EU RISK MANAGEMENT PLAN FOR PHESGO

RMP version to be assessed as part of this application:

RMP version number: 3.0

Data lock point for this RMP: 28 June 2023

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
30-Nov-2023 15:51:34	Deputy QPPV	PPD
01-Dec-2023 01:25:43	Company Signatory (PV)	PPD

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Rationale for Submitting an Updated RMP

The EU RMP has been updated from version 2.1 to version 3.0 in order to reflect updates related to the completion of the Final Clinical Study Report (CSR) for the FeDeriCa Study and of FeDeriCa Study-related additional pharmacovigilance activities.

Summary of Significant Changes in this RMP

In this version, following completion of the clinical study FeDeriCa, 'lack of efficacy due to immunogenicity' previously classified as important potential risk by the MAH, is proposed to be removed from the list of safety concerns. This is supported by the evidence provided by final analysis data of the FeDeriCa study, which are consistent with observations made with the available evidence from the pivotal clinical studies with intravenous pertuzumab and trastuzumab (CLEOPATRA, NEOSPHERE, TRYPHAENA, and APHINITY), where no such risk was identified.

These changes have been made in Part II Module SIV.3, Module SVII, Module SVIII, Part III.2, Part III.3, Part V.1 (Table 21), Part V.3 (Table 22), and Part VI II.A and II.B. In addition, Part II Module SIV.1 and Module SV.1 have been updated to align with language in the Periodic Benefit Risk Evaluation Report (PBRER).

Annex 2 has been updated with completed pharmacovigilance activity information. Annex 7 has been updated by including reference to Final CSR Study WO40324 (FeDeriCa) and cumulative exposure from marketing experience (Table 1).

Other RMP Versions under Evaluation

None

Details of Currently Approved RMP

RMP Version Number: 2.1

Approved with Procedure Number EMEA/H/C/005386/0000

Date of approval (opinion date): 21 December 2020

See page 1 for signature and date

PPD (QPPV)	Date

See page 1 for signature and date

PPD	Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Pertuzumab/trastuzumab
Pharmacotherapeutic group(s) (ATC Code)	L01XY02
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Phesgo™
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Pertuzumab and trastuzumab are recombinant humanized monoclonal antibodies
	Summary of mode of action: Pertuzumab and trastuzumab are recombinant humanized immunoglobulin (Ig)G1 monoclonal antibodies which target the human epidermal growth factor receptor 2 (HER2). Both substances bind to distinct HER2 subdomains without competing and have complementary mechanisms for disrupting HER2 signaling: • Pertuzumab specifically binds to the extracellular dimerization domain (subdomain II) of HER2 and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-activated intracellular signaling through two major signaling pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively.

	• Trastuzumab binds to sub-domain IV, of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated proliferation and survival signals in human tumor cells that over express HER2. The administration of the two substances results in augmented antitumor activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are given in combination. Additionally, both substances mediate antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, both pertuzumab and trastuzumab mediated ADCC are exerted preferentially on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.
	Important information about its composition: Trastuzumab and pertuzumab are produced in mammalian (Chinese hamster ovary) cells by recombinant DNA.
Hyperlink to the Product Information	EU PI
Indication(s) in the EEA	Current: **Early breast cancer** Phesgo is indicated for use in combination with chemotherapy in: • The neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • The adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. **Metastatic breast cancer** Phesgo is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Dosage in the EEA	Current: Loading dose: 1200 mg pertuzumab/600 mg trastuzumab Maintenance dose (every 3 weeks thereafter): 600 mg pertuzumab/ 600 mg trastuzumab
Pharmaceutical form(s) and strengths	Current: Solution for injection 1200 mg/600 mg/15 mL, 1 vial Solution for injection 600 mg/600 mg/10 mL, 1 vial
Is or will the product be subject to additional monitoring in the European Union?	Yes

EEA = European Economic Area; INN= International non-proprietary name.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALND	Axillary lymph node dissection
ARR	Administration-related reaction
CCOD	Clinical cut-off date
CHF	Congestive Heart failure
CI	Confidence interval
COPA	Controlling Profitability Analysis
CSR	Clinical Study Report
DCIS	Ductal carcinoma in situ
DLP	Data lock point
DoT	Duration of therapy
EBC	Early Breast Cancer
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU RMP	EU Risk Management Plan
GD	Gestation day
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HER	Human epidermal growth factor receptor
IBD	International birth date
IV	Intravenous
LCIS	Lobular carcinoma in situ
LVD	Left ventricular dysfunction
LVEF	Left ventricular ejection fraction
MAA	Marketing authorization applicant
MAP	Mitogen-activated protein
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PBRER	Periodic benefit-risk evaluation report

Abbreviation	Definition
pCR	Pathologic complete response
PH FDC SC	Perjeta/Herceptin fixed-dose combination, subcutaneous (Phesgo)
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
RoW	Rest of World
SC	Subcutaneous
SLNB	Sentinel lymph node biopsy
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
tpCR	Total pathological complete response
ULN	Upper limit of normal

PART II: SAFETY SPECIFICATION

This risk management plan (RMP) presents information for Phesgo™, a fixed dose combination (FDC) for subcutaneous (SC) injection of pertuzumab and trastuzumab. Phesgo contains the same active substances as the centrally authorized reference medicinal products Perjeta® (pertuzumab) and Herceptin® (trastuzumab) and is also referred to as PH FDC SC.

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

This section is not applicable, as Phesgo does not contain a new active substance. Epidemiology of the indications and target populations is identical to the reference medicinal products.

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

This section is not applicable, as Phesgo does not contain a new active substance. No new nonclinical studies have been conducted with Phesgo, and therefore there is no new nonclinical information beyond that presented with the reference medicinal products.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Clinical trial exposure data available at the time of the primary analysis of Study WO40324 (Phase III, randomized, multicenter, open-label, two-arm study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in combination with chemotherapy in patients with HER2-positive early breast cancer [FeDeriCa]) (clinical cut-off date: 4 July 2019) is presented below by duration of exposure (Table 2), age group and gender (Table 3), dose (Table 4), and ethnic (Table 5) or racial origin (Table 6).

Clinical trial exposure data available at the time of the primary analysis of Study MO40628 (A study to evaluate patient preference and satisfaction of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in participants with HER2-positive early breast cancer [PHranceSCa]) (clinical cut-off date: 24 February 2020) is presented below by duration of exposure (Table 7), age group and gender (Table 8) and ethnic (Table 9) or racial origin (Table 10).

Table 2 Duration of Exposure (Study WO40324, FeDeriCa)

Cumulative Duration of Exposure for Risk Management Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)	
Duration of exposure	Patients	Person time*	Patients	Person time*
<1 month	4 (1.6%)	1	8 (3.2%)	2
>= 6 months	94 (37.3%)	675	102 (41.1%)	732
1 to <3 months	22 (8.7%)	47	11 (4.4%)	25
3 to <6 months	127 (50.4%)	623	122 (49.2%)	602
Total patients number/person time	247 (98.0%)	1346	243 (98.0%)	1360

n = number of patients exposed to HER2 Targeted Therapy.
* Person time is the sum of exposure across all patients in months.

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Table 3 Age Group and Gender (Study WO40324, FeDeriCa)

Extent of Exposure by Age group and Gender for Risk Management Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)						Pertuzumab + Trastuzumab FDC SC Arm (N=248)			
	Patients			Person time*			Patients		Person time*	
	Male	Female	Total	Male	Female	Total	Female	Total	Female	Total
18 - 40	0	46 (18.3%)	46 (18.3%)	NE	261	261	35 (14.1%)	35 (14.1%)	191	191
41 - 64	2 (0.8%)	167 (66.3%)	169 (67.1%)	11	921	932	185 (74.6%)	185 (74.6%)	1055	1055
>=65	0	32 (12.7%)	32 (12.7%)	NE	153	153	23 (9.3%)	23 (9.3%)	113	113
>=75	0	3 (1.2%)	3 (1.2%)	NE	3	3	3 (1.2%)	3 (1.2%)	16	16
Cumulative Total	2 (0.8%)	245 (97.2%)	247 (98.0%)	11	1336	1346	243 (98.0%)	243 (98.0%)	1360	1360

n = number of patients exposed to HER2 Targeted Therapy.
* Person time is the sum of exposure across all patients in months.
>=65 Age group category contains also subjects with >=75 age group.
Cumulative Total excludes count of >=75 age group.

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Table 4 Dose (Study WO40324, FeDeriCa)

Extent of Exposure by Dose Received for Risk Management Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)	
Dose of Exposure	Patients	Person time*	Patients	Person time*
Herceptin, 8-mg/kg IV (loading)	246 (97.6%)	14	0	NE
Herceptin, 6-mg/kg IV (maintenance)	244 (96.8%)	39	0	NE
**Herceptin, 600-mg SC (fixed)	61 (24.2%)	7	0	NE
Perjeta, 840-mg IV (loading)	247 (98.0%)	15	0	NE
Perjeta, 420-mg IV (maintenance)	244 (96.8%)	44	0	NE
FDC 1200mg Pertuzumab + 600 mg Trastuzumab + 30,000 U rHuPH20 (loading)	0	NE	243 (98.0%)	15
FDC 600mg Pertuzumab + 600 mg Trastuzumab + 20,000 U rHuPH20 (maintenance)	0	NE	237 (95.6%)	45
Total	247 (98.0%)	119	243 (98.0%)	60

n = number of patients exposed to HER2 Targeted Therapy.
* Person time is the sum of exposure across all patients in months.
** Patients in Pertuzumab IV + Trastuzumab IV Arm are allowed to switch from Herceptin IV to Herceptin SC after surgery.
Person time of each treatment includes loading and maintenance dose from both Neoadjuvant and Adjuvant phase.

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Table 5 Ethnic Origin (Study WO40324, FeDeriCa)

Extent of Exposure by Ethnic Origin for Risk Management Plan: Safety Population

Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)	
	Patients	Person time*	Patients	Person time*
Hispanic or Latino	32 (12.7%)	183 (13.6%)	41 (16.5%)	252 (18.5%)
Not Hispanic or Latino	195 (77.4%)	1058 (78.6%)	186 (75.0%)	1041 (76.5%)
Not Stated	16 (6.3%)	88 (6.5%)	12 (4.8%)	50 (3.6%)
Unknown	4 (1.6%)	19 (1.4%)	4 (1.6%)	18 (1.3%)
Cumulative Total	247 (98.0%)	1347	243 (98.0%)	1361

n = number of patients exposed to HER2 Targeted Therapy.
* Person time is the sum of exposure across all patients in months.

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Table 6 Racial Origin (Study WO40324, FeDeriCa)

Extent of Exposure by Race for Risk Management Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)	
	Patients	Person time*	Patients	Person time*
American Indian or Alaska Native	10 (4.0%)	59 (4.4%)	9 (3.6%)	58 (4.2%)
Asian	52 (20.6%)	251 (18.6%)	50 (20.2%)	250 (18.4%)
Black or African American	3 (1.2%)	17 (1.3%)	3 (1.2%)	17 (1.3%)
White	161 (63.9%)	912 (67.7%)	163 (65.7%)	955 (70.2%)
Multiple	2 (0.8%)	11 (0.8%)	3 (1.2%)	15 (1.1%)
Unknown	19 (7.5%)	97 (7.2%)	15 (6.0%)	65 (4.8%)
Cumulative Total	247 (98.0%)	1347	243 (98.0%)	1361

n = number of patients exposed to HER2 Targeted Therapy
* Person time is the sum of exposure across all patients in months.

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Table 7 Duration of Exposure (Study MO40628, PHranceSCa)

Cumulative Duration of Exposure for Risk Management Plan by Treatment Period, Safety-Evaluable Population

Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)		PH FDC SC Cross-Over (N=160)		PH IV Continuation (N=22)		PH FDC SC Continuation (N=137)	
Duration of exposure	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
< 1 month	0	NE	0	NE	2 (9.1%)	2	27 (19.7%)	15
1 to < 3 months	158 (98.8%)	332	160 (100%)	334	9 (40.9%)	19	44 (32.1%)	92
3 to < 6 months	2 (1.3%)	7	0	NE	11 (50.0%)	46	66 (48.2%)	279
>= 6 months	0	NE	0	NE	0	NE	0	NE
Total patients number/person time	160 (100%)	339	160 (100%)	334	22 (100%)	66	137 (100%)	386

N = number of patients exposed to HER2 Targeted Therapy for the administration route and period of interest.
* Person time is the sum of exposure across all patients in months.
Each patient is represented in both PH IV and PH FDC SC cross-over columns and either P+H IV or PH FDC in continuation period, depending on their choice of treatment, with the
exception of one patient who switched during the continuation period who is represented in both columns for the continuation period.
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Table 8 Age Group and Gender (Study MO40628, PHranceSCa)

Extent of Exposure by Age group and Gender for Risk Management Plan by Treatment Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)		PH FDC SC Cross-Over (N=160)		PH IV Continuation (N=22)		PH FDC SC Continuation (N=137)	
Age (years)	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
18 - 40	43 (26.9%)	91	43 (26.9%)	90	7 (31.8%)	20	35 (25.5%)	98
41 - 64	97 (60.6%)	205	97 (60.6%)	201	14 (63.6%)	45	83 (60.6%)	241
>=65	20 (12.5%)	42	20 (12.5%)	43	1 (4.5%)	1	19 (13.9%)	47
>=75	2 (1.3%)	5	2 (1.3%)	4	0	NE	2 (1.5%)	6
Total patients number/person time	160 (100%)	339	160 (100%)	334	22 (100%)	66	137 (100%)	386

N = number of patients exposed to HER2 Targeted Therapy for the administration route and period of interest.
* Person time is the sum of exposure across all patients in months.
>=65 Age group category includes subjects within >=75 age group.
Total patients number/person time excludes count of >=75 age group.
All patients included in the study are female.
Each patient is represented in both PH IV and PH FDC SC cross-over columns and either P+H IV or PH FDC in continuation period, depending on their choice of treatment, with the exception of one patient who switched during the continuation period who is represented in both columns for the continuation period.
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Table 9 Ethnic Origin (Study MO40628, PHranceSCa)

Extent of Exposure by Ethnic Origin for Risk Management Plan by Treatment Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)		PH FDC SC Cross-Over (N=160)		PH IV Continuation (N=22)		PH FDC SC Continuation (N=137)	
Ethnic Origin	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
Hispanic or Latino	38 (23.8%)	82	38 (23.8%)	79	7 (31.8%)	20	30 (21.9%)	88
Not Hispanic or Latino	113 (70.6%)	238	113 (70.6%)	237	12 (54.5%)	41	100 (73.0%)	275
Not reported	4 (2.5%)	8	4 (2.5%)	8	2 (9.1%)	4	3 (2.2%)	12
Unknown	5 (3.1%)	10	5 (3.1%)	10	1 (4.5%)	1	4 (2.9%)	11
Total patients number/person time	160 (100%)	339	160 (100%)	334	22 (100%)	66	137 (100%)	386

N = number of patients exposed to HER2 Targeted Therapy for the administration route and period of interest.
* Person time is the sum of exposure across all patients in months.
Each patient is represented in both PH IV and PH FDC SC cross-over columns and either P+H IV or PH FDC in continuation period, depending on their choice of treatment, with the
exception of one patient who switched during the continuation period who is represented in both columns for the continuation period.
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Table 10 Racial Origin (Study MO40628, PHranceSCa)

Extent of Exposure by Race for Risk Management Plan by Treatment Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)		PH FDC SC Cross-Over (N=160)		PH IV Continuation (N=22)		PH FDC SC Continuation (N=137)	
Race	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
American Indian or Alaska Native	8 (5.0%)	17	8 (5.0%)	17	2 (9.1%)	8	6 (4.4%)	16
Asian	12 (7.5%)	25	12 (7.5%)	25	1 (4.5%)	3	11 (8.0%)	18
Black or African American	4 (2.5%)	9	4 (2.5%)	8	0	NE	4 (2.9%)	13
Native Hawaiian or Other Pacific Islander	0	NE	0	NE	0	NE	0	NE
White	129 (80.6%)	274	129 (80.6%)	270	17 (77.3%)	52	111 (81.0%)	328
Unknown	7 (4.4%)	15	7 (4.4%)	14	2 (9.1%)	2	5 (3.6%)	12
Multiple	0	NE	0	NE	0	NE	0	NE
Total patients number/person time	160 (100%)	339	160 (100%)	334	22 (100%)	66	137 (100%)	386

N = number of patients exposed to HER2 Targeted Therapy for the administration route and period of interest.
* Person time is the sum of exposure across all patients in months.
Each patient is represented in both PH IV and PH FDC SC cross-over columns and either P+H IV or PH FDC in continuation period, depending on their choice of treatment, with the
exception of one patient who switched during the continuation period who is represented in both columns for the continuation period.
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PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

The development program for Phesgo is in line with the Perjeta development program, and therefore the exclusion criteria selected for Study WO40324 (FeDeriCa) and presented in Table 11 are similar to those chosen for clinical studies conducted for Perjeta in combination with Herceptin and chemotherapy.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Phesgo Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients were excluded: • With Stage IV (metastatic) breast cancer • Who have received any previous systemic therapy for treatment or prevention of breast cancer, or radiation therapy for treatment of cancer • With history of concurrent or previously treated non-breast malignancies • With history of invasive breast cancer • Who have a past history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) if they have received any systemic therapy for its treatment or radiation therapy to the ipsilateral breast	Such patients were excluded from clinical trials because relapse or progression of the other malignancy could confound interpretation of trial efficacy data.	No	No warning or exclusion included in the Phesgo EU SmPC, since this is considered part of routine assessment of a patient's eligibility for treatment (part of routine oncology practice). This concern is not considered by the marketing authorization applicant (MAA) to be a sufficient reason to limit physician options in treatment of patients with active infections with pertuzumab, trastuzumab and chemotherapy.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
• With high-risk for breast cancer who have received chemopreventative drugs in the past • With multicentric breast cancer, unless all tumors are HER2-positive • With bilateral breast cancer • With history of other malignancy within 5 years prior to screening			
Patients who have undergone an excisional biopsy of primary tumor and/or axillary lymph nodes	Such patients were excluded from clinical trials because removal of primary tumor and/or axillary lymph nodes could confound efficacy results, specifically pathologic complete response (pCR) assessment	No	No warning or exclusion included in the Phesgo EU SmPC, since this is considered part of routine assessment of a patient's eligibility for treatment (part of routine oncology practice). This concern is not considered by the MAA to be a sufficient reason to limit physician options in treatment of patients with active infections with pertuzumab, trastuzumab and, chemotherapy.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) prior to initiation of neoadjuvant therapy	Such patients were excluded from clinical trials because ALND or SLNB could confound efficacy results, specifically pathologic complete response (pCR) assessment	No	No warning or exclusion included in the Phesgo EU SmPC, since this is considered part of routine assessment of a patient's eligibility for treatment (part of routine oncology practice). This concern is not considered by the MAA to be a sufficient reason to limit physician options in treatment of patients with active infections with pertuzumab, trastuzumab and chemotherapy.
Treatment with any investigational drug within 28 days prior to randomization	Such patients were excluded from clinical trials because the other investigational agent could confound interpretation of trial safety and efficacy data.	No	No warning or exclusion included in the EU SmPC. Co-administration of investigational agents is beyond the scope of the Phesgo EU SmPC.
Serious cardiac illness or medical conditions, history of ventricular dysrhythmias or risk factors for ventricular dysrhythmias	Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents	No	EU SmPC includes guidance on the increased risk of cardiac toxicity associated with HER2-targeted agents Cardiac risk should be carefully considered and balanced against the

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			medical need of the individual patient before use of Phesgo.
Inadequate bone marrow function	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	EU SmPCs for docetaxel and paclitaxel clearly indicate the high risk of myelosuppression and the need to monitor blood counts before and during therapy
Impaired liver function or known active liver disease.	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	EU SmPC for Phesgo indicates that Phesgo has not been studied in patients with hepatic impairment. EU SmPCs for cytotoxic agents commonly used in patients with breast cancer (e.g. docetaxel, paclitaxel, doxorubicin and epirubicin) indicate that clearance may be reduced and/or toxicity increased in patients with hepatic impairment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Inadequate renal function with serum creatinine $> 1.5 \times$ ULN	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	EU SmPC for Phesgo indicates that there is limited data on patients with severe renal impairment EU SmPCs for docetaxel and paclitaxel do not include information on patients with severe renal impairment; for doxorubicin and epirubicin, SmPCs indicate that dose reductions may be required for renal impairment.
Current severe, uncontrolled systemic disease that may interfere with planned treatment	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	No warning or exclusion included in the EU SmPC for Phesgo. Assessment of a patient's fitness for chemotherapy is part of routine oncology practice
Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the last dose of HER2-targeted therapy	Pregnant patients were excluded in clinical trials as studies in animals have shown reproductive related toxicity	No	EU SmPC includes clear instruction that patients should not be treated with Phesgo when pregnant and should use effective contraception

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			during treatment with Phesgo and for 7 months after stopping treatment
Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study	Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy	No	No warning or exclusion included in the EU SmPC for Phesgo. Assessment of a patient's fitness for chemotherapy is part of routine oncology practice
Concurrent, serious, uncontrolled infections, or known infection with HIV	Such patients may not be able to tolerate taxane- or anthracycline-based therapy and are at increased risk of infectious complications associated with myelosuppression	No	No specific warning or exclusion included in the EU SmPC for Phesgo since assessment of a patient's fitness for chemotherapy is part of routine oncology practice. This concern is not considered by the MAA to be a sufficient reason to limit physician options in treatment of patients with active infections with Phesgo. However, Section 4.4 of the Phesgo EU SmPC indicates that patients treated with pertuzumab, trastuzumab and docetaxel are at increased risk of

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel. The SmPCs of cytotoxic agents commonly used in patients with breast cancer (e.g., docetaxel, paclitaxel, doxorubicin and epirubicin) provide extensive warnings about the risks of neutropenia and its complications.
Known hypersensitivity to study drugs, excipients, and/or murine proteins	Patients with known hypersensitivity to pertuzumab or to any of its excipients were excluded from clinical trials to avoid risk of anaphylactic shock/reaction.	No	Patients with hypersensitivity to the active substance or to any of the excipients is contraindicated as per EU SmPC. In addition, a statement regarding permanent discontinuation of Phesgo for any patient who experiences a NCI CTCAE Grade 4 reaction, is included in Section 4.4 of the EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Current chronic daily treatment with corticosteroids	Such patients may not be able to tolerate taxane- or anthracycline--based therapy and are at increased risk of infectious complications associated with myelosuppression	No	No specific warning or exclusion included in the EU SmPC since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice).

EU=European Union; HER2=Human epidermal growth factor receptor 2; HBV=Hepatitis B virus; HCV=Hepatitis C virus; MAA=Marketing authorization applicant; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SmPC=Summary of Product Characteristics.

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

The clinical trial development program for Phesgo is unable to detect adverse drug reactions that are:

- Rare
- Caused by prolonged or cumulative exposure
- Adverse reactions that have a long latency

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Available exposure for special populations from FeDeriCa and PHranceSCa (both trials have similar populations) are described below in Table 12.

Table 12 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in the clinical development program, including: • Patients with known severe hepatic impairment; • Patients with current known infection with HIV, HBV or HCV were excluded.
Patients with renal impairment	• Patients with a serum creatinine $>$ 2.0 mg/dL or 177 µmol/L or $>$ 1.5 × upper limit of normal were not included in the clinical development program.
Patients with cardiovascular impairment	Not included in the clinical development program, including the following groups: • Patients with a left ventricular ejection fraction <55% in history or at screening. • Patients with a clinically significant cardiovascular disease, such as uncontrolled hypertension, unstable angina, a history of CHF or serious cardiac arrhythmias. • Patients with a cumulative dose of prior anthracyclines $>$ 360 mg/m^2 of doxorubicin or equivalent.
Population with relevant different ethnic origin	Please refer to Table 5 and Table 9.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

Other:	
Children	Children and adolescents below the age of 18 years were not included in the clinical development program.
Elderly aged ≥75 years old	These patients were not excluded from the clinical trial program for Phesgo. The number of patients aged > 75 years exposed via participation in clinical trials remains small. Please refer to Table 3 and Table 8.
Male breast cancer patients	Male breast cancer patients were not excluded from the clinical trial program for Phesgo. However, the number of male breast cancer patients exposed via participation in clinical trials remains small. Please refer to Table 3 and Table 8.

CHF = congestive heart failure; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus.

Use in Pregnancy and Lactation

Pregnant and breastfeeding women were not included in the clinical development program as studies in animals have shown reproductive related toxicity (see Section SVII.3, Important Identified Risks, Oligohydramnios). Even though the EU SmPC includes clear instruction that patients should not be treated with Phesgo when pregnant and should use effective contraception during treatment with Phesgo and for 7 months after stopping treatment, a few non-serious cases were reported from post-marketing sources. Current routine risk minimization measures in place are considered adequate to manage the risk, including the warning in the EU SmPC to use effective contraception during treatment with pertuzumab + trastuzumab and for 7 months after treatment has concluded. Pregnancy related maternal and fetal/infant information on all reports of women exposed to HER2 treatment, including risks of oligohydramnios, will continue to be monitored per routine pharmacovigilance (PV) activities as part of the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Kadcyla, Perjeta and Phesgo (see Part III).

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

For the European Economic Area (EEA), Rest of World (RoW) and US, patient exposure for the current reporting interval is defined as the sum of new and maintenance patient numbers in the reporting interval whereas cumulative patient is defined as the sum of all individual new patients exposed to pertuzumab + trastuzumab (Phesgo) since international birth date (IBD) to data lock point (DLP) (28 June 2023).

To estimate the exposure, monthly volume sales in mg is divided by the monthly average dose per patient, where the patient in loading dosage is considered as a new patient. This estimation method takes into careful consideration the volume sold data, ensuring that any volume exceeding the quantity of the drug consumed by maintenance patients at a specific point indicates the initiation of treatment for new patients. Conversely, when volume falls below the threshold of drug consumption by maintenance patients during a given period, it suggests the possibility of treatment discontinuation by some patients. Such patients are captured as drop-off patients, leading to a reduction in the group of maintenance patients. This method allows the estimation of both new patients and patients in the maintenance phase, while also encompassing the treatment discontinuation factor even in the absence of explicit persistence data.

As such, in any given reporting interval, the interval exposure will include not only new patients, but also capture the majority of patients who received Phesgo in the previous reporting interval(s) and continued receiving treatment in the current reporting interval (so-called maintenance patients).

Cumulative patient exposure from Marketing Experience refers to the total number of patients who have ever been exposed to Phesgo up to a specific point of time. It is calculated as the 'Sum of the previous cumulative patient exposure and the sum of new patients in the current interval'. Cumulative patient exposure includes new, maintenance as well as dropped off patients from all intervals.

Taking this all into consideration calculating cumulative exposure by adding intervals of patient exposure would lead to double counting of maintenance patients and result in significant overestimation of cumulative patient exposure.

As availability of robust sources differs across countries and regions, the best available databases across the major regions are selected in order to provide the most accurate estimates.

The market exposure data presented below for the EEA and RoW of Phesgo are estimated based on the following internal available information: volume and mass of commercial product (Phesgo) shipped to each country where pertuzumab + trastuzumab (Phesgo) is now launched and available. This methodology is used for both the last

PBRER reporting period (29 December 2022 to 28 June 2023) and the cumulative period (IBD to 28 June 2023).

In the interval and cumulative patient exposure estimation, patients are incorporated who are receiving the product through the Free Goods pool, which encompasses Commercial Access Programs, Samples, and Charitable. It is important to note that specific details regarding these programs and donations are lacking, as the information is solely available in the form of volume data. Consequently, the specific type of program or donation associated with individual patients is unable to be identified. The same patient exposure methodology is applied to Free Goods volume as is for the volume sold (both types of volume are aggregated together). This consistent approach ensures that patients are categorized into the same buckets (new, maintenance, and drop-offs) across both types of volume. Incorporating Free Goods volume is a standard practice for all patient exposure estimations.

A detailed explanation for each region's methodology can be found in the sections below.

Methodology for the European Economic Area and the Rest of the World (all territories excluding United States, Japan)

The market exposure data presented below for the EEA and for the RoW for Phesgo (pertuzumab + trastuzumab) was calculated based on internal available information: kg volume sold of commercial product (Phesgo), and additional factors, such as epidemiology or stock-pilling from the best available sources at the time of the extraction and calculation (Roche-sponsored market research and internal databases).

The calculation takes into account the number of actual Phesgo loading vials sold, on which a treatment duration and persistence as well as compliance factor is applied to account for the patients staying on treatment, in addition to allocating a calculated number of maintenance vials sold to account for mid-course switching (from Perjeta + Trastuzumab to Phesgo). The above-mentioned persistence rate is time-adjusted and is based on the countries' estimated date of launch (first month with volume of Phesgo sold locally).

The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]) and is provided on a monthly basis; therefore, cumulative exposure is available from IBD to the nearest point of DLP (i.e., 28 June 2023).

The loading dose per patient is 1200 mg pertuzumab/600mg trastuzumab whereas maintenance dose per patient is 600 mg pertuzumab/600mg trastuzumab.

Exposure per indications is currently estimated based on projected adoption and verification of usage from Roche-sponsored market research with oncologists and other

prescribers in the largest European countries for Phesgo in countries where such information is available and for Perjeta in countries where such information is not yet available.

Due to the lack of reliable and robust data from countries in the EEA and RoW, US demographics assumptions have been applied to ex-US exposures.

To estimate the exposure in each individual country, monthly volume sales in vials are smoothened out using exponential smoothening with damping factor in order to account for stock-in procedures and reduce the variability induced by such processes.

The volume for all countries is split into EBC (includes Neo-Adjuvant, Adjuvant Only and Adjuvant Continuation**)** and MBC (includes 1L, 2L+) based on information collected through Roche-sponsored market research and other syndicated sources. The volume split between EBC and MBC exposure is calculated to be 56.4% and 43.6% respectively for the interval from December 2022 to June 2023.

The first Phesgo volume sold in a specific country enables the calculation of the associated “New Patients.” In the following months, the volume required for Maintenance Patients is subtracted from the total volume to get New Patients.

To estimate the duration of therapy (DoT) at an EBC)/ MBC level, the DoTs are estimated in each segment (1L and 2L+ in MBC, Adjuvant Only, Neo-Adjuvant Only, Neo-Adjuvant + Adjuvant Continuation and Adjuvant Continuation Only) based on primary and syndicated data collected that reflect real-world use of Phesgo in these settings.

A certain weight to the DoTs is attributed in each individual patient segment, proportional to the size of the segment in real practice, to calculate a final DoT number and indication split for EBC and MBC respectively.

All patients who have completed their estimated DoT are considered as drop-offs. Hence, based on the estimated DoT and persistence rate, the total number of Drop-Offs are calculated for each month, which in turn helps in further identifying the patients continuing the treatment for subsequent months.

In a Month X, the number of Cumulative Patients is equivalent to the total number of new patients from IBD to Month X.

Methodology for the United States

The patient exposure data presented are based on Perjeta assumptions that U.S. sales are split such that 65% are used in patients with EBC and 35% in the MBC setting. Patient exposure is calculated from actual Phesgo loading vials sold, in addition to

allocating a calculated number of maintenance vials sold to account for mid-course switching.

As of the reporting period ending 28 June 2023, interval reporting now includes patients continuing on therapy at the beginning of the interval period. These continuing patients are not included in cumulative exposure calculations.

According to data obtained via Perjeta patient tracking activities, approximately 25% of patients receiving Phesgo for EBC and 41% of patients receiving Phesgo for MBC in the U.S. are aged 65 years or older. Epidemiology data indicate 0.8% of patients with breast cancer are male.

No estimated pediatric exposures are available. Perjeta assumptions are used as no Phesgo data is available to inform whether these assumptions would be different.

SV.1.2 Exposure

Since the IBD until last PBRER DLP (28 June 2023), an estimated cumulative total of 63,359 patients have received RO7198574 / pertuzumab + trastuzumab from marketing experience (see Annex 7, Table 1).

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. There is no evidence that pertuzumab or trastuzumab have such effects, which makes it highly unlikely that Phesgo will be misused for illegal purposes.

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

There are no non-important risks for Phesgo, therefore this section is not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Phesgo is intended to treat patients in line with the currently approved therapeutic indications for Perjeta and to provide an alternative to intravenous infusions of Perjeta and Herceptin, which is considered standard of care when combined with chemotherapy for patients with HER2-positive breast cancer. The active substances in Phesgo are identical to and from the same origin as those in the approved Perjeta and Herceptin formulations.

The risks associated with the use of Phesgo include (a) those related to pertuzumab in combination with trastuzumab and (b) those associated with the subcutaneous route of administration. In line with these aspects, the MAA proposes the following approach for the Phesgo risk management plan:

a) **To address risks related to pertuzumab in combination with trastuzumab:** The list of risks/risk categories are based on those outlined in the current Perjeta EU RMP (version 11.0) and amended, as appropriate, based on results from the pivotal FeDeriCa trial. Both the Perjeta EU RMP and Herceptin EU RMP were taken into consideration when determining the risk categories.

   Rationale for the approach:

   Perjeta is approved for use in combination with Herceptin and chemotherapy in HER2-positive early and metastatic breast cancer. The aim of the MAA for Phesgo is to register the same range of indications as those approved for Perjeta.

   Since its initial approval, approximately 344,281 patients have been treated with Perjeta, and always in combination with Herceptin. The Applicant is of the opinion that this represents an adequate body of evidence to identify adverse events, including those occurring at low frequencies, which may manifest in patients receiving these medicinal products in combination. Furthermore, the current Perjeta EU RMP addresses risks associated with both Perjeta and Herceptin as a causal relationship to a particular medicinal product may be difficult to ascertain.

b) **To address risks related to route of administration:** The Applicant considers the risk of administration-related reactions (ARRs) as an important identified risk and the risk of medication errors (altered safety and efficacy) as an important potential risk. These risks will be monitored by routine pharmacovigilance (PV) activities.

Rationale for the approach:

Since Perjeta is available as IV infusion, the risks related to the SC route of administration are based on the risks associated with Herceptin SC.

Based on the previous results from the Herceptin SC studies and the data from the pivotal FeDeriCa study, the Applicant has adjusted the risk categorization for the risks already associated with the SC route of administration.

Based on results from the FeDeriCa and PHranceSCa primary analyses, Phesgo in combination with chemotherapy has a comparable safety profile to that of Perjeta and Herceptin IV formulations in combination with chemotherapy. No new or unexpected toxicities were observed other than those that are known for agents that target the HER2 family of receptors.

The risks associated with Phesgo are presented below. Current pharmacovigilance plans and risk minimization measures in place are considered adequate to manage risks associated with Phesgo. The cumulative benefit-risk profile of Phesgo is considered positive and unchanged in all indications.

Important Identified Risk of Congestive heart failure / Left ventricular dysfunction

Risk-benefit impact:

The impact of congestive heart failure/left ventricular dysfunction on the benefit-risk balance of Phesgo is considered to be low. The incidence of CHF in patients receiving pertuzumab, trastuzumab and chemotherapy is low. Careful monitoring and following the dose management algorithm suggested in the product label further reduces the likelihood of a heart failure/left ventricular dysfunction event. The current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Important Identified Risk of Administration-related Reactions

Risk-benefit impact:

ARRs are clinically manageable with standard therapeutic interventions. The safety profile of Phesgo is well-characterized based on FeDeriCa and PHranceSCa data, in addition to experience with Herceptin SC and Mabthera SC. The cumulative benefit-risk profile of Phesgo is considered positive and unchanged in all indications.

Important Potential Risk of Oligohydramnios

Risk-benefit impact:

Current routine risk minimization measures in place are considered adequate to manage the risk, including the warning in the SmPC to use effective contraception during treatment with Phesgo and for 7 months after treatment has concluded. Pregnancy-related maternal and fetal/infant information on all reports of women exposed to HER2 treatment, including risks of oligohydramnios, will continue to be monitored per routine

pharmacovigilance activities as part of the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Kadcyla, and Perjeta (Section III.1).

Important Potential Risk of Lack of efficacy due to immunogenicity

Risk-benefit impact:

The impact of the risk of lack of efficacy due to immunogenicity on the overall benefit-risk balance of the product is considered low due to the immunogenicity data available to date for pertuzumab (IV), trastuzumab (SC), rHuPH20 in trastuzumab (SC) studies, and Phesgo.

Important Potential Risk of Medication errors (altered safety and efficacy)

Risk-benefit impact:

One case of medication error has been reported to date in the Phesgo clinical program. Similar to trastuzumab, routine measures for Phesgo have been implemented (i.e., different packaging and statements in the SmPC). Since the commercialization of Herceptin SC, no notable increase of medication errors has been reported which may suggest that packaging and relevant statements in the SmPC have been shown to be effective in mitigating the risk.

The MAA has conducted a comprehensive risk assessment for medication errors with the use of Phesgo which concludes that the following use-related risks for Phesgo are mitigated to an acceptable level:

- Risk of confusion of Phesgo maintenance dose with Phesgo loading dose
- Risk of administering Phesgo intravenously
- Risk of confusion of Phesgo with Herceptin (SC), Herceptin (IV) or Perjeta
- Risk related to injection of a large volume (loading dose of 15mL and maintenance dose of 10mL)

Further details on the use related risk assessment are provided in Annex 7.

Additional Risk Minimization Activities: As routine PV activities are considered adequate to address these risks, no additional risk minimization activities are proposed.

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

The MAH proposes to no longer consider ‘lack of efficacy due to immunogenicity’ as an important potential risk. The proposal is supported by evidence provided by final analysis data of the FeDeriCa study (for details, see Final CSR, report 1127623, Section 9), which corroborates the observations from clinical studies with intravenous pertuzumab and trastuzumab.

In FeDeriCa (final analysis data), for pertuzumab, ADA data were available from 245 ADA-evaluable patients in the P+H IV arm and 241 ADA-evaluable patients in the

Phesgo arm. Twenty-six (26) patients in the P+H IV arm (10.6%) and 31 patients in the Phesgo arm (12.9%) were determined to be ADA-positive (treatment-induced) for pertuzumab. Of the patients that tested positive for ADAs, 3 and 2 patients in the P+H IV and Phesgo arms, respectively, had developed neutralizing antibodies (NAbs). In both treatment groups, there was no substantial difference between anti-pertuzumab ADA positive and negative patients and anti-pertuzumab NAb positive and negative patients with respect to overall survival: between 90 and 100% in all groups were alive by the end of the study. Of the 57 patients who tested positive for ADAs to pertuzumab in both treatment arms, only 6 ADA positive patients in the Phesgo arm experienced ARRs, which were low grade (i.e., Grade 1 or 2). Furthermore, 4 ADA positive patients in the P+H IV arm experienced IRRs: 3 low grade (i.e., Grade 1 or 2) and 1 high grade (i.e., Grade 3 or higher). Of the 5 patients who tested positive for NAbs to pertuzumab in both treatment arms, only 1 ADA positive patient in the Phesgo arm experienced an ARR, which was low grade. These data suggest that positive ADA status did not have an impact on the immune related AEs to monitor.

In FeDeriCa (final analysis data), for trastuzumab, ADA data were available from 245 ADA-evaluable patients in the P+H IV arm and 241 ADA-evaluable patients in the Phesgo arm. Of these patients, the number of patients who were ADA-positive for trastuzumab was very low, including 1 patient in the P+H IV arm (0.4%) and 5 patients in the Phesgo arm (2.1%). Of the patients that tested positive for ADAs, only 1 patient in the Phesgo arm had developed neutralizing antibodies. Similar to results for anti-pertuzumab ADAs, anti-trastuzumab ADAs did not impact overall survival. Only one patient in the Phesgo group who had developed ADAs died. ADAs developed by this patient were not neutralizing antibodies. Of the 6 patients who tested positive for ADAs to trastuzumab in both treatment arms, only 1 ADA positive patient in the Phesgo arm experienced an ARR, which was low grade (Grade 2). The 1 patient who tested positive for NAbs to trastuzumab in the Phesgo arm did not experience any immune related AEs to monitor. These data suggest that positive ADA status did not have an impact on the immune related AEs to monitor.

In FeDeriCa (final analysis data), for rHuPH20, anti-rHuPH20 antibodies were applicable for the Phesgo arm only. There were 238 ADA-evaluable patients, of which 15 were positive for anti-rHuPH20 antibodies. None of the patients tested positive for NAbs. rHuPH20 provides no therapeutic benefit; however, an analysis of potential impact to efficacy was conducted. No patient with ADAs died. Of the 15 patients who tested positive for anti-rHuPH20 antibodies, only 3 ADA-positive patients experienced an ARR, which were low grade (ie, Grade 1 or 2). These data suggest that positive ADA status did not have an impact on the immune related AEs to monitor.

In addition, the immunogenicity of pertuzumab (IV) has been completely assessed in 15 clinical studies in 1558 pertuzumab-treated patients (TOC2297g, BO16934, BO17004, BO17931, JO17076, TOC2572g, TOC2664g, TOC2682g, TOC2689g, TOC3258g, WO20024, WO20698, MO28113, BO25114, and WO29217). In these

studies, the incidence of ADA formation was low, where 45 of 1558 patients (2.9%) were determined to be ADA positive. Furthermore, when ADAs were detected, they were often transient and titers tended to be low. Across these studies, patients developing ADA did not experience anaphylactic/hypersensitivity reactions or AEs clearly related to ADA development (the exception being hypersensitivity reactions possibly due to ADA in the 2 of 366 patients treated with pertuzumab in early Phase I/II studies), and there was no clear evidence of impact of ADA on PK or efficacy. Most patients with detectable ADA were able to continue study treatment, sometimes for prolonged periods.

The immunogenicity of trastuzumab (SC) has been completely assessed in three clinical studies in 749 trastuzumab (SC)-treated patients (BP22023, BO22227, and BO25159). In these studies, 150 of 749 patients (20%) were determined to be ADA positive. However, exploratory analyses showed that the occurrence of anti-trastuzumab antibodies in these studies did not appear to have any clinical consequences with respect to PK, efficacy, and/or safety.

The immunogenicity of rHuPH20 has been completely assessed in three trastuzumab (SC) clinical studies in 749 trastuzumab (SC)-treated patients (BP22023, BO22227, and BO25159). In these studies, 82 of 749 patients (11%) were determined to be positive for anti-rHuPH20 antibodies. However, exploratory analyses showed that the occurrence of anti-rHuPH20 antibodies in these studies did not appear to have any clinical consequences with respect to PK, efficacy, and/or safety.

The presence of ADAs to pertuzumab, trastuzumab, and rHuPH20 has not been found to be clearly associated with loss of efficacy or immune-related AEs. Although cases of Grade 3 hypersensitivity reactions have been reported in patients with ADAs to pertuzumab (IV), most patients with ADAs do not develop severe reactions and have continued pertuzumab treatment as planned. Although an adverse effect of ADA formation on efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common.

Based on data available to date, further investigation of ADA formation in clinical trials is not likely to yield significant new information. The lack of apparent clinical consequences in most patients means that ADA testing is unlikely to be introduced into routine clinical practice in the future. Upon completion of the FeDeriCa study, no additional PV or specific risk minimization measures are planned for patients receiving Phesgo to further characterize the potential risk of lack of efficacy due to immunogenicity, and the MAH proposes to remove this risk from the RMP.

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

Congestive heart failure/Left ventricular dysfunction

MedDRA Terms:

Adverse events (AEs) in the MedDRA SMQ Cardiac failure (wide)

Significant left ventricular ejection fraction (LVEF) declines were defined as any LVEF decline of $\geq$10%-points from baseline to an absolute value of $<$50%. Note that reporting of cardiac dysfunction is based on a single LVEF decline, which is a conservative approach, as many LVEF declines are not confirmed at the next assessment.

Potential mechanisms:

Since both pertuzumab and trastuzumab target HER2, there is a potential risk of cardiac dysfunction, particularly in patients who have received prior anthracycline treatment. HER2 signaling is required for the growth, repair and survival of cardiomyocytes. These repair mechanisms involve HER2-HER4 heterodimeric receptors which trigger the myocyte survival pathways required during the activation of acute stress signals mainly by anthracyclines (Crone et al. 2002; Negro et al. 2004; Sawyer et al. 2002). Available clinical evidence to date from studies in MBC and EBC suggests a similar or only slightly increased risk of cardiotoxicity with the addition of pertuzumab to trastuzumab. It is possible that the maximum effect on cardiomyocytes is already exerted by trastuzumab and that the addition of pertuzumab does not add to this (Carver 2010; Stortecky and Suter 2010; Zuppinger and Suter 2010).

Evidence source(s) and strength of evidence:

Randomized clinical trial data, based on safety results from FeDeriCa and PHranceSCa.

Characterization of the risk:

Frequency with 95% CI

In FeDeriCa, the incidence of cardiac dysfunction AEs (any grade) was comparable between the two arms and occurred in 41 (16.3%) patients in the P+H IV arm vs. 41 (16.5%) patients in the Phesgo arm. A summary of cardiac dysfunction events is provided in Table 13 below. The results of the final analyses did not show any additional relevant safety information with regard to this risk.

In PHranceSCa, the incidence of cardiac dysfunction AEs is provided in Table 14 below. Overall, cardiac dysfunction events were reported in 11 (6.9%) patients. The number of patients with AEs in the cross over period was 5 (3.1%) during P+H IV administration and 4 (2.5%) during Phesgo administration. The number of patients with AEs in the continuation period was 0 during the P+H IV administration and 3 (2.2%) during Phesgo administration. The results of the final analyses did not show any additional relevant safety information with regard to this risk.

Table 13 Summary of Cardiac Dysfunction Events from FeDeriCa

Cardiac Dysfunction Adverse Events by Treatment Regimen: Seriousness, Outcomes, Severity, Frequency with 95% CI for Risk Management
Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Number of patients with at least one AE	41 (16.3%)	41 (16.5%)
95% CI for % of patients with at least one AE [1]	(11.94%, 21.42%)	(12.13%, 21.75%)
Difference in % of patients with at least one AE		0.3%
95% CI for difference		(-6.63%, 7.15%)
Total number of AEs	49	46
Number (%) of patients with at least one AE by worst grade [a]		
Grade 1	23 (9.1%)	31 (12.5%)
Grade 2	14 (5.6%)	9 (3.6%)
Grade 3	4 (1.6%)	1 (0.4%)
Grade 4	0	0
Grade 5	0	0
Number of patients with at least one serious AE	2 (0.8%)	3 (1.2%)
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	16 (6.3%)	21 (8.5%)
Recovering/Resolving	4 (1.6%)	2 (0.8%)
Recovered/Resolved	22 (8.7%)	19 (7.7%)
Resolved with sequelae	1 (0.4%)	0
Unknown outcome	0	0

Investigator text for AEs encoded using MedDRA version 22.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
a = Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
95% CI for difference is calculated using Wald method.

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Table 14 Summary of Cardiac Dysfunction Events from PHranceSCa

Cardiac Dysfunction Adverse Events by Treatment Period: Seriousness, Outcomes, Severity, Frequency with 95% CI for Risk Management Plan, by Treatment Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)	PH FDC SC Cross-Over (N=160)	PH IV Continuation (N=21)	PH FDC SC Continuation (N=137)	All Patients (N=160)
Number of patients with at least one AE	5 (3.1%)	4 (2.5%)	0	3 (2.2%)	11 (6.9%)
95% CI for % of patients with at least one AE [1]	(1.02%, 7.14%)	(0.69%, 6.28%)	(0.00%, 16.11%)	(0.45%, 6.27%)	(3.48%, 11.97%)
Total number of AEs	5	4	0	3	12
Number of patients with at least one AE by worst grade[a]					
Grade 1	2 (1.3%)	0	0	1 (0.7%)	3 (1.9%)
Grade 2	2 (1.3%)	4 (2.5%)	0	2 (1.5%)	7 (4.4%)
Grade 3	1 (0.6%)	0	0	0	1 (0.6%)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one Serious AE	1 (0.6%)	1 (0.6%)	0	0	2 (1.3%)
Number of patients with at least 1 AE resulted in fatal outcome	0	0	0	0	0
Number of patients with at least 1 AE Not Recovered/Not Resolved	0	1 (0.6%)	0	0	1 (0.6%)
Number of patients with at least 1 AE Recovering/Resolving	0	0	0	1 (0.7%)	1 (0.6%)
Number of patients with at least 1 AE Recovered/Resolved	5 (3.1%)	3 (1.9%)	0	2 (1.5%)	9 (5.6%)
Number of patients with at least 1 AE Resolved with Sequelae	0	0	0	0	0
Number of patients with at least 1 AE with Unknown outcome	0	0	0	0	0

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
a = Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
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Seriousness/Outcomes

The incidence of serious cardiac dysfunction AEs were similar in each FeDeriCa treatment arm (2 [0.8%] P+H IV and 3 [1.2%] Phesgo patients). In PHranceSCa, 2 patients (1.3%) experienced a serious AE (one each during P+H IV and Phesgo cross-over administration).

There have been no cardiac dysfunction events with a fatal outcome. Please refer to Table 13 and Table 14 above.

Severity and Nature of Risk:

In FeDeriCa and PHranceSCa, the majority of events were Grade 1 and 2. Grade 3 events were infrequent, and occurred in 4 (1.6%) P+H IV vs. 1 (0.4%) FeDeriCa Phesgo patients and in 1 patient (0.6%) in PHranceSCa (P+H IV cross-over administration).

Impact on quality of life:

Cardiac failure may have a significant impact on the quality of life on individual patients and the presence of pre-existing risk factors or co-morbidities need to be taken into account when determining the benefit risk evaluation for individual patients.

Risk factors and risk groups:

Risk factors such as age of 60 years or older, prior chemotherapy, registration LVEF less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer (Advani et al. 2016; Russo et al. 2014; Yu et al. 2015).

Anthracycline exposure: Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease (Fiuza 2009; Geiger et al. 2010). The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose (Senkus and Jassem 2011).

Adjuvant breast radiotherapy: A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s (Chargari et al. 2011). Among patients treated during 1973 – 82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993 – 2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards (Chargari et al. 2011). Internal mammary chain irradiation increases heart dose exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease (Chargari et al. 2011).

Preventability:

Careful monitoring and early detection of (asymptomatic) LVEF reduction from baseline is a reliable screening mechanism for the individual patient decisions to continue or stop treatment with anticancer agents in general (Geiger et al. 2010). All patients enrolled in Phesgo trials undergo routine cardiac monitoring by echocardiogram or MUGA scan.

Impact on the benefit-risk balance of the product:

The impact of congestive heart failure (CHF) / left ventricular dysfunction (LVD) on the benefit-risk balance of Phesgo is considered to be low. The incidence of CHF in patients receiving Phesgo and chemotherapy is low. Careful monitoring and following the dose management algorithm suggested in the product label further reduces the likelihood of a heart failure / LVD event. The current PV plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of this safety concern is considered to be low because of the low frequency of CHF in patients with EBC receiving Phesgo and chemotherapy and because most cardiac events appear to be asymptomatic reversible declines in LVEF.

Administration-Related Reactions

MedDRA terms:

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

Potential mechanism:

It has been hypothesized 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 (Calogiuri et al. 2009).

Evidence source(s) and strength of evidence:

Randomized clinical trial data, based on safety results from FeDeriCa and PHranceSCa.

Characterization of the risk:

Frequency with 95% CI

Frequency with 95% CI details from FeDeriCa are provided in Table 15 below. ARRs occurring within 24 hours of HER2-targeted therapy were slightly higher in the Phesgo

arm compared to the P+H IV arm (34 patients [13.5%] P+H IV vs. 43 patients [17.3%] Phesgo) and were low grade for the majority. The results of the final analyses did not show any additional relevant safety information with regard to this risk.

For PHranceSCa, the incidence of ARRs is provided in Table 16 below. Overall, ARR events were reported in 52 patients (32.5%). The number of patients with AEs in the cross-over period was 9 (5.6%) during P+H IV administration and 38 (23.8%) during Phesgo administration. The number of patients who experienced AEs in the continuation period was 0 during P+H IV administration and 13 (9.5%) during Phesgo administration. The results of the final analyses did not show any additional relevant safety information with regard to this risk.

Table 15 Summary of Administration-Related Reactions Events from FeDeriCa

Administration Related Reactions (ARRs) Adverse Events by Treatment Regimen: Seriousness, Outcomes, Severity, Frequency with 95% CI for Risk Management Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Number of patients with at least one AE	34 (13.5%)	43 (17.3%)
95% CI for % of patients with at least one AE [1]	(9.53%, 18.34%)	(12.84%, 22.64%)
Difference in % of patients with at least one AE		3.8%
95% CI for difference		(-2.88%, 10.57%)
Total number of AEs	45	79
Number (%) of patients with at least one AE by worst grade [a]		
Grade 1	18 (7.1%)	38 (15.3%)
Grade 2	13 (5.2%)	5 (2.0%)
Grade 3	3 (1.2%)	0
Grade 4	0	0
Grade 5	0	0
Number of patients with at least one serious AE	2 (0.8%)	0
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	3 (1.2%)	2 (0.8%)
Recovering/Resolving	0	1 (0.4%)
Recovered/Resolved	32 (12.7%)	40 (16.1%)
Resolved with sequelae	0	0
Unknown outcome	0	0

Investigator text for AEs encoded using MedDRA version 22.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
a = Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
95% CI for difference is calculated using Wald method.

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Table 16 Summary of Administration-Related Reactions Events from PHranceSCa

Administration Related Reactions (ARRs) Adverse Events by Treatment Period: Seriousness, Outcomes, Severity, Frequency with 95% CI for Risk Management Plan, by Treatment Period,
Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)	PH FDC SC Cross-Over (N=160)	PH IV Continuation (N=21)	PH FDC SC Continuation (N=137)	All Patients (N=160)
Number of patients with at least one AE	9 (5.6%)	38 (23.8%)	0	13 (9.5%)	52 (32.5%)
95% CI for % of patients with at least one AE [1]	(2.60%, 10.41%)	(17.39%, 31.11%)	(0.00%, 16.11%)	(5.15%, 15.68%)	(25.32%, 40.34%)
Total number of AEs	10	55	0	31	96
Number of patients with at least one AE by worst grade[a]					
Grade 1	7 (4.4%)	35 (21.9%)	0	10 (7.3%)	45 (28.1%)
Grade 2	2 (1.3%)	3 (1.9%)	0	3 (2.2%)	7 (4.4%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one Serious AE	0	0	0	0	0
Number of patients with at least 1 AE resulted in fatal outcome	0	0	0	0	0
Number of patients with at least 1 AE Not Recovered/Not Resolved	0	0	0	0	0
Number of patients with at least 1 AE Recovering/Resolving	0	1 (0.6%)	0	0	1 (0.6%)
Number of patients with at least 1 AE Recovered/Resolved	9 (5.6%)	38 (23.8%)	0	13 (9.5%)	52 (32.5%)
Number of patients with at least 1 AE Resolved with Sequelae	0	0	0	0	0
Number of patients with at least 1 AE with Unknown outcome	0	0	0	0	0

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
[a] = Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
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Seriousness and outcomes

Two patients with serious ARR events were reported in the FeDeriCa P+H IV arm, and there were none in PHranceSCa. None of the ARR events had a fatal outcome. Please also refer to Table 15 and Table 16, above.

Severity and Nature of Risk:

The severity of reported ARR events in FeDeriCa and PHranceSCa are presented by NCI CTCAE grade, and the majority of the events were Grade 1 or 2 (Table 15 and Table 16).

Impact on quality of life:

ARRs are known to occur with trastuzumab. Serious ARRs to trastuzumab IV and trastuzumab SC including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress have been reported. Interruption of administration may help control such symptoms and the injection 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 Phesgo.

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

Preventability:

Pre-medication may be used to reduce risk of occurrence of ARRs. The MAA describes how ARRs can be managed in the SmPC. For Phesgo administration, these reactions can usually be managed by slowing the administration or temporarily stopping the infusion until resolution of the symptoms. It should also be noted that Phesgo 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 Phesgo is well-characterized and based on FeDeriCa data and experience with Herceptin SC and Mabthera SC. The cumulative benefit-risk profile of Phesgo 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.

Information on Important Potential Risks

Oligohydramnios

MedDRA terms:

MedDRA PTs coded to SMQ Pregnancy and neonatal topics.

Potential mechanisms:

Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in an embryo-fetal study when pertuzumab was administered intravenously from gestation day (GD)19 through GD50 to pregnant cynomolgus monkeys (the period of organogenesis in this species is GD20–50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure, at clinically relevant pertuzumab concentrations, were confirmed.

The embryo-fetal effects observed with pertuzumab and trastuzumab are consistent with the role HER-family members play in the development and differentiation of ectodermal/epithelial tissues, including that of renal tissue (Bader et al. 2007).

Evidence source(s) and strength of evidence:

Oligohydramnios has not been reported in patients treated with Phesgo but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab.

No clinical studies have been performed in pregnant women.

Characterization of the risk:

Frequency with 95% CI:

Frequency with 95% CI details from FeDeriCa for pregnancy and neonatal events (i.e., exposure during pregnancy, exposure during breast-feeding, pregnancy complications, oligohydramnios, or congenital abnormalities) are presented in Table 17. Two events were retrieved for FeDeriCa as part of the search criteria; however, neither of these events were related to a pregnancy. Both events were reports of epidermolysis: one Grade 2 event in the P+H IV arm and one Grade 1 event in the Phesgo arm. The results of the final analyses did not show any additional relevant safety information with regard to this risk.

One patient in PHranceSCa experienced a pregnancy and neonatal event during Phesgo cross-over administration (Table 18). The event of Grade 2 mastitis was considered unrelated to Phesgo and was resolved. It should be noted that this patient was not pregnant. This patient was included in this category because the PT reported (Mastitis) was part of the search criteria. The results of the final analyses did not show any additional relevant safety information with regard to this risk.

Table 17 Summary of Pregnancy and Neonatal Events from FeDeriCa

Exposure During Pregnancy / Exposure during Breast Feeding / Pregnancy Complications / Oligohydramnios / Congenital Abnormalities
Adverse Events by Treatment Regimen: Seriousness, Outcomes, Severity, Frequency with 95% CI for Risk Management Plan: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Number of patients with at least one AE	1 (0.4%)	1 (0.4%)
95% CI for % of patients with at least one AE [1]	(0.01%, 2.19%)	(0.01%, 2.23%)
Difference in % of patients with at least one AE		0.0%
95% CI for difference		(-1.50%, 1.51%)
Total number of AEs	1	1
Number (%) of patients with at least one AE by worst grade [a]		
Grade 1	0	1 (0.4%)
Grade 2	1 (0.4%)	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	0	0
Recovering/Resolving	0	0
Recovered/Resolved	1 (0.4%)	1 (0.4%)
Resolved with sequelae	0	0
Unknown outcome	0	0

Investigator text for AEs encoded using MedDRA version 22.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
a = Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
95% CI for difference is calculated using Wald method.

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Table 18 Summary of Pregnancy and Neonatal Events from PHranceSCa

Exposure During Pregnancy / Exposure during Breast Feeding / Pregnancy Complications / Oligohydramnios / Congenital Abnormalities Adverse Events by Treatment Period: Seriousness,
Outcomes, Severity, Frequency with 95% CI for Risk Management Plan, by Treatment Period, Safety-Evaluable Population
Protocol: MO40628
Primary Analysis

	PH IV Cross-Over (N=160)	PH FDC SC Cross-Over (N=160)	PH IV Continuation (N=21)	PH FDC SC Continuation (N=137)	All Patients (N=160)
Number of patients with at least one AE	0	1 (0.6%)	0	0	1 (0.6%)
95% CI for % of patients with at least one AE [1]	(0.00%, 2.28%)	(0.02%, 3.43%)	(0.00%, 16.11%)	(0.00%, 2.66%)	(0.02%, 3.43%)
Total number of AEs	0	1	0	0	1
Number of patients with at least one AE by worst grade[a]					
Grade 1	0	0	0	0	0
Grade 2	0	1 (0.6%)	0	0	1 (0.6%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number of patients with at least one Serious AE	0	0	0	0	0
Number of patients with at least 1 AE resulted in fatal outcome	0	0	0	0	0
Number of patients with at least 1 AE Not Recovered/Not Resolved	0	0	0	0	0
Number of patients with at least 1 AE Recovering/Resolving	0	0	0	0	0
Number of patients with at least 1 AE Recovered/Resolved	0	1 (0.6%)	0	0	1 (0.6%)
Number of patients with at least 1 AE Resolved with Sequelae	0	0	0	0	0
Number of patients with at least 1 AE with Unknown outcome	0	0	0	0	0

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of any study drug through 28 days after last dose of study treatment. When an AE start date is partially or fully missing, and it is unclear to which treatment period the AE should be assigned, the AE is assigned to all relevant treatment periods.
[a] = Grades are based on NCI CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
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Seriousness/Outcomes

No pregnancy or neonatal events were reported in FeDeriCa up to the primary analysis. In PHranceSCa, pregnancy/neonatal-related events were experienced by 1/160 patients (0.6%) during the treatment cross-over period. The event of Grade 2 mastitis was considered unrelated to Phesgo and was resolved. As of the CCOD, there were no pregnancies reported during the study. It should be noted that this patient was not pregnant. This patient was included in this category because the PT reported (Mastitis) was part of the search criteria. As of the CCOD, there were no pregnancies reported during the study.

Severity and Nature of Risk:

Oligohydramnios is classified as a potential risk based on non-clinical data and because cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab. No events of oligohydramnios have been reported in patients receiving Phesgo.

Impact on quality of life:

Oligohydramnios is associated with serious risks to fetal development and therefore may have a significant impact on an individual patient. Women of childbearing potential are advised to use effective contraceptive measures during treatment and for 7 months after the last dose of Phesgo.

The need to avoid pregnancy during and for 7 months after Phesgo treatment may affect patients' quality of life. However, patients are likely to face the same restrictions even without Phesgo administration, since most treatment for breast cancer (chemotherapy, hormone therapy and radiotherapy) are associated with significant risks to the developing fetus.

Risk factors and risk groups:

Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive Phesgo treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios (Maeda et al. 2014). Pregnant women with sickle cell disease are at

increased risk of oligohydramnios (Kuo and Caughey 2016). Primiparity is associated with an increased rate of oligohydramnios (Wielgos et al. 2015).

Preventability:

The risk of oligohydramnios is avoidable providing effective contraceptive measures are applied by women of childbearing potential during treatment and for 7 months after the last dose of Phesgo.

Impact on the benefit-risk balance of the product:

Current routine risk minimization measures in place are considered adequate to manage the risk, including the warning in the SmPC to use effective contraception during treatment with Phesgo and for 7 months after treatment has concluded. Pregnancy-related maternal and fetal/infant information on all reports of women exposed to HER2 treatment, including risks of oligohydramnios, will continue to be monitored per routine PV activities as part of the Global Enhanced Pharmacovigilance Pregnancy Program for Herceptin, Kadcyla, and Perjeta (Section III.1).

Public health impact:

The public health impact associated with this safety concern is considered to be low. Pregnancies are usually contraindicated in patients with advanced malignancy due to the risks of cytotoxic drugs, hormone therapy and/or radiotherapy, as well as the limited life expectancy of the mother.

Medication Errors (Altered Safety and Efficacy)

MedDRA terms: HLGT Medication Errors

Potential mechanisms:

Medication errors are usually attributed to human error.

Evidence source (and strength of evidence):

One case of incorrect route of drug administration has been reported to date in the Phesgo clinical program. Similar to trastuzumab, routine measures for Phesgo have been implemented (i.e., different packaging and statements in the SmPC). Since the commercialization of Herceptin SC, no notable increase of medication errors has been reported which may suggest that packaging and relevant statements in the SmPC have been shown to be effective in mitigating the risk.

The MAA has conducted a comprehensive risk assessment for medication errors with the use of Phesgo which concludes that the following use-related risks for Phesgo are mitigated to an acceptable level:

- Risk of confusion of Phesgo maintenance dose with Phesgo loading dose
- Risk of administering Phesgo intravenously
- Risk of confusion of Phesgo with Herceptin (SC), Herceptin (IV) or Perjeta
- Risk related to injection of a large volume (loading dose of 15mL and maintenance dose of 10mL)

Further details on the use related risk assessment are provided in Annex 7.

Characterization of the risk:

In the Phesgo clinical program to date for 1 of 660 patients has been reported with an incorrect route of drug administration, which occurred in the FeDeriCa study.

Seriousness/Outcomes:

In the FeDeriCa study, a patient randomized to the Phesgo arm received their first loading dose of Phesgo (15 mL) at study Cycle 5, Day 1 by IV infusion instead of SC injection due to errors in preparation and administration of the dose at the site. At the next visit, the patient reported experiencing nausea, emesis, and asthenia for 3 days after her last visit, when the medication error occurred. The investigator hospitalized the patient immediately for Grade 4 GI toxicity with symptoms of nausea, vomiting, and diarrhea. The event fully resolved and the patient received the next dose of Phesgo as planned (maintenance dose by SC injection) at Cycle 6, Day 1 with no untoward events observed. Nausea, vomiting and diarrhea are common AEs observed with anti-cancer treatment, hence it was not likely that the product administration error contributed to the Grade 4 GI toxicity. In the FeDeriCa trial (WO40324) one event of incorrect route of drug administration was reported as Grade 4 in severity.

Impact on quality of life:

In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Phesgo.

Phesgo should only be prescribed by a physician and administered under the supervision of a healthcare professional.

One case of incorrect route of drug administration has been reported to date in the Phesgo clinical program. The patient received the next dose of Phesgo as planned (maintenance dose by SC injection) with no untoward events observed.

Risk factors and risk groups:

Not applicable

Preventability:

Confusion of one dose strength with another could occur, most likely when selecting the vial, but possibly also (when several doses are prepared at the same time) when labeling the syringe or when selecting the syringe.

In order to mitigate this risk, the trade name is different, and product and dose colors have been established, which are used on the carton box, on the vial label itself, and the vial cap, that are distinctly different from those used for HER2 products already on the market. For additional information, refer to Annex 7.

In addition, the loading dose comes in a 20 ml vial, whereas the maintenance dose comes in a smaller 15 ml vial, which also is likely to help with differentiation.

The Phesgo vial label contains a peel-off sticker to be transferred from the Phesgo vial onto the syringe that will be used to administer the dose to the patient. The label specifies the route of administration and the dose strength, including the color scheme of the Phesgo Vial. The peel-off sticker allows the HCPs to clearly identify the contents of the dosing syringe, and therefore enable full traceability of the product until it is administered to the patient.

A use-related risk assessment was conducted for medication errors with the use of Phesgo in the marketed setting, including the risk of administering Phesgo intravenously, and it was concluded that this and other use-related risks for Phesgo are mitigated to an acceptable level with the proposed risk mitigation measures.

Impact on the benefit-risk balance of the product:

The distinctive packaging that is summarized above, as well as the precautionary statements included in the SmPC, will minimize potential medication errors.

Public health impact:

No potential public health impact of this safety concern.

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

There is no missing information for Phesgo.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 19 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Congestive heart failure / Left ventricular dysfunction Administration-related reactions
Important potential risks	Oligohydramnios Medication errors (altered safety and efficacy)
Missing information	None

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 Questionnaire – Pregnancy-Related Adverse Events

Oligohydramnios has been classified as an important potential risk for Phesgo. The guided questionnaire was implemented as part of the Global Enhanced Pharmacovigilance Pregnancy Program to request additional information on the mother's medical and obstetric history, the current pregnancy, fetal and infant condition, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life (Annex 4).

Other forms of routine pharmacovigilance activities:

Presentation of cumulative data in Periodic Safety Update Reports (PSURs) for all safety concerns presented in this RMP.

Global Enhanced Pharmacovigilance Pregnancy Program for the safety concern Oligohydramnios.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine PV activities are considered by the MAH/Applicant to be sufficient to obtain and analyze relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no on-going additional PV activities for Phesgo.

Table 20 Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
None				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
WO40324 (FeDeriCa, Completed)	• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} of pertuzumab SC within Phesgo compared with Perjeta IV • To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab Ctrough of trastuzumab SC within Phesgo compared with Herceptin IV • To evaluate the efficacy of Phesgo + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• Lack of efficacy due to immunogenicity	• Updated Immunogenicity Report	• Completed; February 2021
	• To evaluate the safety of Phesgo compared with Perjeta IV and Herceptin IV		• Final CSR, Report 1127623	• Completed; October 2023

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no post-authorization efficacy studies planned for Phesgo.

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

V.1 ROUTINE RISK-MINIMIZATION MEASURES

Table 21 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Congestive heart failure / Left ventricular dysfunction	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Phesgo is a prescription only medicine
Oligohydramnios	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Phesgo is a prescription only medicine
Administration-related reactions	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration

Safety concern	Routine risk minimization activities
	SmPC Section 4.4 Special 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: Phesgo is a prescription only medicine.
Medication errors (altered safety and efficacy)	**Routine risk communication:** Section 4.2 of the EU SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** At the beginning of Section 4.2 of the SmPC, there is a statement re-enforcing the need to check the vial labels to ensure that the drug being prepared and administered is Phesgo. Additionally, the fact that Phesgo should be administered via subcutaneous injection only is stated. Outer and inner packaging differentiation: between each strength of Phesgo as well as between HER2 approved products - peel off label - subcutaneous is stated in bold and red on the vial and packaging, in addition to the SmPC. - difference in vial size **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMIZATION MEASURES

Table 22 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Congestive heart failure / Left ventricular dysfunction	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, "Left ventricular dysfunction" part and Section 4.4 "Left ventricular dysfunction (including congestive heart failure)" provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Oligohydramnios	**Routine risk communication:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None	**signal detection:** Global Enhanced Pharmacovigilance Pregnancy Program Questionnaire for pregnancy-related adverse events *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Administration-Related Reactions (ARRs)	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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: Phesgo is a prescription only medicine. **Additional risk minimization measures:** None	
Medication errors (altered safety and efficacy)	**Routine risk communication:** Section 4.2 of the EU SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** At the beginning of Section 4.2 of the SmPC, there is a statement re-enforcing the need to check the vial labels to ensure that the drug being prepared and administered is Phesgo. Additionally, the fact that Phesgo should be administered via subcutaneous injection only is stated. Outer and inner packaging differentiation: between each strength of Phesgo as well as between HER2 approved products - peel off label - subcutaneous is stated in bold and red on the vial and packaging, in addition to the SmPC. - difference in vial size	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None	

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Sponsor Reports

Final CSR Study WO40324 (FeDeriCa). A phase III, randomized, multicenter, open-label, two-arm study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in combination with chemotherapy in patients with HER2-positive early breast cancer. Report No. 1127623; October 2023.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR PHESGO

This is a summary of the risk-management plan (RMP) for Phesgo™ (pertuzumab and trastuzumab fixed dose combination for subcutaneous injection). The RMP details important risks of Phesgo, how these risks can be minimized, and how more information will be obtained about Phesgo's risks and uncertainties (missing information).

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

This summary of the RMP for Phesgo should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of 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 Phesgo's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Phesgo is authorized for metastatic and early breast cancers (see SmPC for the full indication). It contains pertuzumab and trastuzumab as the active substances, and it is given by subcutaneous injection.

Further information about the evaluation of Phesgo's benefits can be found in Phesgo's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page

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

Important risks of Phesgo, together with measures to minimize such risks and the proposed studies for learning more about Phesgo's 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 as 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.

Important information that may affect the safe use of Phesgo is not yet available, and it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Phesgo 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 Phesgo. 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 about 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	Congestive heart failure / Left ventricular dysfunction Administration-related reactions
Important potential risks	Oligohydramnios Medication errors (altered safety and efficacy)
Missing information	None

II.B Summary of Important Risks

Important Identified Risk: Congestive heart failure / Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Randomized clinical trial data, based on safety results from FeDeriCa.
Risk factors and risk groups	Risk factors such as age of 60 years or older, prior chemotherapy, registration left ventricular ejection fraction (LVEF) less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer (Advani et al. 2016; Russo et al. 2014; Yu et al. 2015).
Risk-minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects Package Leaflet: Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach. Package Leaflet: Section 2 ‘Heart Problems’ provides recommendations for patients **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Administration-related reactions	
Evidence for linking the risk to the medicine	Randomized clinical trial data, based on safety results from FeDeriCa.
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 Phesgo.
Risk-minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects Package Leaflet: Section 4 Possible side 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. Section 2 of the package leaflet, 'Injection reactions' provides guidance for patients on observation period after administration. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Potential Risk: Oligohydramnios	
Evidence for linking the risk to the medicine	Oligohydramnios has not been reported in patients treated with Phesgo but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. No clinical studies have been performed in pregnant women.

Risk factors and risk groups	Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive Phesgo treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur. Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios (Maeda et al. 2014). Pregnant women with sickle cell disease are at increased risk of oligohydramnios (Kuo and Caughey 2016). Primiparity is associated with an increased rate of oligohydramnios (Wielgos et al. 2015).
Risk-minimization measures	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach. Package Leaflet: Section 2 ‘Pregnancy, breast-feeding and contraception’ provides recommendations for patients **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None

Additional pharmacovigilance activities	None

Important Potential Risk: Medication errors (altered safety and efficacy)	
Risk-minimization measures	**Routine risk communication:** Section 4.2 of the EU SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** At the beginning of Section 4.2 of the SmPC, there is a statement re-enforcing the need to check the vial labels to ensure that the drug being prepared and administered is Phesgo. Additionally, the fact that Phesgo should be administered via subcutaneous injection only is stated. Outer and inner packaging differentiation: between each strength of Phesgo as well as between HER2 approved products - peel off label - subcutaneous is stated in bold and red on the vial and packaging, in addition to the SmPC. - difference in vial size **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Advani PP, Ballman KV, Dockter TJ, et al. Long-Term Cardiac Safety Analysis of NCCTG N9831 (Alliance) Adjuvant Trastuzumab Trial. J Clin Oncol 2016;34:581-7.
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Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods 2008;333:1-9.
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Maeda A, Bateman BT, Clancy CR, et al. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. Anesthesiology 2014;121:1158-65.
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Yu AF, Yadav NU, Lung BY, et al. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat 2015;149:489-95.

II.C Post-Authorization Development Plan

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

There are no studies that are conditions of the marketing authorization or specific obligation of Phesgo.

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

There are no studies required for Phesgo.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

- Guided Questionnaire for pregnancy related adverse events

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, Pertuzumab+Trastuzumab FDC SC 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):_____
☐ Drug: **Pertuzumab + Trastuzumab FDC SC** Lot Number(s):_____

Maternal Information

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

Guided Questionnaire
Pregnancy-Related Adverse Events

☐	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 Aneuploidy Screening/testing (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

Guided Questionnaire
Pregnancy-Related Adverse Events

* 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	Diagnostic tests: ☐ Ultrasonography	Start date / Gestational age	Contributing factors

	☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction			
☐	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			

Guided Questionnaire
Pregnancy-Related Adverse Events

FOR INTERNAL USE ONLY
Company Awareness Date:
MCN:

Completed by:

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

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

E-mail: ..... Tel. No.: .....

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

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

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

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

.....

Guided Questionnaire
Pregnancy-Related Adverse Events

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

This annex is not applicable as there are no additional risk minimization activities for Phesgo beyond routine pharmacovigilance.