symptomatic or clinical significant asymptomatic cardiac events" (all assessment), compared with age group ≤50 years:

AC—>T (27/456, 5.9% vs. 21/594, 3.5%)

AC—>TH (63/476, 13.2% vs. 57/592, 9.6%)

TCH (24/448, 5.4% vs. 28/608, 4.6%)

Region:

The regional data was available for following five regions: Asia (no of patients, n=157), Europe (n=1352), Middle east (n=122), North America (n=1106), Oceania (n=324), South Africa (n=48), and South America (n=65). All cardiac events were compared across these regions.

AC—>T:

- Asia (13/56, 23.2%; Grade 3-4: 1/56, 1.8%)
- Europe (146/454, 32.2% Grade 3-4: 15/454, 3.3%)
- Middle East (17/44, 38.6%, Grade 3-4: 2/44, 4.5%)
- North America (151/357, 42.3%, Grade 3-4: 21/357, 5.9%)
- Oceania (30/102, 29.4%, Grade 3-4: 1/102, 1.0%)
- South Africa (2/13, 15.4%, Grade 3-4: 0/13 0.0%)
- South America (7/24, 29.2%, Grade 3-4: 1/24, 4.2%).

AC—>TH:

- Asia (18/52, 34.6%; Grade 3-4: 3/52, 5.8%)
- Europe (170/450, 37.8% Grade 3-4: 29/450, 6.4%)

- Middle East (15/41, 36.6%, Grade 3-4: 2/41, 4.9%)
- North America (208/380, 54.7%, Grade 3-4: 27/380, 7.1%)
- Oceania (52/108, 48.1%, Grade 3-4: 8/108, 7.4%)
- South Africa (12/18, 66.7%, Grade 3-4: 1/18, 5.6%)
- South America (11/19, 57.9%, Grade 3-4: 0/19, 0.0%).

TCH:

- Asia (12/49, 24.5%, Grade 3-4: 3/49, 6.1%)
- Europe (177/448, 39.5%, Grade 3-4: 28/448, 6.3%)
- Middle East (13/37, 35.1%, Grade 3-4: 0/37, 0.0%)
- North America (179/369, 48.5%, Grade 3-4: 29/369, 7.9%)
- Oceania (49/114, 43%, Grade 3-4: 12/114, 10.5%)
- South Africa (8/17, 47.1%, Grade 3-4: 3/17, 17.6%)
- South America (10/22, 45.5%, Grade 3-4: 1/22, 4.5%).

Summary

In AC—>T arm, the highest percentage of cardiac events were reported in North American patients, followed by Middle Eastern and European. In the AC—>TH arm, the highest percentage of cardiac events were observed in South African patients, followed by South American and North American patients. In the TCH arm, the highest percentages of cardiac events were observed in North American patients, followed by South Africa and South America. The number of Grade 3-4 events reported was low and precluded meaningful comparison between the sub groups.

There was no discernible pattern observed in the Herceptin containing treatment arms across region.

- **BO16348 (HERA):**

10-year median follow-up HERA data

Across the three study arms, AEs within the cardiac dysfunction risk were mainly mild-to-moderate in severity, comprising Grades 1 and 2 of severity (refer to Table 15). In all of the clinical trial arms, the most commonly occurring Grade 1 and Grade 2 AEs were Oedema Peripheral, Cardiac Failure congestive and Ejection Fraction decreased. No Grade 3 AEs were reported in the Observation arm. Cardiac Failure congestive was the most common Grade 3 AE in all of the trastuzumab-containing arms: trastuzumab 1-year: 13/1682 (0.8%) patients; trastuzumab 2-year: 10/1673 (0.6%) patients. The other Grade 3 AEs in the trastuzumab-containing arms occurred at a frequency of < 0.1%. The most commonly occurring Grade 4 AE was Cardiac Failure congestive and it was observed in the trastuzumab 1-year and 2-year arms

(4/1682 (0.2%) and 8/1673 (0.5%) patients, respectively), as well as the Observation only arm (1/1744 (0.1%) patients).

Stratified data:

Age ≤50 years

- Observation only arm: 5.3% (51/959) patients reported a total 57 AEs. All were Grade 1 events (n=48 in 43 patients) and Grade 2 events (n=9 in 9 patients). No Grade 3 and Grade 4 events were reported.
- Herceptin 1-year arm: 16.2% (153/947) patients reported a total of 172 AEs. Majority were Grade 1 events (n= 114 in 106 patients) and Grade 2 events (n=48 in 47 patients). Nine Grade 3 events in 9 patients (Cardiac failure congestive [n=7], one event each of peripheral oedema and ejection fraction decreased) were reported and one Grade 4 event of cardiac failure congestive was reported.
- Herceptin 2-year arm: 18.6% (172/926) patients reported a total of 200 AEs. Majority were Grade 1 events (n=149 in 134 patients) and Grade 2 (n=42 in 41 patients). There were five Grade 3 events in 5 patients (cardiac failure congestive [n=3] and one event each of peripheral oedema and ejection fraction decreased) and 4 events of Grade 4 cardiac failure congestive were reported in 4 patients.

Age >50 years

Observation only arm: 6.9% (54/785) patients reported a total of 57 events. Majority were reported as Grade 1 (n=42 in 41 patients), and Grade 2 (n=14 in 14 patients). One event of cardiac failure congestive was reported as Grade 4 event. No Grade 3 event was reported.

Herceptin 1-year arm: 19.0% (140/735) patients reported a total of 153 events. Majority were reported as Grade 1 (n=102 in 96 patients), Grade 2 (n=38 in 38 patients). Seven Grade 3 events in 7 patients, cardiac failure congestive [n=6] and one event of cardiac failure chronic), and 4 Grade 4 events in 4 patients (3 events of cardiac failure congestive and one event of cardiac failure) were reported.

Herceptin 2-year arm: 21.2% (158/747) patients reported a total of 187 events. Majority were reported as Grade 1 (n=118 in 106 patients), Grade 2 (n=56 in 52 patients). Seven Grade 3 events of cardiac failure congestive reported in 7 patients and 5 Grade 4 events in 4 patients (cardiac failure congestive[n=4] and pulmonary oedema [n=1]) were reported.

Summary

The >50 years subgroup reported higher percentage of patients with AEs compared with the ≤50 years subgroup in all the three arms. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Table 15 Cardiac Dysfunction, Severity & Frequency: BO16348

ael5_card Summary of Cardiotoxicity, Severity (NCI-CTC Grade) and Frequency, by Body System, Trial treatment (Safety Population)
Protocol(s): BO16348
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	Observation Only N = 1744					Herceptin 1 Year N = 1682					Herceptin 2 Year N = 1673				
	Grade: Total	1 No.	2 No.	3 No.	4 No.	Grade: Total	1 No.	2 No.	3 No.	4 No.	Grade: Total	1 No.	2 No.	3 No.	4 No.
ALL BODY SYSTEMS															
Total Pts with at Least one AE	105	84	23	-	1	293	202	85	16	5	330	240	93	12	8
Total Number of AEs	114	90	23	-	1	325	216	86	16	5	387	267	98	12	9
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS															
Total Pts With at Least one AE	73	61	13	-	-	132	97	37	1	-	147	116	30	1	-
OEDEMA PERIPHERAL	49	38	11	-	-	82	60	21	1	-	101	79	20	1	-
PERIPHERAL SWELLING	17	16	1	-	-	33	22	11	-	-	25	21	4	-	-
OEDEMA	10	9	1	-	-	23	18	5	-	-	27	21	6	-	-
Total Number of AEs	76	63	13	-	-	138	100	37	1	-	153	121	30	1	-
CARDIAC DISORDERS															
Total Pts With at Least one AE	24	15	8	-	1	115	62	36	14	5	157	96	47	10	8
CARDIAC FAILURE CONGESTIVE	19	14	4	-	1	96	48	31	13	4	146	89	39	10	8
CARDIAC FAILURE CHRONIC	2	-	2	-	-	11	6	4	1	-	6	4	2	-	-
LEFT VENTRICULAR DYSFUNCTION	-	-	-	-	-	6	5	1	-	-	9	4	5	-	-
CARDIAC FAILURE	1	1	-	-	-	2	1	-	-	1	-	-	-	-	-
CARDIOMEGALY	1	-	1	-	-	1	1	-	-	-	-	-	-	-	-
DIASTOLIC DYSFUNCTION	-	-	-	-	-	1	1	-	-	-	1	1	-	-	-
LEFT VENTRICULAR FAILURE	1	-	1	-	-	-	-	-	-	-	1	-	1	-	-
VENTRICULAR DYSFUNCTION	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-
Total Number of AEs	24	15	8	-	1	118	63	36	14	5	163	98	47	10	8
INVESTIGATIONS															
Total Pts With at Least one AE	13	11	2	-	-	69	53	13	1	-	68	46	21	1	-
EJECTION FRACTION DECREASED	13	11	2	-	-	69	53	13	1	-	68	46	21	1	-
CARDIOTHORACIC RATIO INCREASED	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-
Total Number of AEs	13	11	2	-	-	69	53	13	1	-	69	47	21	1	-

Investigator text for Adverse Events encoded using MedDRA version 18.0.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE15 31MAR2016:13:19:04 (1 of 2)

Race:

Observation arm:

- Black: 2/6 (33.3%) patients reported 2 events (no Grade 3 and Grade 4 events reported)
- Caucasian: 85/1453 (5.8%) patients reported 93 events (Grade 4: 1 event and no Grade 3 event)
- Oriental: 15/218 (6.9%) patients reported 16 events (no Grade 3 and Grade 4 events reported)
- Other: 3/67 (4.5%) patients reported 3 events (no Grade 3 and Grade 4 events reported)

Herceptin 1-year arm:

- Black: 3/8 (37.5%) patients reported 3 events (Grade 3: 1 event and no Grade 4 event)
- Caucasian: 257/1404(18.3%) patients reported 289 events (Grade 3: 14, Grade 4: 4 events)
- Oriental: 22/213 (10.3%) patients reported 22 events (one Grade 3 event, no Grade 4 events)
- Other: 11/57 (19.3%) patients reported 11 events (no Grade 3 and one Grade 4 event)

Herceptin 2-year arm:

- Black: 1/5 (20.0%) patients reported 1 event (no Grade 3 and Grade 4 events reported)
- Caucasian: 279/1397(20.0%) patients reported 324 events (Grade 3: 11, Grade 4: 8 events)
- Oriental: 36/213 (16.9%) patients reported 46 events (one event each of Grade 3 and Grade 4 were reported)
- Other: 14/58 (24.1%) patients reported 16 events (no Grade 3 and Grade 4 events were reported)

Summary

Majority of the patients included in the trials were Caucasian. Across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2. A meaningful interpretation of the data is impacted by low event counts across other race sub-groups.

- **MO28048 (SafeHER)**
- Overall, the cardiac dysfunction risks were mainly mild-to-moderate in severity, comprising of Grades 1 and 2 events. The most commonly occurring Grade 1 AEs were palpitations and mitral valve incompetence. The most commonly occurring Grade 2 AEs were left ventricular dysfunction and atrial fibrillation. Cardiac failure congestive was the most commonly occurring Grade 3 event. Myocardial infarction and atrial fibrillation were the Grade 4 events. Grade 5 fatal events reported in four patients were acute myocardial infarction, arteriosclerosis coronary artery, cardiac hypertrophy, and cardio-respiratory arrest.

Age ≤65 years

- 39.9% (881 out of 2137) patients reported 1626 AEs. Majority were Grade 1 events (n = 1259 in 736 patients) and Grade 2 (n = 329 in 267 patients). There were 36 Grade 3 events in 32 patients, most frequently occurring were dyspnoea (n = 5), cough (n = 3), asthma, hyperventilation and respiratory distress (n = 1 each). Anaphylactic shock and cardio-respiratory arrest were reported as Grade 4 and Grade 5 events, respectively (n = 1 each).

Age >65 years

- 38.2% (172 out of 432) patients reported 311 AEs. Majority were Grade 1 events (n = 237 in 140 patients) and Grade 2 (n = 61 in 50 patients). There were 12 Grade 3 events in 11 patients (dyspnoea [n = 8], rash, erythema, respiratory failure and drug hypersensitivity [n = 1 each]) and one Grade 4 event of asthma was reported. No Grade 5 events were reported.

Summary

The >65 years sub-group reported higher percentage of patients with AEs compared with the ≤65 years sub-group. For all age groups, majority of the AEs were either Grade 1 or 2 in line with the unstratified outputs.

Race

White: 766/1973 (38.82%) patients reported 1411 events (Grade 3: 37 events in 42 patients, Grade 4: two events in two patients and no Grade 5 events were reported).

Black: 19/31 (61.3%) patients reported 33 events (Grade 3: one event, no Grade 4 or 5 events).

Asian: 176/378 (46.6%) patients reported 315 events (Grade 3: 3 events reported in 3 patients, no Grade 4 and Grade 5 events).

Other: 36/89 (40.4%) patients reported 91 events (two Grade 3 event in two patients, one Grade 5 event, and no Grade 4 events).

N/A (per local regulation): 52/89 (58.42%) patients reported 81 events (no Grade 3, 4 or 5 events).

Unknown: 3/9 (33.3%) patients reported 4 events (no grade 3, 4 or 5 events)

Summary

Majority of the patients included in the trials were White. Across all the race sub-groups, majority of the events reported were Grade 1 and Grade 2

Joint Analysis of NSABP B-31 and N9831

Of the Cardiac dysfunction AEs (as defined in this RMP), only severity data on Cardiac – left ventricular function and Oedema were collected for both Studies B-31 and N9831, i.e., no severity data was collected for CHF, decreased (LV)EF, or other Cardiac failure SMQ AEs.

For Cardiac – left ventricular function, the distribution of Grades 3-5 AEs during Periods 2-4 (defined as any time after the initiation of paclitaxel therapy) in AE-Evaluable patients in the Joint Analysis data were as follows:

- AC->T: 1 (0.1%)
- AC ->T+H: 42 (2.1%)
- AC->T->H: 3 (0.8%)

For Cardiac – left ventricular function, the distribution of Any Grade AEs were as follows:

- AC->T: 28 (1.9%)
- AC ->T+H: 262 (13.1%)
- AC->T->H: 27 (7.6%)

For Oedema, the distribution of Grades 3-5 AEs were as follows:

- AC->T: 1 (0.1%)
- AC ->T+H: 0 (0.0%)
- AC->T->H: 0 (0.0%)

For Oedema, the distribution of Any Grade AEs was as follows:

- AC->T: 25 (1.7%)
- AC ->T+H: 43 (2.2%)
- AC->T->H: 4 (1.1%).

A total of three cardiac deaths were observed in the trastuzumab-containing arms compared with five cardiac deaths in the control arm. These cardiac deaths did not necessarily include CHF (i.e., the category of cardiac death in the Joint Analysis included MI, arrhythmia, and sudden death).

Stratified data

The AEs of cardiac dysfunction were stratified by the presence of number of known risk factors (age >50 years, use of anti-hypertensive medications at baseline, and LVEF at paclitaxel baseline ≤55%), and by race.

In this study, majority of patients were White. Other substantial groups included were Black and Hispanic. Most of these patients were in the AC –>T or AC –>T+H arm. The stratification by race, in patients with 0, 1, 2, or all the 3 of these risk factors is presented below:

Patients with no risk factors:

AC –> T arm:

- Asian (0/8, 0.0%)
- Hispanic (0/26, 0.0%)
- Pacific Islander (0/5, 0.5%)
- White (2/392, 0.5%)
- Black (0/34, 0.0%)
- Unknown (0/2, 0.0%)
- Other (0/3, 0.0%)
- Native American (0/0, 0.0%);

AC –>T+H arm

- Asian patients (1/27, 3.7%)
- Hispanic (0/31, 0.0%)
- Pacific Islander (0/5, 0.0%)
- White patients (7/660, 1.1%)
- Black patients (2/48, 4.2%)
- Unknown (0/3, 0.0%)
- Other (0/8, 0.0%)
- Native American (0/2, 0.0%);

AC –>T –>H arm

- Asian patients (0/4, 0.0%)
- Hispanic (0/5, 0.0%)
- Pacific Islander (0/0, 0.0%)
- White patients (0/102, 0.0%)
- Black patients (0/3, 0.0%)

- Unknown (0/3, 0.0%)
- Other (0/0, 0.0%)
- Native American (0/0, 0.0%);

Patients with one risk factor:

AC –> T arm: Asian (1/11, 9.1%), Hispanic (0/20, 0.0%), Pacific islander (1/6, 16.7%), White (4/421, 1%), Black (1/32, 3.1%), Unknown (0/2, 0.0%), Other (0/2, 0.0%), and Native American (0/2, 0.0%);

AC –>T+H arm: Asian (0/26, 0.0%), Hispanic (0/27, 0.0%), Pacific Islander (0/5, 0.0%), White (24/617, 3.9%), Black (0/39, 0.0%), Unknown (0/6, 0.0%), Other (0/3, 0.0 %), and Native American (0/4, 0.0%);

AC –>T –>H arm: Asian (0/3, 0.0%), Hispanic (1/3, 33.3%), Pacific Islander (0/1, 0.0%), White (2/108, 1.9%), Black (0/7, 0.0%), Unknown (0/0, 0.0%), Other (0/2, 0.0%), and Native American (0/1, 0.0%).

Patients with two risk factors:

AC –> T arm: Asian (0/10, 0.0%), Hispanic (1/10, 10 %), Pacific Islander (0/3, 0.0%), White (3/216, 1.4%), Black (0/33, 0.0%), Unknown (0/0, 0.0%), Other (0/1, 0.0%), and Native American (0/0, 0.0%);

AC –>T+H arm: Asian (2/12 (16.7%), Hispanic (0/12, 0.0%), Pacific Islander (0/1, 0.0%), White (20/302, 6.6%), Black (1/29, 3.4%), Unknown (0/0, 0.0%), Other (0/3, 0.0%), and Native American (0/0, 0.0%);

AC –>T –>H arm: Asian (0/3, 0.0%), Hispanic (0/3, 0.0%), Pacific Islander (0/0, 0.0%), White (2/57 3.5 %), Black (1/7, 14.3%), Unknown (0/0, 0.0%), Other (0/2, 0.0%), and Native American (0/0, 0.0%).

Patients with three risk factors:

AC –> T arm: Hispanic (0/1, 0.0%), White (0/32, 0.0%), Black (0/9, 0.0%), no patient included in any other race

AC –>T+H arm: Asian (0/1, 0.0%); Hispanic (0/2, 0.0%); White (3/34, 8.8%), Black (1/4, 25%), other (0/1, 0.0%), no patient included in any other race

AC –>T –>H arm: White (1/9, 11.1%), Black (0/1, 0.0%), no patient included in any other race.

Summary

A meaningful stratified comparison of cardiac dysfunction by race is impacted by low number of patients and AEs in most of the resulting subgroups.

Neoadjuvant treatment in EBC

MO16432 (NOAH)

Cardiac events reported in at least two patients included: angina pectoris (5 patients in each of the HER2-positive arms), tachycardia (5 patients in each of the HER2-positive arms and one patient in the HER2-negative arm) and palpitations (3 patients in each of the HER2-positive arms and one patient in the HER2-negative arm). None of these cardiac events were reported as Grade 3 or 4 AEs. The myocardial ischemia in the HER2+TC arm was of Grade 2 intensity at worst and recovered on the same day without sequelae.

During the post-operative period, 16 patients experienced 22 cardiac AEs (8.9% [10/112] patients with 15 AEs in HER2 positive + TC, 10.0% [2/20] patients with two AEs in HER2 positive + C→T, 5.9% [4/68] patients with five AEs in HER2 positive + C). In the HER2 positive + C arm, patient [redacted] experienced a Grade 3 pericardial effusion and in the HER2 positive + TC arm, patient [redacted] had a Grade 3 decreased ejection fraction considered related to study medication and reported as an SAE.

Neoadjuvant-adjuvant Treatment in EBC:

BO22227 – (HannaH):

Intravenous (Herceptin IV) & Subcutaneous (Herceptin SC) in EBC:

Severity per CTC Grading

In the IV arm, all AEs were either Grade 1 or Grade 2; there were no Grade 3 -5 AEs.
In the Herceptin SC arm, 4 AEs in 3 patients were Grade 3 in severity; two of these were assessed as serious. There was no Grade 4 or 5 cardiac dysfunction-related AEs in the Herceptin SC arm. Please refer to Table 5 (IV arm) and Table 6 (SC arm).

Stratified data:

Age:

In the Herceptin IV arm, a higher number of patients aged >50 years, reported cardiac dysfunction-related AEs compared with those ≤50 years (31/143, 22%) vs. 25/155, 16%. In the Herceptin SC arm, the number of patients reporting AEs was lower in patients aged >50 years (19/140, 14%) as compared with ≤50 years (28/157, 18%).

In the Herceptin IV arm, Grade 1 events were reported in 12% and 17% patients in age ≤50 and >50 years, respectively. In the SC arm, Grade 1 events were reported in 15% and 11% patients in age ≤50 and >50 years, respectively.

In the Herceptin IV arm, Grade 2 events were reported in 5% and 6% patients in age ≤50 and >50 years, respectively.In the Herceptin SC arm, Grade 2 events were reported in 3% and 2% of the patients in age ≤50 and >50 years sub-groups, respectively.

There were no Grade 3 AEs reported in the Herceptin IV arm, while in the Herceptin SC arm 2 and 1 patient(s) in age group ≤50 and >50 years reported a Grade 3 AE.

No grade 4 or 5 AEs were reported in any of the patients.

Summary: No clear discernible pattern was observed in either of the age groups for cardiac dysfunction-related events.

Race:

Most of the patients enrolled in the study were 'White' (n=208 in the Herceptin IV arm and n=200 in the Herceptin SC arm) followed by Asians (n=61 in IV vs. n=64 in SC arm) 'Other' race was reported in 29 and 33 patients in the Herceptin IV arm and Herceptin SC arms, respectively.

Asian patients reported more Grade 1 events (IV arm: 15 [25%], and SC arm: 15 [23%]) as compared with White (IV arm: 243 [12%], and SC arm: 208 [10%]) and 'Other' (IV arm: 4 [14%], and SC arm: 2 [6%]). Grade 2 events were comparable across all arms. Grade 3 events were reported in 3 patients in the SC arm (1[<1%] white patient, and 2 patients 6%] in 'Other' race). No Grade 4 or 5 events were reported.

Summary

Asian patients reported more AEs across both the arms, compared with the 'White' and 'Other' race patients, most being of low severity and with a trend for more AEs in the IV arm.

MO22982 (PrefHER)
Results from crossover period SC-IV or IV-SC (479 patients for Herceptin SC period and 478 patients for Herceptin IV period).

Herceptin IV (4 cycles):

Two patients with grade 3 Left Ventricular Dysfunctions were reported. Three patients had three Cardiac AEs of Grade 2 severity and eleven had 12 Grade 1 AEs.

Herceptin SC (4 cycles):

One patient with grade 3 left ventricular dysfunction was reported. Two patients had two Cardiac AEs of a Grade 2 severity and nine patients had 12 Grade 1 AEs. Refer to Table 16 below.

Table 16 Cardiac Dysfunction by Severity MO22982 (Crossover SC-IV / IV-SC, EBC)

Cohort 1 and 2 Maximum CTC grade System Organ Class Preferred Term	SC Period (N=479) n	 (%)	 E	IV Period (N=478) n	 (%)	 E
Maximum CTC grade: 3-Severe						
Cardiac Disorders	1	(0.2)	1	2	(0.4)	2
Left Ventricular Dysfunction	1	(0.2)	1	2	(0.4)	2
Cardiac Failure Congestive	0			0		
Maximum CTC grade: 2-Moderate						
Cardiac Disorders	1	(0.2)	1	3	(0.6)	3
Left Ventricular Dysfunction	0			1	(0.2)	1
Cardiac Failure Congestive	1	(0.2)	1	0		
Angina Pectoris	0			1	(0.2)	1
Bradycardia	0			1	(0.2)	1
Palpitations	0			0		
Maximum CTC grade: 1-Mild						
Cardiac Disorders	6	(1.3)	7	9	(1.9)	9
Palpitations	3	(0.6)	3	2	(0.4)	2
Left Ventricular Dysfunction	1	(0.2)	1	2	(0.4)	2
Bradycardia	1	(0.2)	1	2	(0.4)	2
Cardiac Failure Congestive	1	(0.2)	1	0		
Extrasystoles	1	(0.2)	1	0		
Cardiomyopathy	0			0		
Diastolic Dysfunction	0			1	(0.2)	1
Heart Valve Incompetence	0			1	(0.2)	1
Left Ventricular Hypertrophy	0			0		
Mitral Valve Incompetence	0			1	(0.2)	1

Sinus Bradycardia	0	0
Tachycardia	0	0

Notes: [1] All Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Advanced Gastric Cancer:

BO18255 (ToGA):

Across both treatment arms, cardiac AEs were mostly mild-to-moderate in severity. See

Table 3 for a listing of CTC worst grading severity.

Stratified data:

Age:

Fluoropyrimidine/Cisplatin arm:

- ≤50 (n=69): Grade 1: 3 (4.3%) and Grade 2: 1 (1.4%). No Grade 3 or Grade 4 events were reported.
- 50 (n=221): Grade 1: 27 (12.2%), Grade 2: 7 (3.2%), Grade 3: 2 (0.9%), and Grade 4: 1 (0.5%).

Trastuzumab/Fluoropyrimidine/Cisplatin arm

- ≤50 (n=57): Grade 1: 6 (10.5%), Grade 2: 2 (3.5%), No Grade 3 or Grade 4 events were reported.
- 50 (n=237): Grade 1: 30 (12.7%), Grade 2: 6 (2.5%), and Grade 3 and Grade 4: 2 (0.8%).

Summary:

Treatment with Herceptin increases the risk of cardiac dysfunction. Age >50 years is an identified risk factor for cardiac dysfunction. The stratified data from this study confirms this finding.

Gender:

Male patients:

Fluoropyrimidine/Cisplatin arm:

- Male: (n=218): Grade 1: 18 (8.3%), Grade 2: 2 (0.9%), Grade 3: 1(0.5%), and Grade 4: None.
- Females: (n=72): Grade 1: 12 (16.7%) and Grade 2: 2 (2.8%). No Grade 3 or 4 events were reported.

Trastuzumab/Fluoropyrimidine/Cisplatin arm

- Male: Grade 1: 27 (11.9%), Grade 2: 5 (2.2%), Grade 3: 1 (0.4%), and Grade 4: 4(0.9%).
- Female: (n=68): Grade 1: 9 (13.2%), Grade 2: 3 (4.4%). No Grade 3 and 4 events reported.

Summary

Within respective arms, the percentage of AEs was more in female patients. Although no Grade 3 or 4 AEs were reported in female patients.

Race:

Fluoropyrimidine/Cisplatin arm:

- Caucasians (n=105): Grade 1: 5 (4.8%), Grade 2: 3 (2.9%), Grade 3: 2 (1.9%), and Grade 4: 1 (1%).
- Oriental (n=158): Grade 1: 25 (15.8%), Grade 2: 5 (3.2%). No Grade 3 or 4 AEs were reported.

Trastuzumab/Fluoropyrimidine/Cisplatin arm

- Caucasians (n=115): Grade 1: 7 (6.1%), Grade 2: 4 (3.5%), Grade 3: 1 (0.9%), and no Grade 4 events were reported.
- Oriental (n=151): Grade 1: 24 (15.9%), Grade 2: 1 (1.3%), Grade 3: 1 (0.7%), and Grade 4: 2 (1.3%).

Summary

The Oriental patients reported higher numbers of AEs compared with the Caucasians; majority of them were Grade 1. The meaningful comparison of Grade 2, 3, and 4 events is impacted by low numbers of events reported in each of these sub-groups.

Region:

In the Herceptin containing arm, Asian patients reported the most number of Grade 1 AEs as compared with the European patients (25/164, 16.1% vs. 3/99, 3%). A relatively lower number of Grade 2 (Asia: 3, 1.9%; Europe: 3, 3%), Grade 3 (Asia: 1, 0.6%; Europe: 1, 1%), and Grade 4 (Asia: 2[1.3%], Europe: none) events were reported precluding a meaningful analysis.

1.4 RISK GROUPS OR RISK FACTORS

Table 17 Incidence of Cardiac Events by risk factor Subgroup in the AC→T and AC→TH Arms: Safety Population (BCIRG 006) (H2296s)/GO00773

Subgroup	Number of Patients with Cardiac Events per Arm		
	AC→T	AC→TH	p-value*
Age (yr)			
n	1050	1068	—
≤50	2/594 (0.3%)	8/592 (1.4%)	0.0560
>50	4/456 (0.9%)	15/476 (3.4%)	0.0141
Prior or current use of cardiovascular medications at baseline			
n	1050	1068	—
Yes	3/178 (1.7%)	7/186 (3.8%)	0.2253
No	3/872 (0.3%)	16/882 (1.8%)	0.0029
Hypertension at baseline			
n	1050	1068	
Yes	1/182 (0.5%)	7/188 (3.7%)	0.0359
No	5/868 (0.6%)	16/880 (1.8%)	0.0172
Lowest post-baseline LVEF			
n	1015	1041	—
>60%	0/4 (0.0%)	0/0 (0.0%)	NE
70%–75%	0/72 (0.0%)	0/39 (0.0%)	NE
60%–69%	0/397 (0.0%)	2/355 (0.6%)	0.1343
<60%	6/542 (1.1%)	21/647 (3.2%)	0.0137

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; LVEF = left ventricular ejection fraction; NE = not estimable; TCH = docetaxel, carboplatin, and Herceptin.

* Derived from the Pearson χ^2 test.

Table 18 Time to First Cardiac or LVEF Event following Initiation of Docetaxel or Trastuzumab Therapy, AC→T versus AC→TH (BCIRG 006) (H2296s)/GO00773

Covariate[a]	No. of Observations Used	No. of Events	Hazard Ratio		
			Estimate	95% CI	p-value[b]
Treatment[c]	2066	156	2.36	(1.679, 3.383)	<0.0001
0=AC→T					
1=AC→TH					
Age (yr)	2066	156	1.55	(1.131, 2.135)	0.0067
0=≤50					
1=>50					
Nodal status	2066	156	0.98	(0.694, 1.395)	0.9288
0=Negative					
1=Positive					
Prior or current cardiovascular medications at baseline	2066	156	0.83	(0.531, 1.286)	0.3982
0=No					
1=Yes					
Hypertension ongoing at baseline	2066	156	0.85	(0.550, 1.312)	0.4614
0=No					
1=Yes					
Karnofsky performance status	2066	156	1.22	(0.841, 1.771)	0.2950
0=100					
1=<100					
Radiation to left side of the chest	2066	156	1.17	(0.838, 1.632)	0.3573
0=No					
1=Yes					
Absolute decline of >15 points in LVEF	2066	156	5.99	(1.909, 18.812)	0.0022
0=No					
1=Yes					
Baseline LVEF	2066	156	1.01	(0.900, 1.031)	0.3251
LVEF at T, TH, TCH baseline	2064	156	0.96	(0.944, 0.984)	0.0005
LVEF ≥28 days prior to event (continuous time-dependent covariate)[d]	2066	156	0.94	(0.916, 0.956)	<0.0001
LVEF value <55% at least 28 days prior to event[d]	2066	156	3.22	(2.258, 4.594)	<0.0001
0=No					
1=Yes					

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin; LVEF=left ventricular ejection fraction; TCH=docetaxel, carboplatin, and Herceptin.

[a] 0 and 1 indicate coding of variable in the Cox proportional hazards model.

[b] Wald p-value associated with estimated hazard ratio.

[c] All models include indicator variable for treatment.

[d] Time-varying covariate.

Table 19 presents the actual numbers and percentages of patients with a cardiac event in each risk category: age > 50 years, the use of anti-hypertensive medications at baseline, and LVEF at paclitaxel baseline ≤55%. This table illustrates how the incidence of cardiac events in the AC→T+H group was influenced by these factors. Note that, when LVEF at paclitaxel baseline ≤55% and either age > 50 years or use of anti-hypertensive medications at baseline, the incidence of cardiac events in the AC→T+H patients was > 9.5%. In addition, when LVEF at paclitaxel baseline ≤55% and age > 50 years, the incidence of cardiac events in the AC→T+H group was > 9.2% and in the AC→T→H group was >12.5%. It should be noted that some of these percentages were based on small numbers of events in relatively few patients.

Table 20 presents the incidence of cardiac events by the number of risk factors following initiation of paclitaxel or Herceptin+paclitaxel Therapy. The risk factors considered were age >50 years, the use of anti-hypertensive medication, and LVEF ≤55%.

In the AC→T+H group, the risk of a cardiac event increased with the number of risk factors present, from an incidence of 1.3% when no risk factors were present to 9.5% when all three risk factors were present. In the AC→T→H group, the incidence of a cardiac event was 4.2% when any two of the three risk factors were present and 10.0% (1/10) when all three risk factors were presented. The incidence of a cardiac event was 1.5% when any two of the three risk factors were present in AC→T patients.

Table 19 Rates of Cardiac Events by Risk Factor: Patients from the Joint Safety Population with Follow-Up after Paclitaxel Baseline (Joint Analysis: B-31; N9831)

Age > 50	Use of Hypertension Medications at Baseline	LVEF at Paclitaxel Baseline <=55	AC->T	AC->T+H	AC->T->H
Yes	Yes	Yes	0/ 42 (0.0%)	4/ 42 (9.5%)	1/ 10 (10.0%)
		No	0/ 148 (0.0%)	12/ 245 (4.9%)	1/ 50 (2.0%)
	No	Yes	4/ 111 (3.6%)	9/ 98 (9.2%)	2/ 16 (12.5%)
		No	3/ 301 (1.0%)	16/ 483 (3.3%)	2/ 79 (2.5%)
No	Yes	Yes	0/ 14 (0.0%)	2/ 16 (12.5%)	0/ 6 (0.0%)
		No	0/ 45 (0.0%)	1/ 75 (1.3%)	0/ 12 (0.0%)
	No	Yes	4/ 150 (2.7%)	7/ 169 (4.1%)	1/ 34 (2.9%)
		No	2/ 470 (0.4%)	10/ 784 (1.3%)	0/ 114 (0.0%)

A=doxorubicin; C=cyclophosphamide; H=Herceptin; LVEF=left ventricular ejection fraction; T=paclitaxel;

Source: Biostatistics([redacted]) pgm(/immuno/her2/abcjoint/finalos/programs/t_cardiac_rates_hypt) output (t_cardiac_rates_hypt)
Database(Data Received in 2013) Datasets (patcard)
Joint Analysis Final Overall Survival : Generated 17JUL13 12:26 Page 1 of 1

Table 20 Rates of Cardiac Events by Number of Risk Factors following Initiation of Paclitaxel or Herceptin + Paclitaxel Therapy: Patients from the Joint Safety Population with Follow-Up after Paclitaxel Baseline (Joint Analysis: B-31; N9831)

Number of patients with an event/ number of patients per risk factor subset (percent)
(95% CI for the binomial proportion x 100%)

Number of Risk Factors *	AC->T	AC->T+H	AC->T->H
0	2/ 470 (0.4%) (0.0%, 1.0%)	10/ 784 (1.3%) (0.5%, 2.1%)	0/ 114 (0.0%) (100.0%, 100.0%)
1	7/ 496 (1.4%) (0.4%, 2.4%)	24/ 727 (3.3%) (2.0%, 4.6%)	3/ 125 (2.4%) (0.0%, 5.1%)
2	4/ 273 (1.5%) (0.0%, 2.9%)	23/ 359 (6.4%) (3.9%, 8.9%)	3/ 72 (4.2%) (0.0%, 8.8%)
3	0/ 42 (0.0%) (100.0%, 100.0%)	4/ 42 (9.5%) (0.6%, 18.4%)	1/ 10 (10.0%) (0.0%, 28.6%)

A=doxorubicin; C=cyclophosphamide; CI=confidence interval; H=Herceptin; T=paclitaxel;

* The risk factors are: age > 50 years, use of anti-hypertensive medications at baseline, and non-missing LVEF at paclitaxel baseline <= 55.

Source: Biostatistics ([redacted]) pgm(/immuno/her2/abcjoint/finalos/programs/t_cardiac_risk_hypt) output (t_cardiac_risk_hypt)

Database(Data Received in 2013) Datasets (patcard)

Joint Analysis Final Overall Survival : Generated 17JUL13 12:27 (PDRD)

2. ADMINISTRATION-RELATED REACTIONS

Table 21 Administration Related Reactions by System Organ Class and Preferred Term - Study MO28048 (SafeHER) Whole Study, Reduced Event Count

(Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
Number of Administration Related Reactions	743	(39.9)	1087	277	(39.1)	407	1020	(39.6)	1494
Skin And Subcutaneous Tissue Disorders	421	(22.6)	503	173	(24.4)	205	594	(23.1)	708
Rash	183	(9.8)	183	74	(10.4)	74	257	(10.0)	257
Erythema	159	(8.5)	159	75	(10.6)	75	234	(9.1)	234
Pruritus	116	(6.2)	116	35	(4.9)	35	151	(5.9)	151
Urticaria	19	(1.0)	19	8	(1.1)	8	27	(1.0)	27
Rash Pruritic	6	(0.3)	6	4	(0.6)	4	10	(0.4)	10
Pruritus Generalised	8	(0.4)	8	1	(0.1)	1	9	(0.3)	9
Rash Erythematous	3	(0.2)	3	5	(0.7)	5	8	(0.3)	8
Rash Generalised	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Swelling Face	4	(0.2)	4	0		0	4	(0.2)	4
Generalised Erythema	1	(0.1)	1	1	(0.1)	1	2	(0.1)	2
Pruritus Allergic	1	(0.1)	1	0		0	1	(0.0)	1

Respiratory, Thoracic And Mediastinal Disorders	314	(16.8)	349	104	(14.7)	113	418	(16.2)	462
Cough	197	(10.6)	197	57	(8.0)	57	254	(9.9)	254
Dyspnoea	123	(6.6)	123	48	(6.8)	48	171	(6.6)	171
Asthma	12	(0.6)	12	4	(0.6)	4	16	(0.6)	16
Sneezing	5	(0.3)	5	1	(0.1)	1	6	(0.2)	6
Wheezing	4	(0.2)	4	2	(0.3)	2	6	(0.2)	6
Respiratory Failure	2	(0.1)	2	0		0	2	(0.1)	2
Bronchospasm	1	(0.1)	1	0		0	1	(0.0)	1

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AECRI2XP.SAS

Produced: 19 February 2016, 11:43

Source: Listing 16.2.7.8

Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket

[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count

[3] Table presents number and percentage of patients (n (%)) and number of events (E)

[4] Percentages are based on the number of patients in the respective group

[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 14.3.5.9.10.1b Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count (Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
Respiratory, Thoracic And Mediastinal Disorders (contd ...)									
Choking	1	(0.1)	1	0		0	1	(0.0)	1
Hyperventilation	1	(0.1)	1	0		0	1	(0.0)	1
Laryngeal Oedema	0		0	1	(0.1)	1	1	(0.0)	1
Nasal Obstruction	1	(0.1)	1	0		0	1	(0.0)	1
Respiratory Distress	1	(0.1)	1	0		0	1	(0.0)	1
Throat Tightness	1	(0.1)	1	0		0	1	(0.0)	1
Vascular Disorders	66	(3.5)	69	28	(3.9)	29	94	(3.7)	98
Flushing	46	(2.5)	46	22	(3.1)	22	68	(2.6)	68
Hypotension	22	(1.2)	22	7	(1.0)	7	29	(1.1)	29

Circulatory Collapse	1	(0.1)	1	0		0	1	(0.0)	1
General Disorders And Administration Site Conditions	60	(3.2)	62	21	(3.0)	22	81	(3.1)	84
Oedema	22	(1.2)	22	11	(1.6)	11	33	(1.3)	33
Chest Discomfort	17	(0.9)	17	5	(0.7)	5	22	(0.9)	22
Face Oedema	13	(0.7)	13	1	(0.1)	1	14	(0.5)	14
Swelling	6	(0.3)	6	4	(0.6)	4	10	(0.4)	10
Injection Site Hypersensitivity	3	(0.2)	3	1	(0.1)	1	4	(0.2)	4
Sensation Of Foreign Body	1	(0.1)	1	0		0	1	(0.0)	1

Source: Listing 16.2.7.8

Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket

[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count

[3] Table presents number and percentage of patients (n (%)) and number of events (E)

[4] Percentages are based on the number of patients in the respective group

[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 14.3.5.9.10.1b Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count (Safety Population)

System Organ Class / Preferred Term	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
Immune System Disorders	54	(2.9)	54	18	(2.5)	20	72	(2.8)	74
Hypersensitivity	34	(1.8)	34	13	(1.8)	13	47	(1.8)	47
Drug Hypersensitivity	16	(0.9)	16	6	(0.8)	6	22	(0.9)	22
Anaphylactic Reaction	2	(0.1)	2	0		0	2	(0.1)	2
Anaphylactic Shock	1	(0.1)	1	1	(0.1)	1	2	(0.1)	2
Allergic Oedema	1	(0.1)	1	0		0	1	(0.0)	1
Injury, Poisoning And Procedural Complications	30	(1.6)	30	7	(1.0)	7	37	(1.4)	37
Infusion Related Reaction	30	(1.6)	30	7	(1.0)	7	37	(1.4)	37
Eye Disorders	12	(0.6)	13	8	(1.1)	8	20	(0.8)	21
Eye Pruritus	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Eye Swelling	3	(0.2)	3	1	(0.1)	1	4	(0.2)	4

Ocular Hyperaemia	2	(0.1)	2	2	(0.3)	2	4	(0.2)	4
Eye Oedema	1	(0.1)	1	2	(0.3)	2	3	(0.1)	3
Eyelid Oedema	2	(0.1)	2	1	(0.1)	1	3	(0.1)	3
Periorbital Oedema	2	(0.1)	2	0		0	2	(0.1)	2
Gastrointestinal Disorders	4	(0.2)	4	2	(0.3)	2	6	(0.2)	6
Lip Swelling	2	(0.1)	2	0		0	2	(0.1)	2
Tongue Oedema	1	(0.1)	1	1	(0.1)	1	2	(0.1)	2
Oedema Mouth	1	(0.1)	1	0		0	1	(0.0)	1
Swollen Tongue	0		0	1	(0.1)	1	1	(0.0)	1

Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket

[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count

[3] Table presents number and percentage of patients (n (%)) and number of events (E)

[4] Percentages are based on the number of patients in the respective group

[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 14.3.5.9.10.1b Administration Related Reactions by System Organ Class and Preferred Term - Whole Study, Reduced Event Count (Safety Population)

System Organ Class Preferred Term	Cohort A (N=1864) n (%)	E	Cohort B (N=709) n (%)	E	Overall (N=2573) n (%)	E
Cardiac Disorders	3 (0.2)	3	0	0	3 (0.1)	3
Cyanosis	2 (0.1)	2	0	0	2 (0.1)	2
Cardio-Respiratory Arrest	1 (0.1)	1	0	0	1 (0.0)	1
Investigations	0	0	1 (0.1)	1	1 (0.0)	1
Blood Pressure Decreased	0	0	1 (0.1)	1	1 (0.0)	1

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AECRI2XP.SAS

Produced: 19 February 2016, 11:43 Page 4 of 4

Source: Listing 16.2.7.8

Notes: [1] Administration Related Reaction is defined as all events based on a MedDRA basket

[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count

[3] Table presents number and percentage of patients (n (%)) and number of events (E)

[4] Percentages are based on the number of patients in the respective group

[5] Only one event is counted for multiple occurrences of the same AE (preferred term) in a patient

Table 22 Administration-Related Reactions, Severity & Frequency: BO22227 - IV ARM

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	111	(37.2)	94	(31.5)	34	(11.4)	6	(2.0)	-		-	
Total Number of AEs	200		150		44		6		-		-	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS												
Total Pts With at Least one AE	67	(22.5)	57	(19.1)	16	(5.4)	-		-		-	
RASH	44	(14.8)	31	(10.4)	13	(4.4)	-		-		-	
PRURITUS	27	(9.1)	25	(8.4)	2	(0.7)	-		-		-	
ERYTHEMA	8	(2.7)	7	(2.3)	1	(0.3)	-		-		-	
URTICARIA	2	(0.7)	2	(0.7)	-		-		-		-	
PRURITUS GENERALISED	1	(0.3)	1	(0.3)	-		-		-		-	
RASH GENERALISED	1	(0.3)	-		1	(0.3)	-		-		-	
Total Number of AEs	83		66		17		-		-		-	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS												
Total Pts With at Least one AE	41	(13.8)	32	(10.7)	9	(3.0)	-		-		-	
COUGH	24	(8.1)	20	(6.7)	4	(1.3)	-		-		-	
DYSPNOEA	22	(7.4)	18	(6.0)	4	(1.3)	-		-		-	
BRONCHOSPASM	1	(0.3)	-		1	(0.3)	-		-		-	
Total Number of AEs	47		38		9		-		-		-	
IMMUNE SYSTEM DISORDERS												
Total Pts With at Least one AE	22	(7.4)	10	(3.4)	9	(3.0)	4	(1.3)	-		-	
HYPERSENSITIVITY	14	(4.7)	7	(2.3)	4	(1.3)	3	(1.0)	-		-	
DRUG HYPERSENSITIVITY	9	(3.0)	3	(1.0)	5	(1.7)	1	(0.3)	-		-	
Total Number of AEs	23		10		9		4		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (1 of 4)

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB IV; N = 298

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Total Pts With at Least one AE	19 (6.4)	16 (5.4)	3 (1.0)	-	-	-
OEDEMA	15 (5.0)	12 (4.0)	3 (1.0)	-	-	-
CHEST DISCOMFORT	6 (2.0)	6 (2.0)	-	-	-	-
FACE OEDEMA	1 (0.3)	1 (0.3)	-	-	-	-
SWELLING	1 (0.3)	1 (0.3)	-	-	-	-
Total Number of AEs	23	20	3	-	-	-
VASCULAR DISORDERS						
Total Pts With at Least one AE	17 (5.7)	11 (3.7)	4 (1.3)	2 (0.7)	-	-
FLUSHING	12 (4.0)	10 (3.4)	2 (0.7)	-	-	-
HYPOTENSION	5 (1.7)	1 (0.3)	2 (0.7)	2 (0.7)	-	-
Total Number of AEs	17	11	4	2	-	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
Total Pts With at Least one AE	5 (1.7)	3 (1.0)	2 (0.7)	-	-	-
INFUSION RELATED REACTION	5 (1.7)	3 (1.0)	2 (0.7)	-	-	-
Total Number of AEs	5	3	2	-	-	-
EYE DISORDERS						
Total Pts With at Least one AE	2 (0.7)	2 (0.7)	-	-	-	-
EYE PRURITUS	2 (0.7)	2 (0.7)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (2 of 4)

Table 23 Administration-Related Reactions, Severity & Frequency: BO22227 - SC ARM

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	142 (47.8)	121 (40.7)	50 (16.8)	5 (1.7)	-	-
Total Number of AEs	234	168	61	5	-	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Total Pts With at Least one AE	90 (30.3)	68 (22.9)	24 (8.1)	1 (0.3)	-	-
RASH	48 (16.2)	37 (12.5)	11 (3.7)	-	-	-
PRURITUS	26 (8.8)	19 (6.4)	7 (2.4)	-	-	-
ERYTHEMA	21 (7.1)	16 (5.4)	4 (1.3)	1 (0.3)	-	-
RASH PRURITIC	3 (1.0)	2 (0.7)	1 (0.3)	-	-	-
URTICARIA	2 (0.7)	2 (0.7)	-	-	-	-
RASH ERYTHEMATOUS	1 (0.3)	-	1 (0.3)	-	-	-
RASH GENERALISED	1 (0.3)	-	1 (0.3)	-	-	-
SWELLING FACE	1 (0.3)	1 (0.3)	-	-	-	-
Total Number of AEs	103	77	25	1	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	52 (17.5)	39 (13.1)	16 (5.4)	1 (0.3)	-	-
COUGH	35 (11.8)	29 (9.8)	5 (1.7)	1 (0.3)	-	-
DYSPNOEA	21 (7.1)	13 (4.4)	8 (2.7)	-	-	-
ASTHMA	1 (0.3)	-	1 (0.3)	-	-	-
HYPERVENTILATION	1 (0.3)	-	1 (0.3)	-	-	-
LARYNGEAL OEDEMA	1 (0.3)	-	1 (0.3)	-	-	-
Total Number of AEs	59	42	16	1	-	-
IMMUNE SYSTEM DISORDERS						
Total Pts With at Least one AE	20 (6.7)	9 (3.0)	8 (2.7)	3 (1.0)	-	-
DRUG HYPERSENSITIVITY	11 (3.7)	6 (2.0)	3 (1.0)	2 (0.7)	-	-
HYPERSENSITIVITY	9 (3.0)	3 (1.0)	5 (1.7)	1 (0.3)	-	-
Total Number of AEs	20	9	8	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (3 of 4)

stae17irr_se Summary of CTC Grading (Worst Case) for Administration-Related Reactions (MedDRA basket) (Safety Population)
Protocol(s): J22227M
Analysis: SAFETY Center: ALL CENTERS
Treatment: TRASTUZUMAB SC; N = 297

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Total Pts With at Least one AE	18	(6.1)	17	(5.7)	1	(0.3)	-		-		-	
OEDEMA	10	(3.4)	9	(3.0)	1	(0.3)	-		-		-	
CHEST DISCOMFORT	8	(2.7)	7	(2.4)	1	(0.3)	-		-		-	
FACE OEDEMA	4	(1.3)	4	(1.3)	-		-		-		-	
SWELLING	1	(0.3)	1	(0.3)	-		-		-		-	
Total Number of AEs	23		21		2		-		-		-	
VASCULAR DISORDERS												
Total Pts With at Least one AE	18	(6.1)	15	(5.1)	3	(1.0)	-		-		-	
FLUSHING	13	(4.4)	11	(3.7)	2	(0.7)	-		-		-	
HYPOTENSION	5	(1.7)	4	(1.3)	1	(0.3)	-		-		-	
Total Number of AEs	18		15		3		-		-		-	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS												
Total Pts With at Least one AE	7	(2.4)	2	(0.7)	5	(1.7)	-		-		-	
INFUSION RELATED REACTION	7	(2.4)	2	(0.7)	5	(1.7)	-		-		-	
Total Number of AEs	7		2		5		-		-		-	
EYE DISORDERS												
Total Pts With at Least one AE	4	(1.3)	2	(0.7)	2	(0.7)	-		-		-	
EYE PRURITUS	3	(1.0)	2	(0.7)	1	(0.3)	-		-		-	
PERIORBITAL OEDEMA	1	(0.3)	-		1	(0.3)	-		-		-	
Total Number of AEs	4		2		2		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 19.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
Only includes events occurring during treatment phase
AE17 03MAY2017:22:30:47 (4 of 4)

Table 24 Administration-Related Reactions, Overview: MO22982

Cohort 1 and 2 System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Number of Administration Related Adverse Events	61 (12.7)	90	31 (6.5)	38
Skin And Subcutaneous Tissue Disorders	32 (6.7)	45	16 (3.3)	19
Erythema	17 (3.5)	23	6 (1.3)	6
Rash	8 (1.7)	10	6 (1.3)	8
Pruritus	4 (0.8)	4	3 (0.6)	3
Urticaria	1 (0.2)	1	0	
Pruritus Generalised	2 (0.4)	2	0	
Generalised Erythema	1 (0.2)	1	0	
Rash Generalised	0		0	
Rash Pruritic	1 (0.2)	4	1 (0.2)	2
Respiratory, Thoracic And Mediastinal Disorders	18 (3.8)	21	12 (2.5)	13
Cough	9 (1.9)	9	6 (1.3)	6
Dyspnoea	9 (1.9)	12	5 (1.0)	6
Wheezing	0		1 (0.2)	1
Vascular Disorders	8 (1.7)	18	1 (0.2)	1
Flushing	7 (1.5)	17	1 (0.2)	1
Hypotension	1 (0.2)	1	0	

Cohort 1 and 2

System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
General Disorders And Administration Site Conditions	4	(0.8)	5	1	(0.2)	1
Chest Discomfort	2	(0.4)	2	1	(0.2)	1
Oedema	2	(0.4)	3	0		
Immune System Disorders	0			4	(0.8)	4
Drug Hypersensitivity	0			3	(0.6)	3
Hypersensitivity	0			1	(0.2)	1
Gastrointestinal Disorders	1	(0.2)	1	0		
Lip Swelling	1	(0.2)	1	0		

Roche: MO22982/CIL-TS/FINAL/AEC01P.SAS
Produced: 16 March 2016, 11:26

Source: Listing 16.2.7.8
Notes: [1] All administration related Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Table 25 Administration-Related Reactions, Severity & Frequency: MO22982

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Severe				
Number of Administration Related Adverse Events	5 (1.0)	5	2 (0.4)	2
Skin And Subcutaneous Tissue Disorders	4 (0.8)	4	1 (0.2)	1
Erythema	1 (0.2)	1	0	
Generalised Erythema	1 (0.2)	1	0	
Pruritus	1 (0.2)	1	0	
Pruritus Generalised	1 (0.2)	1	0	
Rash Pruritic	0		1 (0.2)	1
Respiratory, Thoracic And Mediastinal Disorders	1 (0.2)	1	1 (0.2)	1
Dyspnoea	1 (0.2)	1	1 (0.2)	1

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Moderate						
Number of Administration Related Adverse Events	14	(2.9)	19	11	(2.3)	11
Skin And Subcutaneous Tissue Disorders	9	(1.9)	13	5	(1.0)	5
Erythema	4	(0.8)	4	3	(0.6)	3
Rash	3	(0.6)	3	1	(0.2)	1
Pruritus	2	(0.4)	2	0		
Rash Pruritic	1	(0.2)	4	1	(0.2)	1
Urticaria	0			0		
Respiratory, Thoracic And Mediastinal Disorders	4	(0.8)	4	3	(0.6)	3
Cough	2	(0.4)	2	1	(0.2)	1
Dyspnoea	2	(0.4)	2	2	(0.4)	2
Immune System Disorders	0			2	(0.4)	2
Drug Hypersensitivity	0			2	(0.4)	2
Hypersensitivity	0			0		

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Moderate						
Vascular Disorders	1	(0.2)	1	1	(0.2)	1
Flushing	1	(0.2)	1	1	(0.2)	1
Hypotension	0			0		
General Disorders And Administration Site Conditions	1	(0.2)	1	0		
Chest Discomfort	1	(0.2)	1	0		

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Mild						
Number of Administration Related Adverse Events	45	(9.4)	66	20	(4.2)	25
Skin And Subcutaneous Tissue Disorders	21	(4.4)	28	11	(2.3)	13
Erythema	12	(2.5)	18	3	(0.6)	3
Rash	6	(1.3)	7	5	(1.0)	7
Pruritus	1	(0.2)	1	3	(0.6)	3
Urticaria	1	(0.2)	1	0		
Pruritus Generalised	1	(0.2)	1	0		
Rash Generalised	0			0		
Respiratory, Thoracic And Mediastinal Disorders	14	(2.9)	16	8	(1.7)	9
Cough	7	(1.5)	7	5	(1.0)	5
Dyspnoea	7	(1.5)	9	2	(0.4)	3
Wheezing	0			1	(0.2)	1
Vascular Disorders	7	(1.5)	17	0		
Flushing	6	(1.3)	16	0		
Hypotension	1	(0.2)	1	0		

Cohort 1 and 2 CTC grade System Organ Class Preferred Term	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Mild						
General Disorders And Administration Site Conditions	3	(0.6)	4	1	(0.2)	1
Chest Discomfort	1	(0.2)	1	1	(0.2)	1
Oedema	2	(0.4)	3	0		
Immune System Disorders	0			2	(0.4)	2
Hypersensitivity	0			1	(0.2)	1
Drug Hypersensitivity	0			1	(0.2)	1
Gastrointestinal Disorders	1	(0.2)	1	0		
Lip Swelling	1	(0.2)	1	0		

Notes: [1] All administration related Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Table 26 Administration-Related Reactions, Global Safety Database: Summary Tabulation of Adverse Events by SOC

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	Preferred Term					
Immune system disorders	Anaphylactic reaction	201	203	3.8	203	1.2
	Anaphylactic shock	99	100	1.9	100	0.6
	Anaphylactoid reaction	29	29	0.5	29	0.2
	Anaphylactoid shock	2	2	0.0	2	0.0
	Drug hypersensitivity	145	81	1.5	150	0.9
	Hypersensitivity	1016	506	9.5	1034	6.2
	Type I hypersensitivity	1	1	0.0	1	0.0
Eye disorders	Eye oedema	9	2	0.0	9	0.1
	Eye pruritus	33	5	0.1	33	0.2
	Eye swelling	38	6	0.1	39	0.2
	Eyelid oedema	28	8	0.2	28	0.2
	Ocular hyperaemia	50	10	0.2	51	0.3
	Periorbital oedema	10	2	0.0	10	0.1
	Periorbital swelling	11	0	0.0	11	0.1
	Swelling of eyelid	14	3	0.1	14	0.1

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Cardiac disorders	Cardiac arrest	112	110	2.1	113	0.7
	Cardio-respiratory arrest	47	46	0.9	47	0.3
	Cardio-respiratory distress	1	1	0.0	1	0.0
	Cardiovascular insufficiency	12	9	0.2	12	0.1
	Cyanosis	64	35	0.7	65	0.4

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Vascular disorders	Circulatory collapse	57	53	1.0	57	0.3
	Flushing	255	50	0.9	260	1.6
	Hypotension	529	285	5.4	536	3.2
	Shock	39	38	0.7	40	0.2
	Shock symptom	3	3	0.1	3	0.0
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	30	30	0.6	30	0.2
	Asthma	123	62	1.2	123	0.7
	Bronchospasm	114	93	1.7	116	0.7
	Choking	8	4	0.1	8	0.0
	Choking sensation	15	5	0.1	15	0.1
	Cough	1373	164	3.1	1403	8.4
	Dyspnoea	2893	1348	25.4	2952	17.7
	Hyperventilation	8	4	0.1	8	0.0
	Irregular breathing	10	0	0.0	10	0.1
	Laryngeal oedema	18	15	0.3	18	0.1
	Laryngospasm	6	2	0.0	6	0.0
	Nasal obstruction	12	2	0.0	12	0.1
	Oropharyngeal swelling	1	0	0.0	1	0.0
	Pharyngeal oedema	6	3	0.1	6	0.0
	Pharyngeal swelling	16	6	0.1	16	0.1
	Respiratory arrest	32	29	0.5	32	0.2
	Respiratory distress	99	87	1.6	99	0.6

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
	Respiratory failure	222	218	4.1	226	1.4
	Sneezing	46	0	0.0	46	0.3
	Stridor	8	3	0.1	8	0.0
	Tachypnoea	31	17	0.3	31	0.2
	Throat tightness	41	13	0.2	41	0.2
	Upper airway obstruction	1	1	0.0	1	0.0
	Wheezing	87	25	0.5	87	0.5
Gastrointestinal disorders	Lip oedema	6	3	0.1	6	0.0
	Lip swelling	14	3	0.1	14	0.1
	Mouth swelling	10	2	0.0	10	0.1
	Oedema mouth	4	2	0.0	4	0.0
	Swollen tongue	19	5	0.1	19	0.1
	Tongue oedema	5	2	0.0	5	0.0

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Skin and subcutaneous tissue disorders	Angioedema	58	45	0.8	58	0.3
	Circumoral oedema	1	1	0.0	1	0.0
	Circumoral swelling	1	0	0.0	1	0.0
	Erythema	912	129	2.4	955	5.7
	Nodular rash	1	0	0.0	1	0.0
	Pruritus	1169	110	2.1	1199	7.2
	Pruritus allergic	2	0	0.0	2	0.0
	Rash	2582	335	6.3	2642	15.9
	Rash erythematous	117	19	0.4	117	0.7
	Rash pruritic	111	13	0.2	114	0.7
	Skin swelling	4	1	0.0	4	0.0
	Urticaria	329	75	1.4	334	2.0

Table 27 Administration-Related Reactions, Global Safety Database: Summary Tabulation Adverse Event by Outcome

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/ Resolved With Sequelae	Recovering/Resolving	Unknown	
Acute respiratory failure	0	12	0	4	1	6	0	4	3	30
Anaphylactic reaction	0	6	0	2	43	101	1	21	29	203
Anaphylactic shock	0	6	0	2	13	70	1	6	2	100
Anaphylactoid reaction	0	0	0	1	1	18	0	6	3	29
Anaphylactoid shock	0	0	0	0	0	2	0	0	0	2
Angioedema	1	3	1	3	7	25	1	6	11	58
Asthma	0	3	0	21	28	31	2	16	22	123
Blood pressure decreased	0	1	0	8	35	63	0	14	25	146
Blood pressure diastolic decreased	0	0	0	0	7	2	0	0	15	24
Blood pressure systolic decreased	0	0	0	0	1	3	0	1	6	11
Bronchospasm	4	5	1	3	19	63	1	13	7	116
Cardiac arrest	1	63	1	2	12	21	6	1	6	113
Cardio-respiratory arrest	1	35	0	1	0	8	0	1	1	47
Cardio-respiratory distress	0	0	0	0	0	0	0	1	0	1
Cardiovascular insufficiency	0	2	0	2	2	4	1	0	1	12
Chest discomfort	5	1	12	46	150	130	2	47	32	425
Choking	0	0	0	1	4	1	0	1	1	8
Choking sensation	0	0	0	2	6	5	0	1	1	15
Circulatory collapse	3	8	0	1	18	20	1	2	4	57
Circumoral oedema	0	0	0	0	0	1	0	0	0	1

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/ Resolved With Sequelae	Recovering/Resolving	Unknown	
Circumoral swelling	0	0	0	0	0	1	0	0	0	1
Cough	14	5	13	296	553	253	3	128	138	1403
Cyanosis	9	1	0	5	4	36	2	5	3	65
Drug hypersensitivity	0	0	0	6	50	73	0	5	16	150
Dyspnoea	81	63	64	453	878	758	32	317	306	2952
Erythema	5	0	16	151	303	297	3	106	74	955
Eye oedema	0	0	0	4	2	3	0	0	0	9
Eye pruritus	0	0	0	8	12	7	0	3	3	33
Eye swelling	0	0	0	9	13	9	0	3	5	39
Eyelid oedema	0	0	0	2	9	10	0	4	3	28
Face oedema	0	0	0	18	20	32	1	13	13	97
Flushing	3	0	7	27	76	96	2	25	24	260
Hypersensitivity	0	3	11	67	283	464	3	55	148	1034
Hyperventilation	0	0	0	1	1	6	0	0	0	8
Hypotension	14	9	10	49	121	213	0	37	83	536
Infusion related reaction	0	6	15	19	232	782	4	109	257	1424
Injection site hypersensitivity	0	0	0	0	4	1	0	0	0	5
Injection site urticaria	0	0	0	1	1	7	0	0	0	9
Irregular breathing	0	0	0	0	10	0	0	0	0	10
Laryngeal oedema	1	0	0	1	1	12	0	2	1	18
Laryngospasm	0	0	0	0	1	4	1	0	0	6

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/ Resolved With Sequelae	Recovering/Resolving	Unknown	
Lip oedema	0	0	0	1	0	2	0	3	0	6
Lip swelling	1	0	0	2	3	5	0	1	2	14
Mouth swelling	0	0	0	4	4	1	0	0	1	10
Nasal obstruction	0	0	0	4	3	4	0	0	1	12
Nodular rash	0	0	0	0	0	1	0	0	0	1
Ocular hyperaemia	2	0	0	10	19	12	0	2	6	51
Oedema	1	2	2	105	134	110	1	61	57	473
Oedema mouth	0	0	0	2	0	2	0	0	0	4
Oropharyngeal swelling	0	0	0	0	1	0	0	0	0	1
Periorbital oedema	1	0	0	0	3	3	0	0	3	10
Periorbital swelling	0	0	0	1	6	1	0	0	3	11
Pharyngeal oedema	0	0	0	2	1	1	0	0	2	6
Pharyngeal swelling	0	0	1	2	2	7	0	2	2	16
Pruritus	4	0	16	318	373	269	4	108	107	1199
Pruritus allergic	0	0	0	0	1	1	0	0	0	2
Rash	2	2	22	455	851	647	8	333	322	2642
Rash erythematous	0	0	1	23	48	22	0	12	11	117
Rash pruritic	0	0	3	29	45	20	0	12	5	114
Respiratory arrest	2	16	2	1	5	5	0	0	1	32
Respiratory distress	5	20	1	5	13	26	0	18	11	99
Respiratory failure	5	110	1	19	20	36	1	24	10	226

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/ Resolved With Sequelae	Recovering/Resolving	Unknown	
Sensation of foreign body	0	0	1	1	4	1	0	0	1	8
Shock	1	8	0	5	7	11	1	3	4	40
Shock symptom	0	0	0	0	0	1	0	1	1	3
Skin swelling	0	0	0	2	0	1	0	0	1	4
Sneezing	0	0	0	3	19	16	0	2	6	46
Stridor	1	0	0	1	1	3	0	1	1	8
Swelling	2	0	5	77	113	36	0	24	32	289
Swelling face	1	0	4	22	32	26	0	17	11	113
Swelling of eyelid	0	0	1	2	6	1	0	3	1	14
Swollen tongue	0	0	3	4	5	6	0	0	1	19
Tachypnoea	1	1	0	6	7	12	0	2	2	31
Throat tightness	1	0	1	2	11	14	2	4	6	41
Tongue oedema	0	0	0	1	1	2	1	0	0	5
Tracheal obstruction	0	0	0	0	0	0	0	1	0	1
Type I hypersensitivity	0	0	0	0	0	1	0	0	0	1
Upper airway obstruction	0	0	0	1	0	0	0	0	0	1
Urticaria	3	0	10	48	69	109	3	41	51	334
Wheezing	6	0	3	4	34	21	0	8	11	87
Total	**181**	**391**	**228**	**2378**	**4762**	**5074**	**88**	**1636**	**1916**	**16654**

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/ Resolved With Sequelae	Recovering/Resolving	Unknown	
Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AE										

Table 28 Administration-Related Reactions, Global Safety Database: Summary Tabulation Event Outcome by Action Taken

Outcome	Blank	Coman	Dose Increased	Dose Interrupted	Dose Modified NOS	Dose Not Changed	Dose Reduced	Drug Withdrawn	Infusion Rate Decreased	Not Applicable	Unknown	Total No. Drug Events
Coman	0	181	0	0	0	0	0	0	0	0	0	181
Fatal	0	0	0	4	0	19	1	46	0	247	74	391
Not Applicable	0	0	0	0	0	0	0	1	0	224	4	229
Not Recovered/Not Resolved	2	0	2	64	1	878	13	276	0	197	975	2408
Not Reported	0	0	3	127	1	334	11	280	3	114	3951	4824
Recovered/Resolved	1	0	4	423	7	1437	27	1211	14	303	1699	5126
Recovered/Resolved With Sequelae	0	0	0	6	0	25	0	27	0	4	26	88
Recovering/Resolving	1	0	1	78	1	448	7	395	4	112	599	1646
Unknown	0	0	0	46	3	300	3	285	0	217	1070	1924
Data cutoff: 24 September 2018. Exposure cut-off: 24 September 2018. Comanifestations are counted as AE												

3. OLIGOHYDRAMNIOS

Table 29 Oligohydramnios, Global Safety Database: Summary Tabulation of Adverse Events by SOC

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
System Organ Class	Preferred Term					
Infections and infestations	Omphalitis	1	0	0.0	1	1.0
Blood and lymphatic system disorders	Thrombocytopenia neonatal	1	1	1.2	1	1.0
Metabolism and nutrition disorders	Failure to thrive	11	10	12.0	11	10.6
Nervous system disorders	Agitation neonatal	1	1	1.2	1	1.0
Respiratory, thoracic and mediastinal disorders	Meconium aspiration syndrome	1	1	1.2	1	1.0
	Neonatal anoxia	1	1	1.2	1	1.0
	Neonatal respiratory distress syndrome	5	5	6.0	5	4.8
	Transient tachypnoea of the newborn	2	2	2.4	2	1.9
Pregnancy, puerperium and perinatal conditions	Jaundice neonatal	1	0	0.0	1	1.0
	Low birth weight baby	1	0	0.0	1	1.0
	Neonatal disorder	1	1	1.2	1	1.0
	Oligohydramnios	46	41	49.4	47	45.2
	Polyhydramnios	4	4	4.8	4	3.8
	Premature baby	12	8	9.6	12	11.5
	Small for dates baby	5	1	1.2	5	4.8
	Umbilical cord abnormality	2	1	1.2	2	1.9
General disorders and administration site conditions	Death neonatal	2	2	2.4	2	1.9

		No. Patients with at least 1 AE/PT	Serious Adverse Events		Total Adverse Events	
			N	%	N	%
Investigations	Amniotic fluid volume decreased	6	4	4.8	6	5.8
Total		**N/A**	**83**	**100.0**	**104**	**100.0**

Table 30 Oligohydramnios, Global Safety Database: Summary Tabulation Adverse Event by Outcome

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Agitation neonatal	0	0	0	0	0	1	0	0	0	1
Amniotic fluid volume decreased	0	0	0	1	1	4	0	0	0	6
Death neonatal	0	1	1	0	0	0	0	0	0	2
Failure to thrive	1	1	0	1	1	5	1	0	1	11
Jaundice neonatal	0	0	0	0	1	0	0	0	0	1
Low birth weight baby	0	0	1	0	0	0	0	0	0	1
Meconium aspiration syndrome	0	0	0	0	0	1	0	0	0	1
Neonatal anoxia	0	0	0	1	0	0	0	0	0	1
Neonatal disorder	0	0	0	0	0	1	0	0	0	1
Neonatal respiratory distress syndrome	0	0	0	0	1	2	0	0	2	5
Oligohydramnios	0	0	5	3	13	13	0	0	13	47
Omphalitis	0	0	0	0	1	0	0	0	0	1
Polyhydramnios	0	0	0	0	2	2	0	0	0	4
Premature baby	0	2	8	0	0	0	0	1	1	12

Preferred Term	Event outcome									Total No. AEs
	Coman	Fatal	Not Applicable	Not Recovered/ Not Resolved	Not Reported	Recovered/Resolved	Recovered/Resolved With Sequelae	Recovering/Resolving	Unknown	
Small for dates baby	0	0	0	0	2	3	0	0	0	5
Thrombocytopenia neonatal	0	0	0	0	0	1	0	0	0	1
Transient tachypnoea of the newborn	0	0	0	0	0	1	0	0	1	2
Umbilical cord abnormality	0	1	1	0	0	0	0	0	0	2
Total	**1**	**5**	**16**	**6**	**22**	**34**	**1**	**1**	**18**	**104**

Table 31 Oligohydramnios, Global Safety Database: Summary Tabulation of Event Outcome by Action Taken

	Coman	Dose Interrupted	Dose Not Changed	Drug Withdrawn	Not Applicable	Unknown	Total No. Drug Events
Coman	1	0	0	0	0	0	1
Fatal	0	0	0	0	4	1	5
Not Applicable	0	0	0	1	15	0	16
Not Recovered/Not Resolved	0	0	1	4	1	0	6
Not Reported	0	1	0	6	4	11	22
Recovered/Resolved	0	5	3	10	9	7	34
Recovered/Resolved With Sequelae	0	0	0	0	0	1	1
Recovering/Resolving	0	0	0	0	0	1	1
Unknown	0	0	0	3	8	7	18
Total	**1**	**6**	**4**	**24**	**41**	**28**	**104**

4. IMMUNOGENICITY/ HYPERSENSITIVITY AND ANAPHYLAXIS OF HERCEPTIN SC

Table 32 Brighton collaboration criteria terms: BO22227

Pt.#	AE: preferred term	Treated?	Outcome of AE	CTC grade	Phase of treatment	Trastuzumab cycle
[redacted]	Tachycardia	Yes	Resolved	1	Neoadjuvant	5
	Tachycardia	No	Resolved	1	Neoadjuvant	5
	Tachycardia	No	Resolved	1	Neoadjuvant	3
	Tachycardia	Yes	Resolved	1	Adjuvant	17
	Tachycardia	No	Persisting	1	Follow-up	N/A
	Hypotension	No	Resolved	2	Neoadjuvant	4
	Hypotension	No	Resolved	1	Neoadjuvant	7
	Hypotension	No	Persisting	1	Adjuvant	18
	Hypotension	Yes	Resolved	2	Adjuvant	9
	Laryngeal oedema	No	Resolved	2	Neoadjuvant	4
	Rash generalised	No	Resolved	2	Adjuvant	11

Table 33 Summary of Anti-Trastuzumab Antibodies (SP): BO22227

		Herceptin IV N = 298	Herceptin SC N = 297
Number of patients with ADA results		298	297
	BL with no post-BL	2	2
Number of patients evaluable for ADA to trastuzumab		296	295
Evaluation of ADA			
	response BL→post-BL		
Positive Response			
	positive→positive	5	7
	NAb positive	2[a]	3[b]
	negative→positive	28	46
	NAb positive	1	3
	no sample→positive	0	0
	NAb positive	0	0
ADA Incidence (%) [c]		11.1% (33/296)	18.0% (53/295)

ADA = anti-drug antibody; BL = baseline; IV = intravenous; NAb = neutralizing antibody; SC = subcutaneous; SP = safety analysis population.

[a] One patient tested NAb positive at baseline only.

[b] Two patients tested NAb positive at baseline only.

[c] ADA incidence (%) is the cumulative number of post-baseline antibody positive patients of the treatment and treatment-free follow-up phases combined, irrespective of response at BL.

Source: etabsum_SAF_ABTRASetabsum_SAF_ABTRAS; elata_SAFelata_SAF

Table 34 Summary of the Incidence of Anti-Trastuzumab Antibodies (SP) (New Definition)

	Herceptin IV N = 298	Herceptin SC N = 297
Number of patients with ADA results	298	297
BL with no post-BL	2	2
Number of patients evaluable for ADA to trastuzumab	296	295
Evaluation of ADA		
Treatment- induced ADA	28	46
NAb positive	1	3
Treatment-enhanced ADA	2	1
NAb positive	2 [a]	0
Treatment-unaffected ADA	16	15
NAb positive	3 [b]	4 [b]
ADA Incidence (%) [c]	10.1% (30/296)	15.9% (47/295)

ADA = anti-drug antibody; BL = baseline; IV = intravenous; NAb = neutralizing antibody; SC = subcutaneous; SP = safety analysis population.

[a] One patient tested NAb positive at baseline only.

[b] Three patients tested NAb positive at baseline only.

[c] Incidence of ADA (%) is the cumulative treatment-induced and treatment-enhanced ADA of the treatment and treatment-free follow-up phases combined.

Treatment-induced ADA = a patient with negative or missing BL ADA results and at least one positive post-BL ADA result.

Treatment -enhanced ADA = a patient with positive ADA result at BL who has one or more post-BL titer results that are at least 0.60 titer units greater than the BL titer result (four-fold increase of titer).

Treatment-unaffected ADA = a post-baseline evaluable patient with a positive ADA result at BL and (a) where all post-BL titer results are less than 0.60 titer units greater than the BL titer result (no 4-fold increase of titer), or (b) where all post-BL results are negative, irrespective of the response at BL.

Source: etabsum2_SAF_ABTRASetabsum2_SAF_ABTRAS; elata_SAFelata_SAF

Table 35 Summary of Anti-rHuPH20 Antibodies (SP): BO22227

	Herceptin SC
	N=297
Number of patients with ADA results	297
BL with no post-BL	2
Number of patients evaluable for ADA to trastuzumab	295
Evaluation of ADA response BL→post-BL	
Positive Response	
positive→positive	21
Nab positive	0
negative→positive	48
Nab positive	0
no sample→positive	1
Nab Positive	0
ADA Rate (%)[a]	23.7% (70/295)

ADA=anti-drug antibody; BL=baseline Nab=Neutralizing Antibody.

[a] ADA rate (%) is the cumulative antibody rate of the treatment and treatment-free follow-up phases combined

Table 36 Summary of Anti-rHuPH20 Antibodies (SP) (New Definition)

		Herceptin SC N = 297
Number of patients with antibody results		297
	BL with no post-BL	2
Number of patients evaluable for antibodies to rHuPH20		295
Evaluation of anti-rHuPH20 Antibodies		
	Treatment-induced	49
	Treatment-enhanced	13
	Treatment-unaffected	9
Incidence of anti-rHuPH20 antibodies (%)[a]		21.0% (62/295)

BL = baseline.

[a] Incidence of anti-rHuPH20 antibodies (%) is the cumulative treatment-induced and treatment-enhanced anti-rHuPH20 antibodies of the treatment and treatment-free follow-up phases combined.

Treatment-induced ADA = a patient with negative or missing BL ADA results and at least one positive post-BL ADA result.

Treatment -enhanced ADA = a patient with positive ADA result at BL who has one or more post-BL titer results that are at least 0.60 titer units greater than the BL titer result (four-fold increase of titer)

Treatment-unaffected ADA = a post-baseline evaluable patient with a positive ADA result at BL and (a) where all post-BL titer results are less than 0.60 titer units greater than the BL titer result (no four-fold increase of titer), or (b) where all post-BL results are negative, irrespective of the response at BL.

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Table 37 Hypersensitivity and Anaphylaxis Observed in SC Patient Population: BO22227

Patient N0	SAE?	Duration of adverse event	preferred term	Additional treatment given?	Trial medication adjustment	Relation to trial medication	Outcome of adverse event	Chemotherapy adjustment	Phase of treatment	Trastuzumab cycle
Trastuzumab SC										
[redacted]	No	1	Drug hypersensitivity	Yes	None	Yes	Reso- no sequel	Dosage modified	Neo-adjuvant	CYCLE 2
	No	1	Hypersensitivity	Yes	None	Yes	Reso- no sequel	Dosage modified	Neo-adjuvant	CYCLE 2
	No	1	Drug hypersensitivity	Yes	None	Yes	Reso - no sequel	Dosage modified	Neo-adjuvant	CYCLE 2
	No	1	Drug hypersensitivity	Yes	None	Yes	Reso - no sequel	Dosage modified	Neo-adjuvant	CYCLE 3
	No	1	Drug hypersensitivity	Yes	None	Yes	Reso - no sequel	Dosage modified	Neo-adjuvant	CYCLE 4

Table 38 Summary of Anti-Trastuzumab Antibodies (Safety Population; Cohort 1): MO22982

	SC SID/IV N=122			IV/SC SID N=122		
	de Novo	Non de Novo	Overall	de Novo	Non de Novo	Overall
Number of Patients with an trastuzumab ADA result at BL	27	93	120	29	92	121
Evaluation of Trastuzumab immunogenicity at BL						
Number of Patients with trastuzumab ADA-positive results at BL	2	1	3	3	2	5
BL Trastuzumab immunogenicity rate	7.4% (2/27)	1.1% (1/93)	2.5% (3/120)	10.3% (3/29)	2.2% (2/92)	4.1% (5/121)
Number of Patients with at least 1 ADA result	28	94	122	29	93	122
Number of Patients with ADA result at BL only	3	5	8	1	2	3
Number of Patients evaluable for ADA to Trastuzumab	25	89	114	28	91	119
Evaluation of trastuzumab ADAs at BL to Post-BL						
Pos at BL to Pos Post-BL	0	0	0	0	2	2
Neg at BL to Pos Post-BL	0	0	0	1	1	2
No BL to Pos Post-BL	0	0	0	0	0	0
Post-BL Trastuzumab ADA rate	0% (0/25)	0% (0/89)	0% (0/114)	3.6%% (1/28)	3.3% (3/91)	3.4% (4/119)

ADA=anti-drug antibody; BL=Baseline; Neg=negative; Pos=Positive.

Note: Positive is per confirmatory test results.

Table 39 Summary of Anti-rHuPH20 Antibodies (Safety Population; Cohort 1): MO22982

	SC SID/IV n=122			IV/SC SID n=122		
	De Novo	Non de Novo	Overall	De Novo	Non de Novo	Overall
Number of Patients with an rHuPH20 ADA result at BL	27	93	120	29	92	121
Evaluation of rHuPH20 immunogenicity at BL						
Number of patients with rHuPH20 antibody positive results at BL	2	5	7	2	7	9
BL rHuPH20 immunogenicity rate	7.4% (2/27)	5.4% (5/93)	5.8% (7/120)	6.9% (2/29)	7.6% (7/92)	7.4% (9/121)
Number of patients with at least 1 rHuPH20 antibody result	28	94	122	29	93	122
Number of patients with rHuPH20 antibody result at BL only	2	5	7	1	2	3
Number of patients evaluable for antibodies to rHuPH20	26	89	115	28	91	119
Evaluation of rHuPH20 antibody response BL to Post-BL						
Pos at BL to Pos Post-BL	1	2	3	2	5	7
Neg at BL to Pos Post-BL	0	0	0	1	1	2
No BL to Pos Post-BL	0	0	0	0	0	0
Post-BL rHuPH20 antibody rate	3.8% (1/26)	2.2% (2/89)	2.6% (3/115)	10.7% (3/28)	6.6% (6/91)	7.6% (9/119)

Abbreviations: BL=baseline, Neg=negative, Pos=positive

5. SHORT-TERM SAFETY OF HERCEPTIN SC COMPARED TO HERCEPTIN IV

Table 40 Summary of Adverse Events During Crossover Period with or without ISRs: MO22982

Cohort 1 and 2

System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Number of Adverse Events	300 (62.6)	913	258 (54.0)	581

Excluding ISR

Cohort 1 and 2

System Organ Class Preferred Term	SC Period (N=479) n (%)	E	IV Period (N=478) n (%)	E
Number of Adverse Events	275 (57.4)	727	258 (54.0)	580

Roche: MO22982/CIL-TS/FINAL/AEC01P.SAS
Produced: 16 March 2016, 11:26 Page 32 of 52
Source: Listing 16.2.7.1
Notes: [1] All Adverse Events including Serious Adverse Events are included in summary statistics.
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
[3] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[4] Table presents number and percentage of patients (n (%)) and number of events (E).
[5] Percentages are based on the number of patients in the respective group.

Table 41 Overview of Serious Adverse Events During Crossover Period: MO22982

Cohort 1 and 2	SC Period (N=479) n	(%)	E	IV Period (N=478) n	(%)	E
Number of SAEs	4	(0.8)	4	4	(0.8)	5
Study Drug Discontinued Due to SAE	0			1	(0.2)	1
Symptomatic Left Ventricular Systolic Dysfunction Events	0			0		
CTC Grade						
Mild	1	(0.2)	1	0		
Moderate	0			1	(0.2)	1
Severe	3	(0.6)	3	4	(0.8)	4
Life Threatening	0			0		
Death	0			0		
Suspected Causal Relationship to Study Medication						
Yes	0			0		
No	4	(0.8)	4	4	(0.8)	5
SAE Outcome						
Resolved/full recovery	4	(0.8)	4	4	(0.8)	5
Resolved with sequelae	0			0		
Ongoing	0			0		
Died	0			0		

Notes: [1] If a patient has multiple events of the same CTC Grade, relationship or outcome, then they are counted only once in that CTC Grade, relationship or outcome. However, patients can be counted more than once overall.
[2] If an AE start date is partially or fully missing, and it is unclear during to which treatment period the AE started, the AE has been assigned to all relevant treatment periods.
[3] Table presents number and percentage of patients (n(%)) and number of events (E).
[4] Percentages are based on the number of patients in the respective group.

Table 42 Summary of Grade 3 or More Adverse Events during the Treatment Period: Safety Population: MO28048

Table 14.3.1.2 Summary of Serious Adverse Events - Treatment Period
(Safety Population)

	Cohort A (N=1864)			Cohort B (N=709)			Overall (N=2573)		
	n	(%)	E	n	(%)	E	n	(%)	E
Number of SAE	242	(13.0)	316	84	(11.8)	107	326	(12.7)	423
Study Drug Discontinued Due to SAE	24	(1.3)	26	8	(1.1)	8	32	(1.2)	34
Study Drug Interruption Due to SAE	39	(2.1)	46	14	(2.0)	15	53	(2.1)	61
Medical Device Complaint/Events	0			0			0		
Cardiac Adverse Events	31	(1.7)	34	3	(0.4)	3	34	(1.3)	37
CTC Grade									
Mild	19	(1.0)	22	4	(0.6)	4	23	(0.9)	26
Moderate	58	(3.1)	65	21	(3.0)	22	79	(3.1)	87
Severe	157	(8.4)	186	53	(7.5)	65	210	(8.2)	250
Life Threatening	36	(1.9)	41	14	(2.0)	14	50	(1.9)	55
Death	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Suspected Causal Relationship to Study Medication									
Yes	35	(1.9)	38	4	(0.6)	4	39	(1.5)	42
No	211	(11.3)	278	82	(11.6)	103	293	(11.4)	381

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AEV0XP.SAS
Produced: 17 August 2015, 5:40 Page 1 of 2
Source: Listing 16.2.7.2
Notes: [1] If a patient has multiple events of the same CTC grade, relationship or outcome, then they are counted only once in that CTC grade relationship or outcome. However, patients can be counted more than once overall
[2] Table presents number and percentage of patients (n (%)) and number of events (E)
[3] Percentages are based on the number of patients in the respective group

Table 14.3.1.2 Summary of Serious Adverse Events – Treatment Period
(Safety Population)

	Cohort A (N=1864) n	(%)	E	Cohort B (N=709) n	(%)	E	Overall (N=2573) n	(%)	E
SAE Outcome									
Resolved/full recovery	228	(12.2)	295	82	(11.6)	103	310	(12.0)	398
Resolved with sequelae	8	(0.4)	9	0			8	(0.3)	9
Ongoing	8	(0.4)	9	2	(0.3)	2	10	(0.4)	11
Died	3	(0.2)	3	2	(0.3)	2	5	(0.2)	5
Was Any Treatment Necessary in Response to SAE?									
Yes	222	(11.9)	283	76	(10.7)	98	298	(11.6)	381
No	32	(1.7)	33	9	(1.3)	9	41	(1.6)	42

Roche: M028048/CIL-EM/MAIN(CUTOFF=10MAR2015:DATA TRANSFER=23JUL2015)/AEV0XP.SAS
Produced: 17 August 2015, 5:40 Page 2 of 2
Source: Listing 16.2.7.2
Notes: [1] If a patient has multiple events of the same CTC grade, relationship or outcome, then they are counted only once in that CTC grade relationship or outcome. However, patients can be counted more than once overall
[2] Table presents number and percentage of patients (n (%)) and number of events (E)
[3] Percentages are based on the number of patients in the respective group

Table 43 Short term safety of Herceptin SC compared to Herceptin IV: Global Safety Database: Summary Tabulation of Adverse Events by SOC

SOC	Trastuzumab (SC)						Trastuzumab (IV)						Trastuzumab (Form Unknown)					
	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%
Blood	156	2.63	83	7.37	0	0.00	1,056	3.67	705	6.52	36	4.47	145	8.49	24	6.30	0	0.00
Card	227	3.83	133	11.81	2	5.71	1,831	6.36	1,415	13.09	81	10.06	63	3.69	41	10.76	3	5.66
Cong	0	0.00	0	0.00	0	0.00	13	0.05	10	0.09	1	0.12	0	0.00	0	0.00	0	0.00
Ear	31	0.52	4	0.36	0	0.00	115	0.40	30	0.28	1	0.12	2	0.12	0	0.00	0	0.00
Endo	12	0.20	1	0.09	0	0.00	32	0.11	23	0.21	0	0.00	3	0.18	1	0.26	0	0.00
Eye	85	1.44	21	1.87	0	0.00	350	1.22	97	0.90	0	0.00	7	0.41	0	0.00	0	0.00
Gastr	616	10.40	78	6.93	1	2.86	3,442	11.96	899	8.32	50	6.21	271	15.87	36	9.45	1	1.89
Genrl	1,172	19.79	150	13.32	18	51.43	4,965	17.25	1,496	13.84	252	31.30	330	19.32	89	23.36	39	73.58
Hepat	15	0.25	8	0.71	0	0.00	217	0.75	121	1.12	20	2.48	8	0.47	5	1.31	0	0.00
Immun	41	0.69	15	1.33	0	0.00	401	1.39	269	2.49	11	1.37	13	0.76	4	1.05	0	0.00
Infec	361	6.09	86	7.64	3	8.57	1,289	4.48	608	5.63	56	6.96	60	3.51	23	6.04	2	3.77
Inj&P	188	3.17	33	2.93	0	0.00	898	3.12	312	2.89	6	0.75	37	2.17	7	1.84	0	0.00
Inv	322	5.44	109	9.68	0	0.00	2,413	8.38	995	9.21	17	2.11	138	8.08	41	10.76	0	0.00
Metab	108	1.82	18	1.60	0	0.00	477	1.66	156	1.44	13	1.61	46	2.69	8	2.10	1	1.89
Musc	705	11.90	69	6.13	0	0.00	1,852	6.44	301	2.78	1	0.12	144	8.43	6	1.57	0	0.00
Neopl	47	0.79	41	3.64	4	11.43	416	1.45	292	2.70	64	7.95	32	1.87	14	3.67	0	0.00
Nerv	482	8.14	70	6.22	0	0.00	2,386	8.29	626	5.79	41	5.09	134	7.85	14	3.67	1	1.89
Preg	2	0.03	1	0.09	0	0.00	17	0.06	10	0.09	0	0.00	1	0.06	1	0.26	0	0.00
Prod	3	0.05	1	0.09	0	0.00	10	0.03	6	0.06	0	0.00	0	0.00	0	0.00	0	0.00
Psych	133	2.25	16	1.42	0	0.00	455	1.58	87	0.80	5	0.62	18	1.05	3	0.79	0	0.00
Renal	27	0.46	14	1.24	1	2.86	273	0.95	144	1.33	14	1.74	10	0.59	4	1.05	0	0.00

SOC	Trastuzumab (SC)						Trastuzumab (IV)						Trastuzumab (Form Unknown)					
	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%	AEs	%	SAEs	%	Fatal	%
Repro	66	1.11	7	0.62	0	0.00	190	0.66	37	0.34	0	0.00	11	0.64	2	0.52	0	0.00
Resp	333	5.62	84	7.46	6	17.14	2,292	7.96	1,251	11.57	121	15.03	86	5.04	33	8.66	5	9.43
Skin	592	9.99	37	3.29	0	0.00	2,562	8.90	499	4.62	3	0.37	123	7.20	11	2.89	0	0.00
SocCi	1	0.02	0	0.00	0	0.00	12	0.04	3	0.03	0	0.00	0	0.00	0	0.00	0	0.00
Surg	8	0.14	2	0.18	0	0.00	66	0.23	48	0.44	0	0.00	9	0.53	7	1.84	0	0.00
Vasc	190	3.21	45	4.00	0	0.00	748	2.60	368	3.40	12	1.49	17	1.00	7	1.84	1	1.89
Total	**5,923**	**100.00**	**1,126**	**100.00**	**35**	**100.00**	**28,778**	**100.00**	**10,808**	**100.00**	**805**	**100.00**	**1,708**	**100.00**	**381**	**100.00**	**53**	**100.00**

All events from post-marketing source with a latency of ≤1 year from the first dose of Herceptin were compared based on the proportion of AEs, SAEs, and fatal events, reported across the SOCs with a cutoff date of 31 August 2017

Generated using MedDRA Version 19.1.

6. KEY LITERATURE REFERENCED IN THE RMP UPDATE

MRN	Citation
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ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date* Procedure	Change
11.2	26 March 2013	The followings were added as new potential risks: Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin subcutaneous (SC) - added as new potential risk. Relative short-term safety of the higher absolute dose intensity of the SC formulation of trastuzumab compared with the intravenous (IV) formulation of trastuzumab- added as new potential risk. "Absolute dose intensity of the SC formulation" was re-named as "Relative long-term safety of the higher absolute dose intensity of the SC formulation of trastuzumab compared with the IV formulation of trastuzumab" as requested in the 180-day assessment report of the SC formulation marketing authorization application (MAA) in the European Economic Area (EEA). Additional information was also included pertaining to the missing information "Safety of 75mg/m^2 v 100mg/m^2 docetaxel dose."
12.0	19 Nov 2013	Migration into the new EU format and template. Information on the risks is updated as available. However, the characterization of the risks and the mitigation measures are not changed significantly.
13.0	07 April 2014	Version 13.0 was prepared to support the single-use injection device (SID) filing. No new safety concerns have been added.

Version	Approval date* Procedure	Change
13.1	01 July 2014	Prepared in response to the assessment of v13.0 Potential for medication error involving SID added to Section 7.6.
13.2	21 July 2014	Prepared in response to the assessment of v13.1 Updated section 8 added 8.1 and also 16.1 and 16.2.
14.0	27 Aug 2014	Prepared to support the submission of the PrefHER data with a label update. No new safety concerns have been added. Addition of PrefHER data.
15.0	Nov 2014	Annual submission, Prepared also in response to the assessment of the Herceptin Periodic Benefit-Risk Evaluation Report (PBRER) data lock point (DLP) 24 March and the Pharmacovigilance Risk Assessment Committee (PRAC) feedback on the risk management plan (RMP) V.12 and 14 No new safety concerns have been added.
15.1	December 2014	Prepared to support changes to study milestones. No new safety concerns have been added.
15.2	March 2015	Prepared due to Summary of Product Characteristics (SmPC) update and to rectify editorial errors. Submitted with 2y-follow-up data for the BO22227 (HannaH) study No new safety concerns have been added.
16.0	March 2015	Prepared to support the submission of the Study MO28048 (SafeHER) data. No new safety concerns have been added.
16.1	August 2015	Consolidated version prepared by responding to the PRAC Requests for Supplementary Information listed in the Assessment Reports for the Study BO22227 (RMP V 15.2) and the MO28048 (RMP V 16.0) variations. No new safety concerns have been added.
16.2	September 2015	Prepared to support changes to study milestones. No new safety concerns have been added.
16.3	November 2015	Prepared in response to the assessment of version 16.2. Various inconsistencies were removed. No new safety concerns have been added. However, 2 existing safety concerns have been re-named. Immunogenicity information is now presented only for the safety concern of immunogenicity/ Hypersensitivity and Anaphylaxis.

Version	Approval date* Procedure	Change
16.4	28 Feb 2016	Prepared to support change to OHERA milestone
16.5	10 March 2017	Updated to remove information on SID
17.0	April 2017	Updated in response to PRAC assessment questions Exposure from PBRER 1072735 covering the reporting interval 25 September 2015 to 24 September 2016 and medication error and device failure. Updated safety concerns with information from HERA (BO16348), SafeHER (MO28048), PrefHER (MO22982) and global safety database outputs. Updated Annual Data Summary of MotHER. Safety concern of Herceptin SC compared to Herceptin IV updated to add information on immunogenicity. Removed the guided questionnaires (GQs) for infusion related reactions, interstitial lung disease, hemolytic anemia and cardiac adverse events. No new safety concerns have been added.
18.0	28 September 2017	Prepared to support the submission of the Study BO20652 (OHERA) data. Added information on Direct Health Care Professional Communication (DHPC) and post-authorization measure.
19.0	December 2017	Prepared to support the HannaH (BO22227) final data (5-year follow-up data). Revised as per revision 2 of the GVP module V Safety concerns reclassification as per the revised GVP-V definitions of important risks and missing information

Version	Approval date* Procedure	Change
20.0	31 October 2018	Prepared to submit to the European Medicines Agency (EMA) the Annual Data Summaries (ADSs) of the MotHER Registry relating to Herceptin and covering the following time periods: • ADS for the reporting interval of 1 February 2017 through 31 January 2018, presenting annual data (for the reporting interval) and cumulative data from the time of initiation of this registry, 20 December 2008 through the end of the current reporting period 31 January 2018 • ADS for the reporting interval of 1 February 2016 through 31 January 2017, presenting annual data (for the reporting interval) and cumulative data from 20th December 2008 through the end of the reporting period 31 January 2017 In addition, the 2018 ADS (reporting interval of 1 February 2017 through 31 January 2018) is the final report for patients exposed to Herceptin only in the MotHER Registry and is provided in support of the marketing authorization holder's (MAH's) request to close out this RMP commitment of MotHER Registry relating to Herceptin. Updated in response to PRAC assessment comments with respect to E.U. RMP v19.0. Added information on survey results related to the survey to assess compliance with cardiac monitoring label requirements following distribution of DHPC in 2017 (assessed by PRAC under EMEA/H/C/000278/LEG100).

21.0	30 April 2020	• Study BO29159 (MetaPHER) has recently been completed. No new information was obtained for the safety concern of cardiac dysfunction and Immunogenicity/ Hypersensitivity and Anaphylaxis of Herceptin SC. No additional PV activity for the safety concern of cardiac dysfunction and Immunogenicity/Hypersensitivity and Anaphylaxis of Herceptin SC were conducted through this trial. Therefore, no further information from this trial will be presented in the future updates to the RMP. The final CSR for this study was submitted to the EMA with Variation application EMEA/H/C/000278/II/0158, in November 2019 • Cumulative patient exposure data from marketing experience have been updated in line with Periodic Benefit-Risk Evaluation Report) 2018 (Report number 1089226). • Any reference to H4621g/GE28099 (MotHER Pregnancy Registry) has been removed from the RMP as MotHER Registry (H4621g/GE28099) is now closed to all patients exposed to Herceptin, Perjeta (in combination with Herceptin) or Kadcyla. No further additional pharmacovigilance activity will be conducted within the MotHER Registry for the safety concern of oligohydramnios • Additional risk minimization measure of Direct Health Care Professional Communication for increased risk of cardiac dysfunction has been removed as additional risk minimization, hence annex 6 shall be not applicable Table 27 (Exposure to trial drug following randomization (Cohort 1 and 2, Safety population), Table 40 (Cardiac dysfunction, severity & frequency: BO22227 IV arm), Table 41 (Cardiac dysfunction, severity & frequency: BO22227 SC arm) and Table 42 (Summary of Cardiac events, special population) have been replaced with same outputs with better resolution to increase the legibility. No data for those trials have been updated.

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22.0		• MO28048 [SafeHer] has recently been completed. No new information was obtained since the primary analysis for the safety concern of immunogenicity/hypersensitivity and anaphylaxis of Herceptin SC and short term safety of Herceptin SC compared to Herceptin IV. Therefore, no further information from this trial will be presented in the future updates to the RMP. • Cumulative patient exposure data from marketing experience have been updated in line with Periodic Benefit-Risk Evaluation Report (PBRER) 2020 (Report number 1103351) (See SV.1.2) • BO29159 (MetaPHER) has been completed. Any reference to BO29159 (MetaPHER) has been removed from the RMP as BO29159 (MetaPHER) is now closed to all patients exposed to Herceptin, Perjeta and docetaxel. Herceptin SC in combination with Perjeta IV and docetaxel chemotherapy has a comparable safety profile to that of Perjeta and Herceptin IV formulations in combination with chemotherapy. No additional PV activity for the safety concern of cardiac dysfunction and immunogenicity/hypersensitivity will be conducted. Therefore, no further information from this trial will be presented in the future updates to this RMP.

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22.1		• Part II Module SVII.3.1. Presentation of important identified risks and important potential risks, MO28048 (SafeHER) study results were updated. • Part II Module SVII.3.2. Presentation of the Missing Information, MO28048 (SafeHER) study results were updated. • Part III Module III.2 Additional Pharmacovigilance Activities, the references to MO28048 (SafeHER) study from the additional pharmacovigilance activities was removed. • Part III Module III.3 The reference to the MO28048 (SafeHER) study was removed from the Table 46 and indicated as not applicable (NA) for category 3. • Part V Module V.3 the references made to the MO28048 (SafeHER) study in Table 48 was deleted as the study is no longer ongoing. Part VI Module II.B and II.C the references to the MO28048 (SafeHER) study were removed.
23.0		• Part III.1 Routine pharmacovigilance activities: o pregnancy related adverse events (Oligohydramnios).- re-ordered for better clarity o Medication error information was updated to ensure correct trastuzumab product (Herceptin) and not other trastuzumab-containing products are administered. o Annexure 4 (Specific Adverse Drug Reaction Follow-up Forms) was updated to include updated guided questionnaire for medication error