Official Title: A Randomized, Open-Label, 2-arm, Parallel Group, Single Dose, Multi-Centre Study in Healthy Male Subjects to Investigate the Comparability of Pharmacokinetics of the Fixed-Dose Combination of Pertuzumab and Trastuzumab Administered Subcutaneously Using a Handheld Syringe or Using the On-Body Delivery System

NCT Number: NCT05275010

Document Date: Protocol Version 4: 13 December 2022

PROTOCOL

TITLE:	**A RANDOMIZED, OPEN-LABEL, 2-ARM, PARALLEL GROUP, SINGLE DOSE, MULTI-CENTRE STUDY IN HEALTHY MALE SUBJECTS TO INVESTIGATE THE COMPARABILITY OF PHARMACOKINETICS OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB ADMINISTERED SUBCUTANEOUSLY USING A HANDHELD SYRINGE OR USING THE ON-BODY DELIVERY SYSTEM**
PROTOCOL NUMBER:	WP42873
VERSION NUMBER:	*4*
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
NCT NUMBER:	NCT05275010
TEST PRODUCT:	Fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
SPONSOR:	F. Hoffmann-La Roche Ltd
***APPROVAL*:**	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY	
Version	**Date Final**
4	See electronic date stamp on the final page of this document.
3	21 July 2022
2	21 April 2022
1	27 April 2021

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol WP42873 Version 4 has been amended to update the reasons for excluding subjects from the pharmacokinetic (PK) analysis population for the co-primary endpoints. With this update, the reasons for exclusion have been modified so fewer subject will fall into the PK non-evaluable population, therefore enabling more subjects to be included in the primary analysis.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The following changes have been made to Section 6.4:
  - The analysis population has been updated to clarify the primary population.
  - For analysis of $AUC_{0-62\ days}$, the PK sampling time window has been increased from ± 48 hours to ± 120 hours, so subjects with a Day 63 PK sample time deviation outside of a ± 120-hour window of planned sampling time will now be excluded.
  - For analysis of C_{max}, the number of missing PK samples allowed has been increased from 0 to 1, so now subjects with two or more missing PK concentration data on any of Days 3, 5, 7, 9, or 11 will be excluded.
- The description of the secondary endpoint analyses have been simplified and aligned with the wording in the statistical analysis plan (Section 6.5).
- The Sponsor record retention policy has been clarified (Section 7.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 8.4).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, OPEN-LABEL, 2-ARM, PARALLEL GROUP, SINGLE DOSE, MULTI-CENTRE STUDY IN HEALTHY MALE SUBJECTS TO INVESTIGATE THE COMPARABILITY OF PHARMACOKINETICS OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB ADMINISTERED SUBCUTANEOUSLY USING A HANDHELD SYRINGE OR USING THE ON-BODY DELIVERY SYSTEM**
PROTOCOL NUMBER:	WP42873
VERSION NUMBER:	*4*
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
IND NUMBER:	To be determined
TEST PRODUCT:	Fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
PHASE:	Phase I
INDICATION:	Not Applicable
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics and safety of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration (PH FDC SC) given by the on-body delivery system (OBDS) compared to hypodermic needle and syringe in healthy male subjects. Specific objectives and corresponding endpoints for the study are outline below.

Primary Pharmacokinetic Objective	**Corresponding Endpoints**
• To demonstrate comparability of single-dose AUC_{0-62} and C_{max} for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle	• Serum pertuzumab AUC_{0-62} and C_{max} • Serum trastuzumab AUC_{0-62} and C_{max}
Secondary Pharmacokinetic Objectives	**Corresponding Endpoints**
• To demonstrate the comparability of C_{Day21} values for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle	• Serum pertuzumab C_{Day21} • Serum trastuzumab C_{Day21}

• To demonstrate the comparability of C_{Day62} values for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle	• Serum pertuzumab C_{Day62} • Serum trastuzumab C_{Day62}
• To further characterize additional PK parameters for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle	• $AUC_{0-\infty}$ • t_{max} • $t_{1/2}$ • CL/F • Vd/F
Secondary Safety Objectives	**Corresponding Endpoints**
• To demonstrate comparable safety and tolerability of PH FDC SC administered by either the OBDS or by a handheld syringe with hypodermic needle	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE Version 5.0 • Change from baseline in vital signs, LVEF, and ECG parameters • Change from baseline in clinical laboratory test results
• To demonstrate the safety of the OBDS	• Pain at the injection site assessed by the subject using the 100 mm VAS • Skin irritation and sensitization reactions at the site of injection assessed by the study staff using the device monitoring questionnaire in the eCRF
Secondary Device Monitoring Objectives	**Corresponding Endpoints**
• To demonstrate the performance of the OBDS	• Comfort of wearing the device, as reported by the subject using the device monitoring questionnaire Details of performance and ease of use of the OBDS reported by site staff, using the device monitoring questionnaire in the eCRF
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20 within the PH FDC SC, administered using an OBDS compared to a hand-held syringe with hypodermic needle	• Incidence of pertuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of trastuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of rHuPH20 ADAs during the study relative to the prevalence of ADAs at baseline

ADA = anti-drug antibody; AUC_{0-62} = area under the time–concentration curve from the start of dosing to 63 days; $AUC_{0-\infty}$ = area under the time–concentration curve from the start of dosing extrapolated to infinity; C_{Day21} = serum concentration on Day 22; C_{Day62} = serum concentration on Day 63; CL/F = apparent drug clearance; C_{max} = maximum concentration; eCRF = electronic Case Report Form; LVEF = Left Ventricular Ejection Fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OBDS = on-body delivery system; PH FDC SC = fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration; PK = pharmacokinetic; rHuPH20 = recombinant human PH20 hyaluronidase; t_{max} = observed time to maximum concentration; $t_{1/2}$ = terminal elimination half-life; VAS = Visual Analog Scale; Vd/F = apparent volume of distribution

STUDY DESIGN

DESCRIPTION OF STUDY

This is a randomized, open-label, 2-arm parallel-group, single-dose, multi-center study in healthy male subjects to investigate the comparability of pharmacokinetics (PKs) of pertuzumab and trastuzumab within the PH FDC SC administered using the proprietary OBDS or a handheld syringe with hypodermic needle. Subjects will be randomized to one of two dosing arms (Arm 1 or Arm 2) in a 1:1 ratio to receive a single dose of PH FDC SC administered by a healthcare professional subcutaneously into the anterior thigh using either the OBDS or a handheld syringe with hypodermic needle. The study will be conducted at clinical research facilities in New Zealand and Australia.

NUMBER OF SUBJECTS

Approximately 144 male subjects will be randomized.

TARGET POPULATION

Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Signed Informed Consent Form
- Healthy male subjects age 18–45 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 7 months after the dose of PH FDC SC to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., according to female partner calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.
- A body mass index (BMI) between 18 and 32 kg/m^2, inclusive
- Intact normal skin without potentially obscuring tattoos, pigmentation, or lesions in the area for intended injection on the thighs
- Baseline LVEF ≥ 55% measured by echocardiogram (ECHO)
- No history of hypersensitivity or confirmed, clinically significant and clinically relevant allergic reactions, either spontaneously or following any drug administration
- No history of any clinically significant and clinically relevant cardiac condition
- No history of previous anticancer treatments including pertuzumab, trastuzumab, anthracyclines, or any cardiotoxic drugs

- No apparent family history of clinically significant and clinically relevant hypersensitivity, allergy, and severe cardiac diseases
- No contraindications from detailed medical and surgical history and physical examinations
- No previous enrollment in this study protocol and no concurrent enrollment in any other study protocol

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

- Positive urine test for drugs of abuse as per local standard (for alcohol abuse, positive breath test is also acceptable)
- Positive test result for hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV 1 or 2. Showing:

  History of exposure to HBV, HCV, or HIV

  or

  Active viral hepatitis infection (HBV or HCV) or HIV infection
- Systolic blood pressure (BP) $\geq$ 140 mmHg or $<$ 90 mmHg, or diastolic BP $>$ 90 mmHg or $<$ 50 mmHg
- Use of prohibited medications, including non-prescription medications, nutraceuticals, nutritional supplements, or any herbal remedies taken within 10 days or 5 times the elimination half-life (whichever is longer) prior to randomization into the study
- Concomitant subcutaneous, intravenous, or any parenteral drugs within 90 days prior to screening
- Participation in an investigational drug or device study within 90 days or 5 times the elimination half-life (whichever is longer) prior to screening
- Donation of blood over 500 mL within 3 months prior to enrollment
- Known severe hypersensitivity to plaster, medical adhesive tapes, or bandages
- Known allergy to murine proteins, hyaluronidase, bee, or vespid venom, or any other ingredient in the formulation of recombinant human PH20 hyaluronidase (rHuPH20) (Hylenex® recombinant [hyaluronidase human injection]) or any other ingredients and excipients in the formulation of PH FDC SC
- Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, CBC, chemistry panel, and urinalysis)
- Clinically relevant ECG abnormalities on screening or Day -1 ECG:

  Corrected QT interval (QTc) (QT interval corrected through use of Fridericia's formula [QTcF] $>$ 450 msec)

  notable resting bradycardia (heart rate [HR] $<$ 40 bpm)

  notable resting tachycardia (HR $>$ 100 bpm)

  difference between highest and lowest durations of any baseline QTc at a specific time point $>$ 30 msec

  measurement of QT interval imprecise (i.e., flat T waves, arrhythmias, etc.)

  evidence of atrial fibrillation, atrial flutter, right or left bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker

  any other significant abnormality
- History of any cardiac condition
- Lower extremity edema or pathology (e.g., cellulitis, lymphatic disorder or prior surgery, pre-existing pain syndrome, previous lymph node dissection etc.) that could interfere with any protocol-specified outcome assessment
- Any history of clinically significant and clinically relevant allergies, oncologic, psychiatric, gastrointestinal, renal, hepatic, cardiovascular or pulmonary disease

- Concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in this study
- Any clinically relevant history of systemic disease (e.g., malignancy, diabetes mellitus, gastrointestinal, renal, hepatic, cardiovascular, rheumatological, or pulmonary disease)
- History of breast cancer or treatment for breast cancer
- Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose ≥ 10 mg/day methylprednisolone), excluding inhaled corticosteroids
- Receipt of IV antibiotics for infection within 7 days prior to enrollment into the study

END OF STUDY

The end of the study is defined as the date when the last subject, last visit occurs. This is expected to occur 7 months after the last subject is enrolled (i.e., when the last subject has completed the safety follow-up visit at 7 months after administration of study drug).

LENGTH OF STUDY

The length of study will be a maximum of 35 weeks per subject, from screening to follow-up (4 weeks screening, plus 7 months [~31 weeks] follow-up after dose). The total length of the study from screening of the first subject to the end of the study is expected to be approximately 11 months.

INVESTIGATIONAL MEDICINAL PRODUCTS

The IMP for this study is PH FDC SC (600 mg pertuzumab/600 mg trastuzumab/ 20,000U rHuPH20).

Subjects in Arm 1 will receive a single dose of PH FDC SC administered by a healthcare professional using a handheld syringe with hypodermic needle.

Subjects in Arm 2 will receive a single dose of PH FDC SC administered by a healthcare professional using the OBDS.

STATISTICAL METHODS

The analysis of primary and secondary endpoints will be performed after all subjects have completed the Day 63 assessments. A follow-up analysis for safety will be performed once all subjects have completed the 7-month follow-up visit.

DETERMINATION OF SAMPLE SIZE

Approximately 144 subjects will be enrolled, taking into account an assumed drop-out rate of 10%. A total of 130 healthy subjects with fully evaluable pharmacokinetic profiles are required to demonstrate comparability of area under the time-concentration curve from the start of dosing to 63 days ($AUC_{0-62days}$) and maximum concentration (C_{max}) values between the handheld syringe injection administration (reference) and the OBDS (test) with 80% power at 5% significance level, assuming a between-subject coefficient of variation (CV) of 40% and 'test' to 'reference' ratio of 0.95. Standard bioequivalence ranges of 0.8 and 1.25 are used to demonstrate comparability of $AUC_{0-62days}$ and C_{max} values for pertuzumab and trastuzumab administered as PH FDC SC, either by the OBDS or by handheld syringe. Subjects that have non-evaluable PK data may be replaced at the discretion of the Sponsor.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	doxorubicin plus cyclophosphamide
ADA	anti-drug antibody
ARDS	Acute Respiratory Distress Syndrome
ARR	administration related reaction
$AUC_{0-62days}$	area under the time–concentration curve from the start of dosing to 63 days
$AUC_{0-\infty}$	area under the time–concentration curve from the start of dosing extrapolated to infinity
BMI	body mass index
BP	blood pressure
C_{Day21}	serum concentration on Day 22
C_{Day62}	serum concentration on Day 63
CHF	congestive heart failure
ClinRO	clinician reported outcome
CL/F	apparent drug clearance
C_{max}	maximum serum concentration
C_{trough}	trough serum concentration
CV	coefficient of variation
ddAC	dose-dense doxorubicin plus cyclophosphamide
EBC	early breast cancer
EC	Ethics Committee
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
GMR	geometric mean ratio
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCP	health care personnel
HR	heart rate
ICH	International Council for Harmonisation
ILD	interstitial lung disease
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAb	monoclonal antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OBDS	on-body delivery system
pCR	pathologic complete response
PH FDC SC	fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration
PK	pharmacokinetic
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT interval
QTcF	QT interval corrected through use of Fridericia's formula
rHuPH20	recombinant human PH20 hyaluronidase
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
$t_{1/2}$	terminal elimination half-life
t_{max}	observed time to maximum concentration
ULN	upper limit of normal
VAS	visual analog scale
Vd/F	apparent volume of distribution

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE BREAST CANCER

Breast cancer is the second most common invasive malignancy and the most common form of cancer in women (Bray et al. 2018). Approximately 20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2). This is usually the result of amplification of the gene encoding HER2, which is found on chromosome 17 (Wolff et al. 2007). HER2 belongs to the family of human epidermal growth factor receptors (HER) (which also includes HER1 [also known as epidermal growth factor receptor (EGFR)], HER3, and HER4) that mediate normal cell growth, survival, and differentiation (Bublil and Yarden 2007).

These receptors may be activated by external ligands and by dimerization with other HER family members. HER2 activity is mediated by homodimerization (with other HER2 receptors) or heterodimerization (with other HER family receptors), leading to activation of multiple intracellular signaling pathways, including the phosphoinositide 3-kinase/protein kinase B and RAS/Raf/mitogen-activated protein kinase pathways (Olayioye et al. 2000). In the case of HER2, activation may also be achieved by proteolytic cleavage of the extracellular domain (shedding) to leave an activated truncated internal domain. HER2 is also known to play a role in the normal development of myocardial tissue and in the repair of damaged myocardium (Sawyer et al. 2002; Timolati et al. 2006; Zhao et al. 2006).

Primary breast cancers with HER2 amplification and overexpression (hereafter referred to as HER2+ breast cancer) were found to have a poor prognosis, including a greater risk of relapse and shortened survival, compared with tumors without this abnormality (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001). The advent and clinical incorporation of the monoclonal antibody (MAb) trastuzumab (Herceptin®), capable of blocking HER2 oncogenic signaling and thereby effectively killing HER2+ cancer cells, has markedly improved the prognosis of patients with HER2+ breast cancer (Hudis 2007). Subsequently, pertuzumab (Perjeta®), a second MAb that binds to a distinct epitope of HER2 than Herceptin, was shown to provide a complementary mechanism for disrupting HER2 signaling and, thereby, enhanced anti-tumor activity (Eiger et al. 2019). Compared to single HER2 blockade, dual HER2 blockade with Perjeta and Herceptin has been *shown* to improve various clinically relevant outcomes, such as pathological complete response rates, invasive disease-free survival and overall survival (Gianni et al. 2012; Piccart et al. 2021, Swain et al. 2020). In this sense, the combination of Perjeta with Herceptin and chemotherapy has become standard of care for treating HER2+ early and metastatic breast cancer (Denduluri et al. 2018; Giodarno et al. 2018; Cardoso et al. 2019 and 2020). Currently, anti-HER2 therapies with distinct mechanisms of action have become available for the treatment of early-stage (neratinib and ado-trastuzumab emtansine) and metastatic (lapatinib, neratinib, tucatinib, pyrotinib, ado-trastuzumab emtansine, trastuzumab-deruxtecan, and margetuximab) HER2+

breast cancer patients (Cameron et al. 2008; Diéras et al. 2017; von Minckwitz et al. 2019; Modi et al. 2020; Saura et al. 2020; Murthy et al. 2020; Chan et al. 2021; Rugo et al. 2021; Xu et al. 2021).

Herceptin has been developed in a formulation for subcutaneous (SC) administration that can be delivered in under 5 minutes versus the 30–90 minute infusions required for administration of the IV formulation. Herceptin SC has been shown to be preferred over Herceptin IV by HER2+ early breast cancer (EBC) patients in a randomized, cross-over study (Pivot et al. 2013). Besides, Herceptin SC can not only save patient's chair time and active healthcare professional's time per session compared to Herceptin IV, it also holds costs-saving potentials in various healthcare settings (Lopez-Vivanco et al. 2017; Tjalma et al. 2018; O'Brien et al. 2019). Herceptin SC is currently approved in the United States, European Union and more than 100 countries for use in the (neo)adjuvant and metastatic HER2+ breast cancer settings. Data from a Phase IIIb, single-arm safety study of combined treatment with Herceptin SC and Perjeta have shown a safety profile consistent with combined treatment with Herceptin and Perjeta given intravenously (Kümmel et al. 2020).

Roche has developed a new product combining pertuzumab and trastuzumab in one fixed-dose combination for SC injection (hereafter referred to as "PH FDC SC"). The PH FDC SC is a ready-to-use formulation of pertuzumab and trastuzumab co-formulated in a single vial for SC injection use with recombinant human PH20 hyaluronidase (rHuPH20), a permeation enhancer developed to improve dispersion of large volumes of drugs when administered subcutaneously.

The PH FDC SC administration has been proven equivalent to IV Herceptin and Perjeta from a pharmacokinetic (PK), efficacy, and safety perspective (Tan et al. 2020). PH FDC SC can be administered in 5-8 minutes versus hours and is preferred by most patients, as compared to IV administration of Herceptin and Perjeta (O'Shaughnessy et al. 2020). Currently, PH FDC SC (PHESGO®) is approved in the United States and can be administered at home by an HCP (FDA Press release 2020), in the European Union and several other countries in the world. The indications cover the use in patients with early-stage and metastatic HER2-positive breast cancer.

Roche is currently developing an on-body delivery system (OBDS) named SmartDose® Gen II for self- or lay caregiver-SC administration of PH FDC SC to enable a flexible care setting in which healthcare providers and patients can select the place of drug administration according to individual preferences and capabilities worldwide. Improved convenience is particularly important when patients are treated for prolonged periods of time.

In this study, healthy male subjects between 18–45 years will be randomly allocated to receive PH FDC SC administered via an OBDS or via a handheld syringe with

hypodermic needle in order to investigate the comparability of PK parameter values and safety between both administration methods.

1.2 BACKGROUND ON STUDY MEDICATION

1.2.1 Study Drug Nomenclature

Pertuzumab and trastuzumab are both monoclonal antibodies developed by Roche. Throughout the protocol, their international non-proprietary names (pertuzumab, trastuzumab) are used when describing their PK and other properties and when referring to PH FDC SC.

To distinguish the source of trastuzumab that is an investigational medicinal product (IMP) in referenced Roche-sponsored clinical studies, the trade name “Herceptin” is used throughout the protocol when referring to the commercially available trastuzumab drug product. For consistency, the trade name “Perjeta” is also used when referring to the commercially available pertuzumab drug product.

1.2.2 Background on Pertuzumab and Trastuzumab Fixed-dose Combination for Subcutaneous Administration (PH FDC SC)

The PH FDC SC represents a combination of both pertuzumab and trastuzumab in a fixed-dose combination.

A Phase III, randomized, multicenter, open-label, two-arm study (FeDeriCa) compared the PK, efficacy, and safety of PH FDC SC versus Perjeta + Herceptin IV (P + H IV) as neoadjuvant treatment with chemotherapy for EBC in 500 patients with Stage II–III HER2+ breast cancer (Study WO40324; Tan et al. 2020). The primary objective was non-inferiority of the pre-dose Cycle 8 pertuzumab serum trough concentration (C_{trough}) within the PH FDC SC versus pertuzumab IV (non-inferiority margin for the lower bound of the 90% CI of the geometric mean ratio [GMR]: ≥ 0.8). Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} within PH FDC SC was demonstrated as non-inferior compared to Perjeta in the Perjeta + Herceptin IV arm. The GMR of Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough}, SC/C_{trough}, IV values was 1.22 (90% CI: 1.14–1.31). The observed lower limit of the two-sided 90% CI of 1.14 was above the prespecified non-inferiority margin of 0.8. The Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} with PH FDC SC, a key secondary PK endpoint of Study WO40324, was also demonstrated to be non-inferior compared to that with Herceptin IV (P + H IV arm).

Total pathologic complete response (pCR) rates in the intent-to-treat population was 59.7% (95% CI, 53.3-65.8) vs 59.5% (95% CI, 53.2-65.6) for the SC and IV arms, respectively. Incidences of the most common adverse events (occurring in $\geq$ 30% of patients) in the SC and IV arms, respectively, included alopecia (77% and 70.2%), nausea (58.9% and 60.3%), diarrhea (58.5% and 55.2%), anemia (33.9% and 40.9%), and asthenia (28.2% and 30.2%). The incidence of primary cardiac events (New York Heart Association [NYHA] Class III/IV heart failure [HF] and cardiac death) was low (0%

in the IV arm and 0.8% in the SC arm), as well as the incidence of secondary cardiac events (confirmed left ventricular ejection fraction [LVEF] decrease of ≥10 points from baseline and below 50%) (0.8% in the IV arm vs. 0.4% in the SC arm). The incidence of diarrhea was comparable between arms (55.2% in the IV arm vs. 58.5% in the SC arm), with a majority of low-grade events. The incidence of anaphylaxis and hypersensitivity was low in both arms as well (2% vs. 1.6%, respectively), and most cases were low grade. Except for Grade 1–2 adverse events associated with subcutaneous route of administration (local injection site reactions), the safety was comparable between PH FDC SC arm and Perjeta + Herceptin IV arm, and no unexpected safety signals emerged.

In the Phase II, randomized, multicenter international, open-label, cross-over PHranceSCa study (Study MO40628), 160 patients with HER2+ EBC previously submitted to neoadjuvant systemic therapy and breast/axillary surgery were randomized 1:1 to receive adjuvant Perjeta and Herceptin IV for 3 cycles, followed by 3 cycles of PH FDC SC or to receive adjuvant PH FDC SC for 3 cycles followed by 3 cycles of Perjeta + Herceptin IV, in order to assess patients' preferences and satisfaction (O'Shaughnessy et al. 2020). PH FDC SC administration was preferred by 85.0% patients, while Perjeta + Herceptin IV administration was preferred by only 13.8%. Two patients had no preference (1.3%).

The most commonly reported reasons for PH FDC SC administration preference were "requires less time in the clinic" and "feels more comfortable during administration." The majority of patients (92.6%) indicated a "very strong" or "fairly strong" preference with PH FDC SC administration, compared to only 63.6% of patients with Perjeta + Herceptin IV administration. Patient preference results were supported by patient satisfaction results. The vast majority of patients (88.1%) were "very satisfied" or "satisfied" with the PH FDC SC administration, while 67.5% were "very satisfied" or "satisfied" with the Perjeta + Herceptin IV administration. When asked specific questions about their experience with both PH FDC SC and Perjeta + Herceptin IV, patients more often cited PH FDC SC administration as being the less restrictive route of administration and as allowing more time for other activities. The choice of SC administration during the treatment continuation period was consistent with patient preference, with 86.9% of patients choosing to continue their treatment with PH FDC SC administration during the treatment continuation period.

Health care personnel (HCP) indicated time savings and the need for less resource use when using PH FDC SC. The median preparation time for PH FDC SC administration was 5 minutes and the median administration time ranged from 7–8 minutes (compared with median Perjeta + Herceptin IV preparation times of 15–20 minutes and 60–150 minute administration times). The median overall time the patient spent in the treatment room for PH FDC SC treatment ranged from 33–50 minutes (compared with 130–300 minutes for Perjeta + Herceptin IV treatment). PH FDC SC was well tolerated

with a safety profile consistent with the Perjeta + Herceptin IV formulation and no new safety signals.

PH FDC SC (PHESGO) is approved in the United States, European Union and other countries for the treatment of HER-2 positive breast cancer in adults. For further details of nonclinical and clinical studies, please refer to the PH FDC SC Investigator's Brochure, and the Perjeta and Herceptin Investigator's Brochures.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

The PH FDC SC administration by lay caregivers or self-administration by patients at home using an OBDS could increase convenience for patients while simultaneously decreasing health-care costs associated with several clinics and/or hospitals visits. Lay caregiver or self-administration at home with the OBDS holds the potential to allow patients more time to engage in other activities and increase the compliance of those who live far from a hospital or clinic, or experience difficulty travelling (Bittner et al. 2018; Viola et al. 2018).

In order to establish such modalities as laid out above, bioequivalence between an administration with the OBDS and the currently approved handheld injection with a syringe should be shown. The aim of the present study is to demonstrate that the PK and safety profiles of a single dose of PH FDC SC in healthy male subjects are comparable between administration with the OBDS versus administration with handheld syringe with hypodermic needle.

This is the first clinical study in which PH FDC SC will be administered using the OBDS, and it is intended to support the bridging of PH FDC SC handheld syringe with hypodermic needle administration to OBDS administration. In the context of the present study, all PH FDC SC injections, either via OBDS or via handheld syringe will be administered by a healthcare professional in a healthcare setting.

This is a PK study in healthy male subjects 18–45 years of age designed to investigate the comparability of PK parameter values derived after two different ways of administering PH FDC SC, using either the OBDS or handheld syringe with hypodermic needle.

1.3.2 Benefit-Risk Assessment

As described in Section 1.1, Perjeta plus Herceptin-based therapies for HER2-positive breast cancer patients have been shown to improve various clinically relevant outcomes, both in the early and in the metastatic setting. PH FDC SC, a combination of both pertuzumab and trastuzumab in a fixed-dose combination, has been shown equivalent in terms of PK, efficacy, and safety compared to both MAbs administered intravenously, except for low-grade adverse events associated with the subcutaneous route of administration (local injection site reactions), as described in Section 1.2.2. The

advantages of PH FDC SC compared to Perjeta and Herceptin IV are the higher rates of patient preference and satisfaction, as well as timesaving and the need of less resources as indicated by HCP. Transitioning PH FDC SC administration by handheld syringe with hypodermic needle to the OBDS is not expected to change the benefit-risk profile of PH FDC SC. Moreover, as the OBDS provides a "hands-free" PH FDC SC administration modality, it has the potential to improve the workflow and alleviate burden to HCP, as well as to pave the way for home-based administration.

Several studies have demonstrated benefits associated with home administration of SC biotherapeutics, namely its general preference by patients and reduced resource use for drug delivery (Gardulf et al. 2006; Beaute et al. 2010). Given these benefits, efforts are ongoing to assess the feasibility of administering MAbs in the home environment. Previous experiences with the bridging of SC MAbs administration by healthcare professional to patient self-administration at home with the aid of ready-to-use devices has been successful (Bittner et al. 2018).

The initial experience with Herceptin SC home administration by healthcare professionals has been promising, with safety consistent with that in a hospital setting (Cocquyt et al. 2017). Multiple programs and pilot studies in European countries show that Herceptin SC can be effectively administered in the patient's home (Denys et al. 2020; ten Tije et al. 2020).

The benefits of SC home administration become particularly relevant when external factors like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic disrupt and limit usual clinic work flow and increase the risk of exposure to life-threatening clinical conditions to patients with cancer. From the beginning of the SARS-CoV-2 epidemic in China in late 2019 (Zhu et al. 2020) to its rapid worldwide spread, much academic, pharma, and government-driven effort has been directed towards new solutions for oncologic care, focusing especially in decreasing patients' exposure to and risk of acquiring SARS-CoV-2 infection. It has been demonstrated that cancer patients are at higher risk of complications and have higher fatality rates than the general population when infected with SARS-CoV-2 (de Azambuja et al. 2020; Garassino et al. 2020). Perjeta and Herceptin are normally given for 1 year (18 cycles) for patients with HER2+EBC or longer to patients with metastatic disease, ultimately leading to frequent visits to clinics and/or hospitals of a population at a higher risk of complications by SARS-CoV-2 infection. In this sense, PH FDC SC administered at home with the OBDS can potentially reduce high-risk patients' exposure to SARS-CoV-2 while maintaining continuity of treatment, and simultaneously enable a refocusing of resources and HCP to fight the SARS-CoV-2 pandemic. An expanded access, single-arm, multicenter study is currently ongoing in the United States, where PH FDC SC home administration by HCP is already approved by the FDA, to assess the safety of PH FDC SC when administered at home by a home health nursing provider to patients with HER2+EBC (Study AL42478).

As summarized above, while the benefit-risk profile of switching PH FDC SC administration with a handheld syringe with hypodermic needle to the OBDS is expected to be unchanged, PH FDC SC administration with the OBDS has the potential to improve the workflow and alleviate burden to HCP, as well as to enable home-based administration. This has the potential to increase patient's convenience, decrease the exposure of an at-risk population to SARS-CoV-2 infection, and enable a refocusing of resources and HCP. Altogether, the benefit-risk assessment for administration of PH FDC SC with the OBDS is deemed positive.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics and safety of the PH FDC SC administered by the OBDS compared to hypodermic needle and syringe in healthy male subjects.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PRIMARY OBJECTIVE

The objective for this study is below.

To demonstrate comparability of single-dose area under the time–concentration curve from the start of dosing to 63 days (AUC_{0-62}) and maximum serum concentration (C_{max}) for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle, on the basis of the following co-primary endpoints:

- Serum pertuzumab AUC_{0-62} and C_{max}
- Serum trastuzumab AUC_{0-62} and C_{max}

2.2 SECONDARY OBJECTIVES

2.2.1 Pharmacokinetic Objectives

The secondary PK objectives for this study are below.

To demonstrate the comparability of observed serum concentration on Day 22 (C_{Day21}) values for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle, on the basis of the following end points:

- Serum pertuzumab C_{Day21}
- Serum trastuzumab C_{Day21}

To demonstrate the comparability of observed serum concentration on Day 63 (C_{Day62}) values for pertuzumab and trastuzumab within PH FDC SC, administered either by the

OBDS or by a handheld syringe with hypodermic needle, on the basis of the following end points:

- Serum pertuzumab C_{Day62}
- Serum trastuzumab C_{Day62}

To further characterize additional PK parameters for pertuzumab and trastuzumab within PH FDC SC, administered either by the OBDS or by a handheld syringe with hypodermic needle, on the basis of the following end points:

- Area under the time–concentration curve from the start of dosing extrapolated to infinity ($AUC_{0-\infty}$)
- Observed time to maximum concentration (t_{max})
- Terminal elimination half-life ($t_{1/2}$)
- Apparent drug clearance (CL/F)
- Apparent volume of distribution (Vd/F)

2.2.2 Safety Objectives

The safety objectives for this study are below.

To demonstrate comparable safety and tolerability of PH FDC SC administered by either the OBDS or by a handheld syringe with hypodermic needle, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE)
- Change from baseline in vital signs, LVEF, and ECG parameters
- Change from baseline in clinical laboratory test results

To demonstrate the safety of the OBDS, on the basis of the following end points:

- Pain at the injection site assessed by the subject using the 100 mm Visual Analog Scale (VAS)
- Skin irritation and sensitization reactions at the site of injection assessed by the study staff using the device monitoring questionnaire in the electronic Case Report Form (eCRF)

2.2.3 Device Monitoring Objectives

The device monitoring objectives are to demonstrate the performance of the OBDS on the basis of the following end points:

- Comfort of wearing the device, as reported by the subject using the device monitoring questionnaire
- Details of performance and ease of use of the OBDS reported by site staff, using the device monitoring questionnaire in the eCRF (see Section 4.5.9)

2.3 EXPLORATORY OBJECTIVES

2.3.1 Immunogenicity Objectives

The exploratory immunogenicity objectives for this study are below.

To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20 within the PH FDC SC, administered using an OBDS compared to a hand-held syringe with hypodermic needle, on the basis of the following endpoints:

- Incidence of pertuzumab anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline
- Incidence of trastuzumab ADAs during the study relative to the prevalence of ADAs at baseline
- Incidence of rHuPH20 ADAs during the study relative to the prevalence of ADAs at baseline

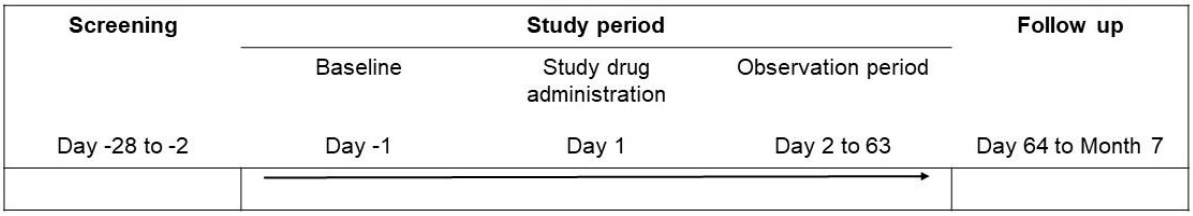
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of the Study Design

This is a randomized, open-label, 2-arm, parallel-group, single-dose, multi-center study in healthy male subjects to investigate the comparability of PK of pertuzumab and trastuzumab within the PH FDC SC administered using the proprietary OBDS or a handheld syringe with hypodermic needle. Figure 1, presents an overview of the study design. The study will be conducted at clinical research facilities in New Zealand and Australia.

Figure 1 Study Schema



Approximately 144 male subjects will be randomized to one of two dosing arms in a 1:1 ratio to receive a single dose of PH FDC SC (600 mg pertuzumab/600 mg trastuzumab) administered by a healthcare professional subcutaneously into the anterior thigh using either the OBDS or a handheld syringe with hypodermic needle. The randomization will be stratified by weight (≤ 75 kg, > 75 kg) at Day -1.

Arm 1: PH FDC SC administered using a handheld syringe with hypodermic needle.

Arm 2: PH FDC SC administered using the OBDS.

During the study period, subjects will be admitted to the clinical research unit on Day −1 and the study drug will be given on the morning of Day 1. The subjects will be discharged after the assessments are performed on Day 2.

Subjects will be followed according to the Schedule of Activities from Day −1 (Appendix 1). The total duration of the study for each subject will be a maximum of 35 weeks:

- Screening: Up to 4 weeks
- Study period: Day −1 to Day 63, including in-clinic period from Day −1 to Day 2
- Safety Follow-up: Day 64 to Month 7 (~35 weeks)

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last subject, last visit occurs. This is expected to occur 7 months after the last subject is enrolled (i.e., when the last subject has completed the safety follow-up visit at 7 months after administration of study drug).

The length of study will be a maximum of 35 weeks per subject, from screening to follow-up (4 weeks screening, plus 7 months [~31 weeks] follow-up after dose). The total length of the study from screening of the first subject to the end of the study is expected to be approximately 11 months.

3.3 RATIONALE FOR STUDY DESIGN

Subcutaneous administration of PH FDC SC by ODBS is being investigated to support home-administration and possible self-administration by the patient. The aim of this OBDS PK qualification study is to demonstrate that the PK and safety profiles of a single dose of PH FDC SC in healthy subjects are comparable between administration by the OBDS versus administration by handheld syringe with hypodermic needle.

This is the first clinical study in which PH FDC SC will be administered using the OBDS. It is a PK study in healthy male subjects 18–45 years of age designed to investigate the comparability of PK parameter values derived following two different ways of administering PH FDC SC, using either the OBDS or a handheld syringe with hypodermic needle.

3.4 RATIONALE FOR PH FDC SC DOSE AND SCHEDULE

The dose selected to be used in this study is consistent with the approved maintenance dose of PH FDC SC (600 mg pertuzumab/600 mg trastuzumab/20,000 units rHuPH20) investigated in Study WO40324 that confirmed non-inferior Cycle 7 C_{trough} and comparable efficacy/safety of pertuzumab/trastuzumab SC versus pertuzumab/trastuzumab IV in patients with EBC (Tan et al. 2019).

Whereas the vial presentations of PH FDC SC occur as two different strengths, dedicated to induction and to maintenance therapy respectively, the OBDS will be

evaluated to administer the maintenance dose only. The loading dose will have no OBDS alternative and will remain available only under the vial presentation.

3.5 RATIONALE FOR SUBJECT POPULATION

According to EMA Guidelines (EMA guideline on investigation of bioequivalence), in order to reduce variability not related to differences between investigational products, bioequivalence studies should normally be performed in healthy subjects, unless the drug carries safety concerns that make this unethical. Healthy female subjects of childbearing potential were excluded from this study as they would be exposed unnecessarily to potentially teratogenic drugs. This approach is also supported by Food and Drug Administration (FDA) guidance (FDA Guidance for industry Bioavailability and Bioequivalence Studies). Additionally, as anti-pertuzumab and anti-trastuzumab antibodies might be developed following injection, the decision was made to perform the study in healthy male subjects as a precaution, to avoid pre-exposing female subjects to pertuzumab and trastuzumab. A similar approach is common and was successfully used in Study BO30185 (dose-finding, Phase I trial to identify the dose of pertuzumab for SC administration in PH FDC SC), where healthy male subjects were also recruited.

4. MATERIALS AND METHODS

4.1 SUBJECTS

Approximately 144 healthy male subjects, aged 18–45 years will be enrolled in this study.

4.1.1 Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Signed Informed Consent Form
- Healthy male subjects age 18–45 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 7 months after the dose of PH FDC SC to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., according to female partner calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- A body mass index (BMI) between 18 and 32 kg/m^2, inclusive
- Intact normal skin without potentially obscuring tattoos, pigmentation, or lesions in the area for intended injection on the thighs
- Baseline LVEF $\geq$ 55% measured by echocardiogram (ECHO)
- No history of hypersensitivity or confirmed, clinically significant and clinically relevant allergic reactions, either spontaneously or following any drug administration
- No history of any clinically significant and clinically relevant cardiac condition
- No history of previous anticancer treatments including pertuzumab, trastuzumab, anthracyclines, or any cardiotoxic drugs
- No apparent family history of clinically significant and clinically relevant hypersensitivity, allergy, and severe cardiac diseases
- No contraindications from detailed medical and surgical history and physical examinations
- No previous enrollment in this study protocol and no concurrent enrollment in any other study protocol

4.1.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

- Positive urine test for drugs of abuse as per local standard (for alcohol abuse, positive breath test is also acceptable)
- Positive test result for hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV 1 or 2, showing:

  History of exposure to HBV, HCV, or HIV

  or

  Active viral hepatitis infection (HBV or HCV) or HIV infection
- Systolic blood pressure (BP) $\geq$ 140 mmHg or $<$ 90 mmHg, or diastolic BP $>$ 90 mmHg or $<$ 50 mmHg
- Use of prohibited medications, including non-prescription medications, nutraceuticals, nutritional supplements, or any herbal remedies taken within 10 days or 5 times the elimination half-life (whichever is longer) prior to randomization into the study
- Concomitant subcutaneous, intravenous, or any parenteral drugs within 90 days prior to screening
- Participation in an investigational drug or device study within 90 days or five times the elimination half-life (whichever is longer) prior to screening
- Donation of blood over 500 mL within 3 months prior to enrollment
- Known severe hypersensitivity to plaster, medical adhesive tapes, or bandages
- Known allergy to murine proteins, hyaluronidase, bee, or vespid venom, or any other ingredient in the formulation of rHuPH20 (Hylenex® recombinant

[hyaluronidase human injection]) or any other ingredients and excipients in the formulation of PH FDC SC

- Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, CBC, chemistry panel, and urinalysis)
- Clinically relevant ECG abnormalities on screening or Day -1 ECG:
  - Corrected QT interval (QTc) (QT interval corrected through use of Fridericia's formula [QTcF] $>$ 450 msec)
  - Notable resting bradycardia (HR $<$ 40 bpm)
  - Notable resting tachycardia (HR $>$ 100 bpm)
  - Difference between highest and lowest durations of any baseline QTc at a specific time point $>$ 30 msec
  - Measurement of QT interval imprecise (i.e., flat T waves, arrhythmias, etc.)
  - Evidence of atrial fibrillation, atrial flutter, right or left bundle branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
  - Any other significant abnormality
- History of any cardiac condition
- Lower extremity edema or pathology (e.g., cellulitis, lymphatic disorder or prior surgery, pre-existing pain syndrome, previous lymph node dissection etc.) that could interfere with any protocol-specified outcome assessment
- Any history of clinically significant and clinically relevant allergies, oncologic, psychiatric, gastrointestinal, renal, hepatic, cardiovascular or pulmonary disease
- Concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in this study
- Any clinically relevant history of systemic disease (e.g., malignancy, diabetes mellitus, gastrointestinal, renal, hepatic, cardiovascular, rheumatological, or pulmonary disease)
- History of breast cancer or treatment for breast cancer
- Current chronic daily treatment (continuous for $>$ 3 months) with corticosteroids (dose $\geq$ 10 mg/day methylprednisolone), excluding inhaled corticosteroids
- Receipt of IV antibiotics for infection within 7 days prior to enrollment into the study

4.2 METHOD OF TREATMENT ASSIGNMENT

4.2.1 Treatment Assignment

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a subject, the study site will obtain the subject's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Male subjects will be randomly assigned to one of two drug administration arms to receive a single dose of PH FDC SC administered either using the OBDS or handheld syringe and needle. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- Weight ($\leq$75 kg, $>$75 kg) at Day $-$1

Eligible subjects will report to the unit on Day $-$1 for baseline assessments and will stay overnight until Day 2. Randomization can occur either on Day $-$1 or on Day 1 pre-dose.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for this study is PH FDC SC
(600 mg pertuzumab/600 mg trastuzumab/20,000U rHuPH20).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 PH FDC SC

The PH FDC SC (maintenance dose: RO7198574/F04-01) will be supplied by the Sponsor as a sterile, colorless to slightly brownish solution for injection containing histidine, hydrochloric acid, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2000 U/mL).

For administration via handheld syringe and needle, PH FDC SC will be supplied in 10 mL solution in a 15 mL vial.

For administration via OBDS, the PH FDC SC will be supplied in a prefilled cartridge with a 10.25 mL drug volume.

Both the vial and prefilled cartridge contain the same formulation of 600 mg of pertuzumab (RO4368451) and 600mg of trastuzumab (RO0452317). For information on the PH FDC SC formulation, see the PH FDC SC Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1. Study drug will be administered on the morning of Day 1. The OBDS (plus adhesive paper) and the handheld syringe with needle (plus cover) will be weighed before injection (loaded with prefilled cartridge and with drug drawn, respectively) and after the injection using a precision balance that measures up to around 100 g with at least two decimal places.

Refer to the pharmacy manual for detailed instructions on drug preparation. Refer to the pharmacy manual and Appendix 4 and Appendix 5 for details on drug administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error,

along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for discontinuation for subjects who experience specific adverse events are provided in Section 5.1.2.

4.3.2.1 Administration of PH FDC SC by handheld syringe and needle

A single 10-mL dose of PH FDC SC (PHESGO) will be administered as a SC injection using a handheld manual syringe, into the anterior thigh midway between the anterior iliac crest and the cephalad border of the patella, while the subject is in a semi-supine position according to the steps in Appendix 4. The goal of the placement angle and needle depth is to achieve uniform placement into every subject's SC tissue. To promote uniformity of needle placement across the study subjects, wherever possible, one of three designated, medically trained healthcare professionals at each site should place the needle in every subject, and needle placement should be uniform from subject to subject.

The dose will be injected over approximately 5 minutes, at a rate of no more than 2 mL/min. The injection rate should be adjusted to a rate that is comfortable for the subject. If there is a request by the subject to interrupt the injection due to discomfort, the pressure on the syringe should initially be eased to alleviate the pain. If the pain is not alleviated, the injection should be stopped, and the subject should be asked when they are comfortable to resume the injection. The start and end times of the injection and overall injection time (minutes/seconds) should be recorded.

The injection should be slowed or interrupted if the subject experiences injection-related symptoms.

The entire SC injection must be given in one site. Splitting the volume into two syringes or injecting at two different sites is not permitted.

After the injection, subjects will be observed for 30 minutes from the end of the injection for injection-related symptoms.

The syringe (including needle and cover) will be weighed prior to injection (after the correct amount of medication has been drawn) and after injection using a balance with the precision specified in Section 4.3.2. The weights must be recorded on the eCRF, along with the temperature of the room, and the actual amount of drug administered will be calculated.

4.3.2.2 Administration of PH FDC SC by OBDS

A single 10-mL dose of PH FDC SC (PHESGO) will be administered by OBDS as a SC injection, into the anterior thigh midway between the anterior iliac crest and the cephalad border of the patella, while the subject is sitting down (semi-supine), according to the steps in Appendix 5. To promote uniformity of OBDS placement across the study

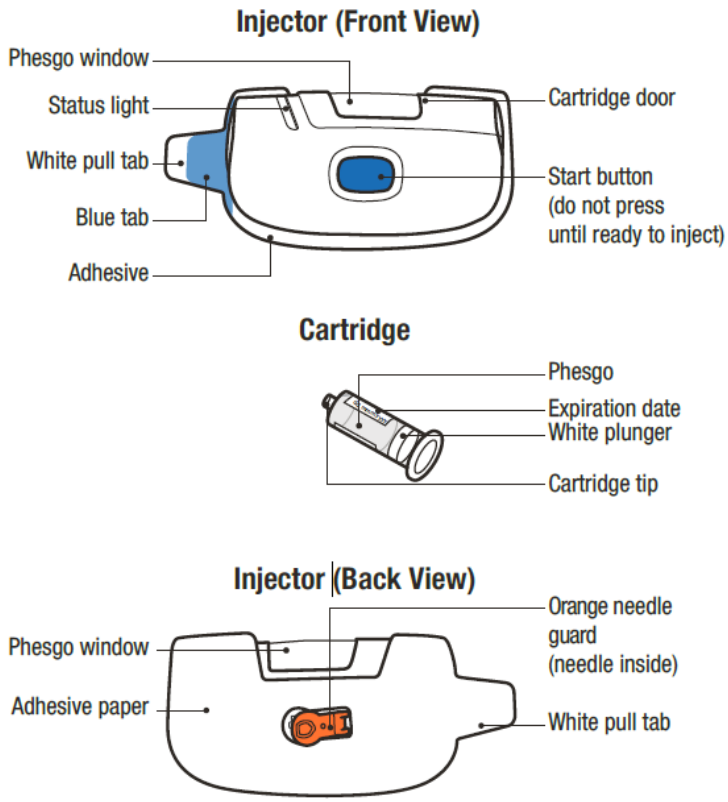
subjects and of device monitoring, wherever possible, one of three designated, medically trained healthcare professionals at each site should perform the OBDS injection for every subject, and placement should be uniform from subject to subject.

The OBDS is supplied as a kit containing one device (injector) and one cartridge pre-filled with PH FDC SC (Figure 2).

When taken out of the refrigerator (2–8°C), the OBDS/cartridge kit needs to be kept at room temperature for approximately 45 minutes to allow the device and drug temperature to equilibrate.

Following removal of the OBDS from the packaging, the cartridge door of the device is opened by the user, which powers the device. The device is now active and must be used within 30 minutes. The user inserts the prefilled cartridge, closes the door, removes the adhesive paper, and attaches the loaded OBDS to the skin. Pressing the start button automatically inserts the needle into the SC tissue and automatically initiates drug administration. The needle is protected within the device by an orange-colored needle guard and can only be deployed when the prefilled cartridge is in place, the cartridge door is closed, the device is adhered to the subject, and the start button has been pressed. Dose administration is started automatically and stops automatically upon completion of the drug delivery. Both visual (status light) and auditory notifications provide feedback on the progress of drug administration. In the event of a drug delivery error, visual and auditory notification will prompt the user (refer to the pharmacy manual for details of the different visual and auditory notifications).

Figure 2 OBDS with PH FDC SC cartridge



OBDS = on-body delivery system; PH FDC SC = fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration.

The overall administration time by OBDS, from activation by pressing the start button, to completion of the injection is approximately 5–10 minutes. The start and end times of the injection and overall injection time (minutes/seconds) should be recorded.

After the injection, subjects will be observed for 30 minutes from the end of the injection for injection-related symptoms.

The OBDS (including adhesive paper) will be weighed prior to injection (after the prefilled cartridge has been inserted) and after injection (including the cartridge and adhesive paper) using a balance with the precision specified in Section 4.3.2. The weights must be recorded on the eCRF, along with the temperature of the room, and the actual amount of drug administered will be calculated.

Device monitoring information will be recorded in the eCRF as shown in Section 4.5.9, Appendix 1, and Appendix 2.

Any device-related issues and remarks will be reported in the eCRF by the investigational staff members and as described in Section 5.4.4.

All devices used in the study will be returned to the Sponsor. Refer to the pharmacy manual for instructions on the return of the devices.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each subject, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that subjects are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only subjects enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

The IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. All devices will be returned to the Sponsor (refer to the pharmacy manual for instructions).

The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the PH FDC SC Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.4 CONCOMITANT THERAPY, SPECIAL DIETARY REQUIREMENTS AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from 30 days prior to initiation of study drug to the 7 month follow up visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. As a general rule, no concomitant medication will be permitted, with the exception of medications to treat adverse events, unless the rationale for exception is discussed and clearly documented between the investigator and Roche.

No prescription medicines, over-the-counter medicines, or herbal remedies are allowed for at least 10 days before study drug dose, through the end of the study unless agreed by the study doctor and Roche.

Meals will be similar in composition and time of administration across both study arms during the in-clinic period from Day −1 to Day 2. The consumption of foods and beverages containing caffeine (e.g., tea, coffee, chocolate, and soft drinks) and alcohol will not be permitted from Day −1 to Day 2. The use of tobacco is not permitted during the in-clinic portion of the study.

Light ambulatory activities will be permitted, with the level of activities kept as similar as possible on all days in the clinical research unit.

Subjects should/must refrain from vigorous activity that might affect absorption of PH FDC SC from the injection site, especially activities involving the thighs, from Day 1 to Day 10.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each subject.

The study will consist of the following:

- Screening: Day −28 to Day −2
- Study period: Day −1 to Day 63, including in-clinic period from Day −1 to Day 2
- Safety Follow Up: Day 64 to 7 months.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled subjects and for subjects who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria before enrollment. Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for 1 rescreening opportunity (for a total of 2 screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. Assessments that meet the eligibility criteria do not need to be repeated if they still fall within the applicable time windows for screening and baseline. The investigator will maintain *detailed* record of all subjects screened and, to *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the subject within 30 days prior to dosing will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Weight and height will also be collected. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At other visits, as indicated in the schedule of activities, abbreviated physical examination will consist of checking the normality or abnormality of the following body systems: general appearance, weight, and cardiorespiratory examination. Any abnormality will be recorded in the subject notes and on the eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure after the subject has remained in a semi-supine position for at least 5 minutes. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST
- HIV serology: HIV-1/2 antibody
- HBV serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and total hepatitis B core antibody (HBcAb), for all subjects; HBV DNA for subjects with negative HBsAg and HBcAb tests and a positive total HBcAb test
- HCV serology: HCV antibody for all subjects; HCV RNA for subjects with a positive HCV antibody test

  If a subject has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the subject has an HCV infection.
- Urinalysis, including dipstick (pH, glucose, protein, blood). If there is a clinically significant positive blood and/or protein result, additional microscopic examination will be performed (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Alcohol: Breath or urine
- Drugs of abuse: Urine test according to local standards including cannabinoids, amphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates

Additional blood or urine samples may be taken at the discretion of the investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor subject safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for a positive urine or blood test for drugs of abuse (e.g., previous occasional intake of a medication or food containing for example codeine, benzodiazepines, or opiates) the test could be repeated to confirm washout.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF.

The following samples will be sent to one or several central laboratories, the Sponsor, or a designee for analysis:

- Serum samples for PK analysis

- Plasma and serum samples for immunogenicity analysis

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. For sampling timepoints, please refer to Appendix 3.

When PK assessments, vital sign assessment, ECG recording, and standard meal are scheduled at the same time points, the following sequence should be followed:

- ECG recording
- Vital sign assessment
- PK blood sampling
- Standard meal

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma and/or serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a subject withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.6 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint (±5 minutes). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a semi-supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate,

including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the subject's permanent study file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. For any post-dose ECG, QTcF only needs to be calculated and recorded in the eCRF if the QTcB reading is $>$450 msec (see Appendix 7 for correction formulas for QTc intervals). Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post-dose timepoint the mean QTcF is $>$500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. The investigator should also evaluate the subject for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.7 Left Ventricular Ejection Fraction

Echocardiography will be used to assess LVEF values. The screening LVEF assessment should be performed within $\leq$28 days prior to randomization and the LVEF value must be $\geq$55% to be eligible for the study.

Echocardiography will be conducted as specified in the schedule of activities.

4.5.8 Clinical Outcome Assessments

Patient-reported outcome (PRO) instrument will be completed in both study arms to assess the level of pain experienced by the subject in relation to the injection of PH FDC SC. On Day 1, pain assessments will be performed prior to, during, and immediately after injection of PH FDC SC when the needle or device is removed, and 2 hours after injection. A questionnaire will also be completed after the injection by subjects in the OBDS arm, to assess the comfort of wearing the OBDS.

A Clinician-reported outcome (ClinRO) questionnaire will be completed to assess any skin irritation or sensitization reactions caused by the adhesion of the OBDS to the skin.

The PRO data will be collected through use of the following instruments: 100 mm VAS (Pain score) and Device Monitoring questionnaire (comfort of OBDS). ClinRO data will

be collected through use of the following instrument: Device Monitoring questionnaire (skin irritation and sensitization reactions to the OBDS).

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

The PRO instruments will be self-administered or interviewer-administered (as appropriate) at the clinic at specified timepoints on Day 1 (see schedule of activities in Appendix 1 and Section 4.5.8).

During Day 1, PRO instruments (VAS pain score and Device Monitoring questionnaire on comfort of wearing the OBDS) should be administered as outlined below:

- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for subjects to complete the instruments, estimated to be 1–2 minutes at each specified timepoint.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Subjects should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Subjects should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the subject to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the subject to complete the item or confirm that the item was intentionally left blank.

The ClinRO instrument (Device Monitoring questionnaire on skin irritation or sensitization reactions) will be completed at the clinic on Day 1 (see schedule of activities in Appendix 1). The ClinRO instrument will be self-administered before and after the injection of study drug with the OBDS. The instrument will be completed on the designated eCRF.

4.5.9 Device Monitoring Assessments

Details of the performance and ease of use of the OBDS will be collected and recorded in the eCRF using the Device Monitoring questionnaire. This will include:

- Preparation of the injection site
- Preparation of the OBDS
- Assessment of skin irritation and sensitization reactions (dermal or other effects) before and after injection
- Pre-filled cartridge inspection before insertion in the OBDS

- Positioning and attachment of the OBDS on the anterior thigh
- Drug delivery
- Removal of the OBDS
- OBDS administration failures

Ease of OBDS attachment, attachment during the injection, ease of OBDS removal, and overall clarity of handling instructions will each be rated on a three-point scale as “good,” “acceptable,” or “poor” by the healthcare professional who administered the SC injection. Subjects will also be asked to rate overall wearing comfort on the same scale (see Section 4.5.8 and Section 4.5.8.1).

Skin irritation and sensitization reactions will be assessed before and after the injection.

In addition, adverse events due to the OBDS will be summarized separately.

Medical Device Complaints

In case of any medical device complaints related to the OBDS, the investigator should report these complaints to the Sponsor as per the instructions in Section 5.4.4.

All devices should be returned to the Sponsor (refer to the pharmacy manual for instructions).

4.6 TREATMENT, SUBJECT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Subjects will receive one dose of study drug. The administration of that study drug must stop if during administration they experience any of the following:

- Severe drug-related adverse event
- NCI CTCAE Grade $\geq$ 3 hypersensitivity reaction
- Any medical condition that the investigator or Sponsor determines may jeopardize the subject's safety if he continues to receive study drug
- Investigator determination that drug discontinuation is in the best interest of the subject

The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Subjects who discontinue study drug will not be replaced.

If a subject requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Subject Discontinuation from the Study

Subjects have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a subject from the study at any time.

Reasons for subject discontinuation from the study may include, but are not limited to, the following:

- Subject withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

Every effort should be made to obtain a reason for subject discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a subject requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Subjects who withdraw from the study will not be replaced unless they have non-evaluable PK data (PK non-evaluable), in which case the subject may be replaced at the discretion of the Sponsor.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all subjects have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The pertuzumab and trastuzumab drug substances in PH FDC SC are identical to the drug substances in the Perjeta, Herceptin IV, and Herceptin SC formulations. The safety plan for subjects in this study is based on the anticipated safety risks of PH FDC SC as observed in Phase III Study WO40324 and Phase II Study MO40628 and on clinical experience with Perjeta IV and with Herceptin IV and SC, in completed and ongoing studies. The anticipated important safety risks for PH FDC SC are outlined below. Please refer to the PH FDC SC, and the Perjeta and Herceptin Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of subjects participating in this study. Eligibility criteria have been designed to exclude subjects at higher risk for toxicities. Subjects will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for discontinuation, are provided below.

5.1.1 Risks Associated with PH FDC SC

5.1.1.1 Hypersensitivity Reactions/Anaphylaxis and Administration-Related Reactions

In Phase III Study WO40324, administration related reactions (ARRs) occurring within 24 hours of HER2-targeted therapy were slightly higher in the PH FDC SC arm compared to the P+H IV arm (34 [13.5%] P+H IV vs. 43 [17.3%] PH FDC SC patients). The most frequently reported preferred terms (PTs) (in ≥5% of cases) included injection site reaction: 1 (0.4%) P+H IV (occurred in a patient who switched to Herceptin SC during the adjuvant treatment period) versus 32 (12.9%) PH FDC SC patients; and infusion-related reaction: 25 (9.9%) P+H IV versus 0 (0%) PH FDC SC patients. The injection site reactions, related to the SC route of administration of PH FDC SC, are the main reason for the observed numerical imbalance of ARRs.

The majority of ARRs were Grade 1 and 2, with Grade 1 events more frequent in the PH FDC SC arm (18 [7.1%] P+H IV vs. 38 [15.3%] PH FDC SC patients). Three patients in the P+H IV arm and none in the PH FDC SC arm experienced Grade 3 events.

The majority of ARR events occurred during the neoadjuvant phase of the study. The ARRs led to withdrawal from the study for two patients (one in each arm).

Overall, hypersensitivity and anaphylaxis events occurred with low and comparable incidence across the treatment arms (5 [2.0%] P+H IV vs. 4 [1.6%] PH FDC SC patients). Except for one event (Grade 3 hypersensitivity related to a concomitant medication at study Cycle 4 in the P+H IV arm), all events occurred after study Cycle 5

(first administration of HER2-targeted therapy) and were related to HER2-targeted therapy (4 [1.6%] patients in each arm). The reported events by PT were injection-related reaction, hypersensitivity, and drug hypersensitivity. All events were Grade 1 (three patients per arm) or Grade 2 (one patient per arm).

The majority of anaphylaxis and hypersensitivity events occurred during the neoadjuvant phase of the study. The incidence of anaphylaxis and hypersensitivity adverse events related to HER2 reported during or within 24 hours of administration were low in both arms (2 [0.8%] P+H IV vs. 2 [0.8%] PH FDC SC), and all low grade (Grade 1 and Grade 2). Three of the events occurred during the first administration of HER2-targeted therapy (study Cycle 5), and one event occurred during the sixth administration of HER2-targeted therapy (study Cycle 10). Of these, two events (one in each arm) occurred during/immediately after HER2-targeted therapy, both during the first administration of HER2-targeted therapy study Cycle 5. Each of these events led to withdrawal from HER2-targeted therapy. Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with PH FDC SC, caution should be exercised as these have been associated with IV pertuzumab in combination with trastuzumab and chemotherapy.

For PH FDC SC administration, subjects should be monitored for at least 30 minutes after their dose. If ARRs occur, subjects must be monitored until complete resolution of signs and symptoms.

Please refer to the PH FDC SC, and the Perjeta and Herceptin Investigator's Brochures for the most recent data related to the risk of hypersensitivity reactions.

5.1.1.2 Symptomatic Left Ventricular Dysfunction

In Phase III Study WO40324, primary cardiac events were defined as either:

- Symptomatic ejection fraction decrease (Heart Failure) NYHA Class III or IV and a drop in LVEF of at least 10 percentage points from baseline and to below 50%.
- Cardiac death, defined as one of the following:

  Definite cardiac death, defined as death due to heart failure, myocardial infarction, or documented primary arrhythmia

  Probable cardiac death, defined as sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology

There were no patients in the P+H IV arm and 2 (0.8%) patients in the PH FDC SC arm who met the criteria for a primary cardiac event: 1 (0.4%) patient had heart failure with LVEF drop of at least 10 percentage points from baseline and to below 50%, and 1 (0.4%) patient with cardiac death.

The event of heart failure was reported in an elderly patient in the PH FDC SC arm. The onset of the adverse event occurred 18 days after Cycle 4 Day 1 of doxorubicin (Adriamycin®) plus cyclophosphamide (AC) every 3 weeks, and became serious 12 days after Cycle 6 Day 1 of PH FDC SC. The overall diagnosis was an event of heart failure (NYHA Class IV) assessed by the investigator as related to HER2 treatment. It led to withdrawal of PH FDC SC treatment and had resolved at the time of the clinical cut-off date.

The event of cardiac death was reported in an elderly patient in the PH FDC SC arm. The event was due to an acute myocardial infarction which occurred after Cycle 2 of dose-dense doxorubicin plus cyclophosphamide (ddAC) (i.e., prior to the start of HER2-targeted therapy).

Both primary cardiac events occurred during the neoadjuvant phase of the study. No primary cardiac events were reported in patients in the adjuvant or treatment-free follow-up period.

Secondary cardiac events were only counted for patients who had not experienced a primary cardiac event (i.e., patients could only be counted in one of these categories). Those events not counted as a secondary cardiac event were still captured as part of adverse event reporting (ejection fraction decreased) and under LVEF assessment.

Overall, 9 (3.6%) versus 4 (1.6%) patients had at least one LVEF decrease of 10 % below the baseline measurement to an absolute LVEF value of $<50\%$ in the P+H IV and PH FDC SC arms, respectively. Of these, the initial LVEF decline was confirmed by a second LVEF assessment for 2 (0.8%) patients in the P+H IV arm and 1 (0.4%) patient in the PH FDC SC arm; therefore overall, 3 patients fulfilled the criteria for secondary cardiac events.

Secondary cardiac events occurred throughout all phases of the study. Some patients are counted in multiple outputs if they had events occurring in more than one phase of the study. The number of patients who experienced at least one LVEF decrease of 10% below the baseline measurement to an absolute LVEF value of $<50\%$ during study were:

- Four (1.6%) and one (0.4%) events in the P+H IV and PH FDC SC arms, respectively, which occurred during the neoadjuvant phase
- Four (1.6%) and three (1.2%) events in the P+H IV arm and PH FDC SC arms, respectively, which occurred during the adjuvant phase
- Three (1.2%) and one (0.4%) events in the P+H IV arm and PH FDC SC arms, respectively, which occurred during the follow-up phase

Subjects with significant cardiac disease or baseline LVEF $<55\%$ are not eligible for this study. Similar to all Perjeta trials, subjects must undergo routine cardiac monitoring by ECHO. During the screening/baseline period, complete medical history information will be collected from all subjects to explore possible risk factors for treatment-associated

congestive heart failure (CHF). If symptomatic left ventricular systolic dysfunction (LVSD) (heart failure; serious adverse event of NCI CTCAE v5.0 Grade 3 or 4; NYHA Class III or IV) develops, the subject must be monitored carefully with repeat LVEF assessments. Symptomatic LVSD should be treated and followed according to standard medical practice. Please refer to the PH FDC SC, and the Perjeta and Herceptin Investigator's Brochures for the most recent data relating to risk of LVSD and CHF.

5.1.1.3 Diarrhea

In Phase III Study WO40324, the incidence and severity of diarrhea events were comparable between the two treatment arms (55.2% P+H IV patients vs. 58.5% PH FDC SC patients). The majority of diarrhea events were Grade 1 and 2 in both arms. The incidence of Grade 3 diarrhea was low and balanced between the two treatment arms (11 [4.4%] P+H IV vs. 17 [6.9%] PH FDC SC patients). There was one Grade 4 event in the P+H IV arm which was assessed as related to paclitaxel by the investigator. No Grade 5 (fatal) events occurred in either arm.

Incidence of all grade diarrhea related to HER2 was comparable between the two treatment arms (32.5% P+H IV vs. 30.6% PH FDC SC patients). Grade 3–4 diarrhea events related to HER2 were reported in 5 (2.0%) P+H IV versus 9 (3.6%) PH FDC SC patients. No events of diarrhea led to withdrawal of HER2-targeted therapy. To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication (e.g., loperamide) should be considered, and subjects should be treated with fluids and electrolytes replacement, as clinically indicated.

5.1.1.4 Rash/Skin Reactions

In the Phase III Study WO40324, there was only one event of serious rash/skin reaction in the PH FDC SC arm, classified as Grade 2 (erythema event).

The rash/skin reaction appeared to be treatable in some patients with standard acne therapies, including topical and oral antibiotics.

5.1.1.5 Mucositis

In the Phase III Study WO40324, the incidence of serious mucositis events was low in both treatment arms (4/252 patients [1.6%] in P+H IV arm vs. 3/248 patients [1.2%] in PH FDC SC arm), with the majority of them (in 6 patients overall) being Grade 3 in severity.

5.1.1.6 Reproductive Risks Associated with Pertuzumab, Trastuzumab, and PH FDC SC

Reproductive toxicity was identified during nonclinical studies with Perjeta. Perjeta administered to pregnant cynomolgus monkeys during organogenesis led to delayed renal development, oligohydramnios, and embryo-fetal deaths. However, reproductive toxicity studies with trastuzumab conducted in female cynomolgus monkeys revealed no trastuzumab-related embryotoxicity or effects on fetal development. There are no

clinical studies of trastuzumab or pertuzumab in pregnant women. The IgGs are known to cross the placental barrier. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Therefore, neither pertuzumab nor trastuzumab should be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Men with female partners of childbearing potential, or with pregnant female partners, participating in the study must remain abstinent or use a condom during the study and for 7 months after the dose of study drug to avoid exposing the embryo. All male participants must also refrain from donating sperm during this same period. Pregnancies in female partners of male participants will be monitored.

5.1.1.7 Interstitial Lung Disease

In the Phase III Study WO40324, incidence of interstitial lung disease (ILD) adverse events was low and balanced between the two treatment arms (2 [0.8%] P+H IV vs. 3 [1.2%] PH FDC SC patients). Both events in the P+H IV arm occurred prior to HER2-targeted therapy and were assessed as related to chemotherapy.

In the PH FDC SC arm, serious adverse events were reported in 1 (0.4%) and 2 (0.8%) patients with ILD which were assessed by the investigator as related to AC chemotherapy and HER2- targeted therapy, respectively. All events were Grade 2 and had resolved by the time of clinical cut-off date.

5.1.2 Management of Subjects Who Experience Adverse Events

Supportive care and medical management of adverse events are at the discretion of the investigator and as per local policy, unless specifically listed below.

5.1.2.1 Management of Symptomatic LVSD and/or LVEF Decline

All subjects must have a baseline LVEF ≥ 55%. LVEF will be monitored regularly according to the Schedule of Activities (see Appendix 1). If an investigator is concerned that an adverse event may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within 3 weeks.

Symptomatic LVSD (CHF) will be assessed as “heart failure” on the basis of NCI CTCAE v5.0 and NYHA classification (see Appendix 6).

Congestive heart failure should be treated and monitored according to standard medical practice. These subjects should be evaluated by a certified cardiologist, and the results of this evaluation should be reported in the eCRF.

Heart failure and asymptomatic LVEF decline adverse events must be graded per NCI CTCAE v5.0 (see Appendix 6) and reported in the eCRF Form as described in Table 2.

5.1.2.2 Management of Hypersensitivity/Anaphylaxis and Administration-Related Reactions

Subjects should be observed closely for hypersensitivity reactions (see Section 5.1.2). Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with PH FDC SC, caution should be exercised as these have been associated with Perjeta IV in combination with Herceptin IV and chemotherapy.

Hypersensitivity reactions/anaphylaxis is a systemic reaction, mediated by interactions between factors released from IgE and mast cells, resulting in an antigen-antibody reaction.

Study drug administration should be stopped in subjects who develop dyspnea or clinically significant hypotension (defined per investigator's discretion).

Subjects who experience any of the following events will be discontinued from study drug:

- Grade 4 allergic reaction
- Grade 3 or 4 hypersensitivity reaction
- Acute Respiratory Distress Syndrome (ARDS)
- Bronchospasm

Administration Related Reactions include:

- Injection-Related Reaction. A systemic reaction with symptoms such as chills, diarrhea, fatigue, headache, nausea, and pyrexia

  Such reactions are likely to be due to a release of cytokine(s) and typically occur during, or very shortly after, the administration of monoclonal antibodies, but they may also show a delayed onset. The majority of adverse events resolve fully.
- Injection-Site Reaction. A local reaction to the site of the injection, with signs and symptoms such as erythema, induration, swelling, pain, hypoaesthesia and discomfort

Subjects who experience ARRs may be managed by:

- Stopping or slowing the injection of PH FDC SC
- Supportive care with antihistamines, antipyretics, corticosteroids or epinephrine as clinically indicated

Subjects should be monitored until complete resolution of signs and symptoms of any systemic reactions.

In order to be able to calculate time to onset of such reactions, the occurrence of associated adverse events must be documented with the date and time of the onset and duration of the event (i.e., resolution of the event).

All ARRs should be recorded as described in Section 5.3.5.1.

5.1.2.3 EGFR-Related Toxicities

Diarrhea

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication (e.g., loperamide) should be considered, and subjects should be treated with fluids and electrolyte replacement, as clinically indicated.

Rash/Skin Reactions

Treatment recommendations for EGFR-associated rash / skin reactions include topical or oral antibiotics, topical pimecrolimus, and topical steroids or systemic steroids (for severe reactions). These agents may be used in subjects experiencing pertuzumab-related rash/skin reactions, as clinically indicated, although they have not been studied in this context.

Mucositis

Mucositis is generally not considered preventable. Although for some cytotoxic agents, mucositis may be reduced by cooling the mouth using ice chips before and during the infusion.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of HER2-targeted therapies must be reported in an expedited manner with use of the Serious Adverse Event Form and classifying the event as an Event of Special Interest that is immediately reportable
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

Heart Failure

Symptomatic LVSD (referred to as heart failure) should be reported as a serious adverse event (see Table 2). If the diagnosis is heart failure, it should be reported as such, and not as individual signs and symptoms of heart failure. Signs and symptoms should be recorded in the Additional Details section of the Serious Adverse Event eCRF. A cardiac consultation is recommended for subjects who develop symptomatic LVSD. Heart failure should be graded according to both NCI CTCAE v5.0 and NYHA Class. LVEF results must also be reported. See Section 5.1.2.1 for management of Symptomatic LVSD and/or LVEF Decline.

Heart failure occurring during the study must be reported (up to Day 63 irrespective of causal relationship and up to the 7 month follow up visit if related to study drug [see Section 5.3.1]) and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

Asymptomatic Declines in Left Ventricular Ejection Fraction

Asymptomatic declines in LVEF should not be reported as adverse events because LVEF data are collected separately in the eForm. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF of ≥ 10 percentage-points from baseline to an LVEF $< 50\%$ must be reported as an adverse event with the term of “ejection fraction

decreased", as per NCI CTCAE v5.0 (see Appendix 6). In addition, a comment in the adverse events comments field should confirm that the event was asymptomatic.

- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment is an adverse event of special interest and must be reported in an expedited manner (see Section 5.2.3). The event must be reported as an adverse event with the term of "ejection fraction decreased", as per NCI CTCAE v5.0 (see Appendix 6) and a comment should be added to the adverse events comments field confirming that the event was asymptomatic.

Table 1 summarizes the reporting conventions for LVSD and heart failure.

Table 1 Reporting Conventions for Left Ventricular Systolic Dysfunction/Congestive Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF of < 10 percentage points from baseline or to an LVEF of ≥ 50%	No additional reporting required; LVEF results to be reported on eForms	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline[a] to an LVEF of < 50%	AE[b] (AE eForm)	Ejection fraction decreased[a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to study treatment discontinuation	AE (AE eForm) and report as a non-serious AEs of special interest on an SAE eForm	Ejection fraction decreased[a]	NCI CTCAE for "ejection fraction decreased"
Heart failure / CHF (symptomatic LVSD)[c]	AE (AE eForm) and SAE (SAE eForm)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; CHF = congestive heart failure; eForm = electronic form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.

[a] Baseline is considered the last LVEF prior to enrolling in study

[b] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

[c] Any symptomatic LVSD event must be reported as "heart failure."

Administration-Related Reactions: Injection-Related Reactions and Injection Site Reactions

The ARRs will be collected during the study. See Sections Section 5.1.2 and Section 5.3.5.1 for details.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 and 5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each subject contact. All adverse events, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until Day 63 after the dose of study drug. After this point only death, serious adverse events, adverse events, or adverse event of special interest that are related to study drug will be reported until 7 month follow up. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all subject evaluation timepoints. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing, and undressing, feeding oneself, using the toilet, and taking medications, as performed by subjects who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Known association of the event with the study drug or with similar treatments
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event
- Association of the event with use of the device only and not the study drug

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration, that are judged to be related to study drug injection and meet the criteria of an ARR (see Section 5.1.2) should be captured as a diagnosis (e.g., "injection-related reaction or "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a subject experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

Table 4 details the reporting conventions for injection-related reactions and injection-site reactions.

Table 4 Reporting Conventions for Injection-Related Reactions and Injection-Site Reactions

Adverse Event	Term to Be Used on AE eCRF Form	eCRF Form to Be Used to Record Symptoms
Systemic Injection Reaction	"Injection-related reaction"	Injection reaction form
Local Injection Reaction	"Injection-site reaction"	Injection reaction form [a]

AE = adverse event; eCRF = electronic Case Report Form.

[a] Symptoms of Injection-site reactions should include 'at injection site' in the description

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Planned hospitalization required by the protocol (e.g., for overnight stays Day −1 to Day 2)

Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The subject has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of subject requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For PH FDC SC, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with PH FDC SC, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until Day 63 after the dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >63 days after the dose of study drug are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Partners of Male Subjects

Male subjects will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within

7 months after the dose of PH FDC SC. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.2 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to the female partner of a male subject exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, the OBDS is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study subject, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the subject's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any death, serious adverse event, adverse event, or adverse event of special interest that occurs after the end of the adverse event reporting period (defined as 63 days after the dose of study drug), if the event is believed to be related to prior exposure to study drug. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper *Clinical Trial Adverse Event/Special Situations Form* using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
PH FDC SC	PH FDC SC, and Perjeta and Herceptin Investigator's Brochures

PH FDC SC = fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of primary and secondary endpoints will be performed after all subjects have completed the Day 63 assessments. A follow-up analysis for safety will be performed once all subjects have completed the 7-month follow-up visit.

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 144 subjects will be enrolled, taking into account an assumed drop-out rate of 10%. A total of 130 healthy subjects with fully evaluable pharmacokinetic profiles are required to demonstrate comparability of $AUC_{0-62days}$ and C_{max} values between the handheld syringe injection administration (reference) and the OBDS (test) with 80% power at 5% significance level, assuming a between-subject coefficient of variation (CV) of 40% and 'test' to 'reference' ratio of 0.95. Standard bioequivalence ranges of 0.8 and 1.25 are used to demonstrate comparability of $AUC_{0-62days}$ and C_{max} values for pertuzumab and trastuzumab administered as PH FDC SC, either by the OBDS or by handheld syringe. PK non-evaluable subjects may be replaced at the discretion of the Sponsor.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of subjects who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The evaluation of comparability between the treatment arms will include summaries of demographic and baseline characteristics, including stratification factor. Continuous

variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by counts and proportions.

6.4 PRIMARY ENDPOINT ANALYSES

The co-primary endpoints of this study are single-dose $AUC_{0-62days}$ and C_{max} values for both pertuzumab and trastuzumab either after administration of PH FDC SC using the handheld syringe with hypodermic needle or using the OBDS.

The analysis will be performed using a per protocol PK population which would include all subjects randomized and adherent to the pre-specified protocol criteria. Subjects will be excluded from the pharmacokinetic analysis population for the following reasons:

- The subject violates the following inclusion or exclusion criteria:

  A body mass index (BMI) between 18 and 32 kg/m^2, inclusive

  Use of prohibited medications, including non-prescription medications, nutraceuticals, nutritional supplements, or any herbal remedies taken within 10 days or 5 times the elimination half-life (whichever is longer) prior to randomization into the study

  Concomitant subcutaneous, intravenous, or any parenteral drugs within 90 days prior to screening

  Participation in an investigational drug or device study within 90 days or 5 times the elimination half-life (whichever is longer) prior to screening

  Current chronic daily treatment (continuous for >3 months) with corticosteroids (dose ≥ 10 mg/day methylprednisolone), excluding inhaled corticosteroids

  Receipt of IV antibiotics for infection within 7 days prior to enrollment into the study

- A subcutaneous injection site other than thigh is used
- Any subject whose injection is not successfully performed (see Appendix 4 and Appendix 5) will be considered as non-evaluable for the PK analysis; however, all data including PK and ADA samples will be collected
- The subject deviates significantly from the PK collection schedule:

  For analysis of $AUC_{0-62days}$, subjects with missing Day 63 PK concentration data or with a Day 63 PK sample time deviation outside a ± 120-hour window of planned sampling time will be excluded

  For analysis of C_{max}, subjects with $2\ or\ more$ missing PK concentration data on any of Days 3, 5, 7, 9, or 11 will be excluded

Subjects who deviate significantly from the PK collection schedule and are therefore PK non-evaluable may be replaced at the discretion of the Sponsor.

Exclusion of subjects will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

Serum concentrations of pertuzumab and trastuzumab at each sampling time point will be presented by listings. Summary statistics of PK parameter values including means, geometric means, medians, ranges, standard deviations and coefficients of variations will be presented.

The bioequivalence of the two administration methods will be assessed by a two one-sided testing procedure. The GMR of the administration by the OBDS relative to the administration by handheld syringe will be estimated together with the two-sided 90% CI based on the log-transformed $AUC_{0-62days}$ and C_{max} values.

The hypothesis to be tested for the co-primary endpoints, observed pertuzumab and trastuzumab $AUC_{0-62days}$ and C_{max} is:

- H_0: the administration by OBDS is not bioequivalent to the administration by the handheld syringe with hypodermic needle (i.e., the GMR is not within the standard bioequivalence margins [0.8; 1.25]), versus
- H_1: the administration by OBDS is bioequivalent to the administration by the handheld syringe with hypodermic needle (i.e., the GMR is within the standard bioequivalence margins [0.8; 1.25])

The null hypothesis will be rejected, and bioequivalence will be concluded if the bounds of the 90% CI of the geometric mean ratio of $AUC_{0-62days}$ and C_{max} values for pertuzumab and trastuzumab administration by the OBDS relative to the administration by the handheld syringe with hypodermic needle are entirely contained within the standard bioequivalence margins (0.8; 1.25) for all co-primary endpoints. Comparability between the two methods will be concluded only if bioequivalence is established for both pertuzumab and trastuzumab $AUC_{0-62days}$ and C_{max}.

The GMR and corresponding 90% CI will be estimated using the analysis of variance method with the log-transformed $AUC_{0-62days}$ and C_{max} values as the dependent variable and treatment arm as a covariate.

6.5 SECONDARY ENDPOINTS

6.5.1 Pharmacokinetic Analyses

All secondary pharmacokinetic parameter values *including* $C_{Day\ 21}$, $C_{Day\ 62}$, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, *CL/F, and Vd/F* will be presented by listings and descriptive summary statistics (such as mean, median, min, max, standard deviation, %CV) separately by groups. *Details of the analysis of the secondary PK endpoints are included in the Statistical Analysis Plan.*

Actual dose delivered will be calculated based on the weight difference of the syringe or OBDS before and after administration.

6.5.2 Safety Analyses

The safety analysis population will include all subjects who have received all or part of the single dose of study medication, with subjects grouped according to method of administration of study medication.

Safety and tolerability will be assessed using reporting of exposure to study treatment, adverse events, changes in clinical laboratory test results and physical examination, including vital signs, electrocardiograms, and echocardiography. As appropriate, listings, summary tables and graphs (subject plots and/or mean plots) will be provided for the safety assessments, using descriptive statistics. Study treatment exposure (such as treatment duration and total dose received) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. For adverse events for which the Common Terminology Criteria for Adverse Events v5.0 does not provide a grading scale, the standard four-point scale (mild, moderate, severe, life-threatening) will be used. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized. Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), LVEF, and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs, LVEF and ECGs will be summarized.

Adverse events due to the OBDS itself will be summarized separately.

6.5.3 Device Related Analyses

Details of the performance and ease of use of the OBDS will be collected and recorded on the eCRF. This will include:

- Preparation of the injection site
- Preparation of the OBDS
- Assessment of skin irritation and sensitization reactions (dermal or other effects) before and after injection
- Prefilled cartridge inspection before insertion in the OBDS
- Positioning and attachment of the OBDS on the anterior thigh
- Drug delivery

- Removal of the OBDS
- OBDS administration failures

Ease of OBDS attachment, attachment during the injection, ease of OBDS removal, overall wearing comfort, and overall clarity of handling instructions will each be rated on a three-point scale as “good”, “acceptable”, or “poor.” Summaries of device assessment will be summarized by counts and proportions.

Comparability of evaluation of pain assessment, and skin irritation and sensitization reactions in the syringe and the OBDS group will include summaries and listings.

6.6 EXPLORATORY ANALYSES

6.6.1 Immunogenicity Analyses

The immunogenicity analysis population will consist of all subjects with at least one ADA assessment. Subjects will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive subjects and ADA-negative subjects at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, subjects are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Subjects are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety and PK endpoints may be analyzed and reported via descriptive statistics.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of

discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Non-eCRF data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. The eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive subject data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be

entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, and images, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws

and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial*s* Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each subject the objectives, methods, and potential risks associated with each optional procedure. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a subject's agreement to participate in optional procedures. Subjects who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the subject or the subjects' legally authorized representative before his or her participation in the study. The case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the subject to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a subject's willingness to continue in the study, the subject or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each subject shall document the informed consent

process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the subject or the subject's legally authorized representative. All signed and dated Consent Forms must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the subject, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique patient identification number. This means that subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law.

Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or subjects unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/*or* other summar*ies of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the subject data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on subject safety and

data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring subject safety and data integrity. The Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately two sites globally will participate to enroll approximately 144 subjects. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and

redacted Clinical Study Reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

http:///The results of this study may be published or presented at scientific congresses. For all clinical trials in subject involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in subjects involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting subjects, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	Screening and Baseline [a]		Study Period														Follow-up [a]
Day (Window)	D –28 to D –2	D –1	D1	D2	D3	D5	D7	D9	D11	D15	D20	D22	D35	D49	D56	D63	Month 7
Informed consent	x																
Inclusion/Exclusion Criteria	x																
Demographic data	x																
Medical history	x																
Medication History	x																
Physical examination [b]	x	x														x	
Randomization [c]		x [c]															
Vital signs [d]	x	x	x	x			x					x				x	
12-Lead ECG [e]	x	x	x	x			x					x				x	
LVEF [f]	x										x [f]				x [f]		
Hematology [g]	x	x	x	x			x					x				x	
Blood Chemistry [h]	x	x	x	x			x					x				x	
Urinalysis [i]	x	x	x													x	
Serology [j]	x																
Alcohol Test [k]	x	x															
Drugs of Abuse [l]	x	x															

Appendix 1
Schedule of Activities (cont.)

	Screening and Baseline [a]		Study Period														Follow-up [a]
Day (Window)	D –28 to D –2	D –1	D1	D2	D3	D5	D7	D9	D11	D15	D20	D22	D35	D49	D56	D63	Month 7
Standardized Meal		x	x	x													
PH FDC SC administration [m]			x														
Pain assessment injection site [n]			x														
Device monitoring [o]			x														
PK sampling (pertuzumab/ trastuzumab)			x [p]	x	x	x	x	x	x	x		x	x	x		x	x
Pertuzumab/Trastuzumab /rHuPH20 ADA (Plasma and serum) [q]			x							x		x				x	x
Pregnancy follow-up of female partner																	x
Concomitant medications [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Overnight stay		x	x														

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; CTCAE v5.0 = Common Toxicity Criteria for Adverse Events; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; OBDS PH FDC SC = 600mg pertuzumab/600mg trastuzumab; PK = pharmacokinetic; RBC = erythrocyte (count); rHuPH20 = human hyaluronidase; WBC = total leukocyte (count).

[a] 7 months ± 10 days after the subject received their dose of PH FDC SC. 1 month = 30 days. For subjects with ongoing cardiac events (regardless of cause) or study treatment-related serious adverse events, adverse events, or adverse events of special interest on Day 63 or study treatment-related serious adverse events, adverse events, or adverse events of special interest occurring between the Day 63 visit and the follow-up visit, subjects should attend the clinic for the follow-up visit and PK/ADA sample collection. For subjects with no cardiac events (regardless of cause) or study treatment-related serious adverse events, adverse events, or adverse events of special interest ongoing at Day 63 and none occurring between Day 63 visit and the follow-up visit, only the pregnancy follow-up of female partners is required, and this visit may be performed by phone call.

[b] A complete physical examination will be performed at screening (including height and weight). An abbreviated exam will be performed on Day −1 (day before dosing), and on Day 63, height will be recorded only at screening.

[c] Randomization either Day −1 or Day1.

[d] Body temperature (oral or aural) will be collected at screening, Day 1 (day of dosing), and Day 63 and as indicated for follow up for AE. Blood pressure, respiration rate, and pulse rate will be taken at screening, on Days −1, 1, 2, 7, 22, and 63. All measurements to be taken after the subject has rested in a semi-supine position for at least 5 minutes.

[e] All ECG measurements in triplicate.

[f] LVEF will be measured by echocardiography on three occasions: at screening, between Days 20 and 35, and between Days 56 and 63.

[g] Hematology includes: hemoglobin, hematocrit, erythrocytes (RBC), platelets, total leukocytes (WBC), and WBC differential count.

[h] Blood chemistry includes: AST, ALT, total bilirubin, alkaline phosphatase, albumin, creatinine, urea, total protein, sodium, chloride, potassium, calcium, phosphate, glucose.

[i] Urinalysis: a midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, and pH. If there is a clinically significant positive blood and/or protein result, urine will be sent to the local laboratory for microscopy and culture.

[j] Serology includes: HIV-1 and -2, Hepatitis B and C.

[k] Alcohol test: either breath test or urine test.

[l] Drugs of abuse: according to local standards including cannabinoids, amphetamines, opiates, methadone, cocaine, benzodiazepines and barbiturates.

[m] The OBDS (with cartridge inserted and along with adhesive paper) and the handheld syringe (including needle and cover) will be weighed before and after the injection to measure the amount of study drug administered. The injection must be given in the anterior thigh midway between the anterior iliac crest and the cephalad border of the patella while the subject is in a semi-supine position. Study drug should not be injected into moles, scars, or bruises or tattooed areas. The duration of the injection in minutes and seconds will be recorded.

Appendix 1
Schedule of Activities (cont.)

[n] Intensity of injection site pain will be assessed in both study arms using a 100 mm Visual Analog Scale at the following time points: 1) on Day 1 pre-dose, 2) during drug injection, 3) after drug injection while removing the device or syringe, and 4) 2 hours after drug injection.

[o] Detailed OBDS monitoring including preparation of the injection site, preparation of the OBDS, prefilled cartridge inspection, positioning and attachment of device at anterior thigh, drug delivery and removal of OBDS, assessment of skin irritation and sensitization reactions (dermal or other effects), AEs due to OBDS injection and administration failure will be reported.

[p] PK sampling on Day 1: pre-dose, then 2 hours, 6 hours, and 12 hours post-dose (see Appendix 3).

[q] Anti-Pertuzumab, anti-trastuzumab and anti-rHuPH20 antibodies will be measured on Day 1 pre-dose and on Days 15, 22, and 63. Samples may also be taken at Follow-Up visit (see footnote a).

[r] Concomitant medication will be collected from Day −1 through Day 63.

[s] Intensity of adverse events will be graded according to CTCAE v5.0. For Adverse Events for which the CTCAE does not provide a grading scale, a four-point scale (mild, moderate, severe and life-threatening) will be used. All adverse events are collected from the time Informed Consent is signed until Day 63. After this point only death, serious adverse events, adverse events or adverse event of special interest that are related to study drug will be reported until 7 month follow up.

Appendix 2
Schedule of Procedures on Day 1 (hours post-dose)

	Pre-dose	Post-dose (hours)						
Procedure		0	1.5	2	4	6	9	12
PH FDC SC Administration		x						
Device monitoring [a]		x						
Standardized Meals			x		x		x	
Weighing of syringe and needle or OBDS [b]	x	x						
Vital Signs	x							
12-Lead ECG [c]	x							
Haematology	x							
Urinalysis	x							
Blood Chemistry	x							
Pharmacokinetic Sampling (pertuzumab/trastuzumab) [d]	x			x		x		x
Anti-pertuzumab, trastuzumab and anti-rHuPH20 Anti-bodies	x							
Pain assessment injection site [e]	x	x		x				

AE = adverse event; OBDS = on-body delivery system; PH FDC SC = fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration; rHuPH20 = human hyaluronidase

[a] Detailed device monitoring, including preparation of the skin, preparation of the OBDS, cartridge inspection, positioning and attachment of device at anterior thigh (before and during injection), drug delivery and removal of OBDS, AEs due to OBDS injection, administration failures

[b] The syringe and needle (including cover) or OBDS (including adhesive paper) should be weighed prior to drug injection (when full) and after drug injection

[c] The subjects should be at rest and semi-supine for at least 5 minutes before recording and remain resting and semi-supine during recordings.

[d] When PK blood draw, vital sign assessment, ECG recording, and standard meals are scheduled at the same time points, the following sequence should be followed: (1) ECG recording; (2) vital sign assessment; (3) PK blood sampling and (4) provide standard meal.

[e] In both study arms by Visual Analog Scale 1) pre-dose, 2) during drug injection, 3) after drug injection while removing the device or syringe, and 4) 2 hours after drug injection.

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint[a]	Sample Type
Day 1	Pre-dose[b]	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum) rHuPH20 ADA (plasma)
	2 hours, 6 hours, 12 hours, post-dose	Pertuzumab/Trastuzumab PK (serum)
Day 2, 3, 5, 7, 9 and 11	NA	Pertuzumab/Trastuzumab PK (serum)
Day 15 and 22	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum) rHuPH20 ADA (plasma)
Day 35 and 49	NA	Pertuzumab/Trastuzumab PK (serum)
Day 63	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum) rHuPH20 ADA (plasma)
Follow-Up[c]	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum) rHuPH20 ADA (plasma)

ADA = anti-drug antibody; PK = pharmacokinetic; rHuPH20 = human hyaluronidase.

All samples will be taken in relation to Day 1 (the day of drug administration); therefore, Day 2 and Day 3 PK sampling refers to 24 and 48 hours, respectively, after study drug administration. PK samples will have the following collection time windows allowed:

- Day 1: ±10 minutes with the exception of the pre-dose sample, which must be taken before administration starts
- Days 2, 3, and 5 (24, 48, and 96 hours): ±2 hours
- Days 7, 9, 11 and 15: ±24 hours
- Days 22, 35, 49, and 63: ±48 hours
- Follow-up visit: ±10 days

[a] Exact date and time of sample collection will be recorded

[b] Pre-dose sample must be taken on the same day of drug administration and before administration starts.

[c] Only for subjects with ongoing cardiac events (regardless of cause) or study treatment-related serious adverse events, adverse events, or adverse events of special interest on Day 63 or study treatment-related serious adverse events, adverse events, or adverse events of special interest occurring between the Day 63 visit and the follow-up visit

Appendix 4
Subcutaneous Injection Using Handheld Syringe and Needle

The appropriate amount of PH FDC SC solution for administration should be withdrawn from the vial. Refer to the pharmacy manual for instructions.

The 27-gauge needle should be attached to the syringe and the volume adjusted to **exactly** 10 mL.

Weigh the syringe and needle with cover using the balance specified in Section 4.3.2. Record the temperature of the room in the eCRF.

Insert the needle under sterile technique into the SC space in the anterior thigh midway between the anterior iliac crest and the cephalad border of the patella according to the instructions provided below.

- Choose a site on one thigh. Avoid areas such as:

  Skin folds

  Moles

  Tattooed areas

  Tender, bruised, red, or hard skin

  Scars or stretch marks

  If the subject has a skin condition such as psoriasis, try to avoid any raised, thick, red, or scaly skin patches or lesions
- The subject's leg should be fully extended at the knee to facilitate the placement of the needle and remain extended during the injection.
- Clean the area of skin to be used for the injection with an alcohol swab. Allow the alcohol to dry and without compromising sterility, slightly pinch and lift the skin of the thigh so that the subcutaneous space can be accessed by the needle. To enter the subcutaneous space, pick up a fold of skin and insert the needle under the skin, parallel to the long axis of the skin fold, at approximately a 30-degree angle to the surface of the skin. A uniform pinch from subject to subject is optimal.
- The needle should be fully inserted, being careful that the tip of the needle is deeper than the dermis but not as deep as the underlying muscle. The goal of the placement angle and needle depth is to achieve uniform placement into every subject's subcutaneous space. The skin should be pinched, and the needle inserted before the skin is released and the pressure on the syringe can be applied. The injection should be manually pushed at a flow rate of no more than 2 mL/min.

After the injection, weigh the syringe and needle with cover, using the same balance that was used before the injection and record the weight on the eCRF.

Appendix 5
Subcutaneous Injection Using On-Body Delivery system

The injection will be performed in the anterior thigh midway between the anterior iliac crest and the cephalad border of the patella, while the subject is sitting down (semi-supine) according to the instructions provided below.

- Remove the PH FDC SC (PHESGO®) OBDS package from the refrigerator and leave at room temperature for approximately 45 minutes to warm the drug and device to room temperature. Do not warm the package in any other way (for example, do not warm it in a microwave or in hot water). Additionally, do not leave the medicine exposed to direct sunlight.
- Check the expiration date on the carton. Do not use it if the date has passed the last day of the month shown. Do not use the product if any part of the packaging is damaged, missing or has been dropped on a hard surface.
- Wash your hands before opening the packaging.
- Remove the injector tray from the carton, and peel away the tray's cover. Do not use the injector if the tray cover on the plastic tray is damaged or missing. Do not yet remove the adhesive paper
- Hook your thumb under the small plastic guard covering the injector. Remove the plastic guard. Do not use the injector if the plastic guard is damaged or missing.
- Remove and inspect the injector for damage. Do not use the injector if it has been damaged or dropped onto a hard surface. Retain the packaging for the return of the device after administration.
- Gently lift up and open the cartridge door. You will hear three quick beeps, and you will see a flashing blue status light (see Figure 2). This means the injector is now active and must be used within 30 minutes.
- Remove and inspect the prefilled cartridge. Check the expiration date on the cartridge. Do not use it if the date has passed the last day of the month shown.
- Check the PHESGO in the cartridge. The medication should be clear and colorless to slightly brown. Do not use if the PHESGO is cloudy, discolored or contains particles. Do not shake the cartridge.
- Clean the cartridge tip with an alcohol wipe.
- Place the clean cartridge, tip first, into the open cartridge door area. Close the cartridge door. You will hear or feel a "click". This means the cartridge door is locked, and the injector is loaded. Do not touch the blue start button until you have placed the loaded injector on the skin.
- Weigh the device (without removing the adhesive paper) using a balance with the precision specified in Section 4.3.2, and record the weight on the eCRF. Record the temperature of the room in the eCRF.

Choosing and Preparing an Injection Site

- Choose a site on one thigh (anterior thigh midway between the anterior iliac crest and the cephalad border of the patella).
- Avoid areas which would affect the performance of the device such as:

  Skin folds

  Moles

  Tattooed areas

  Hairy areas (trim/shave the site before using the device)

  Tender, bruised, red, or hard skin

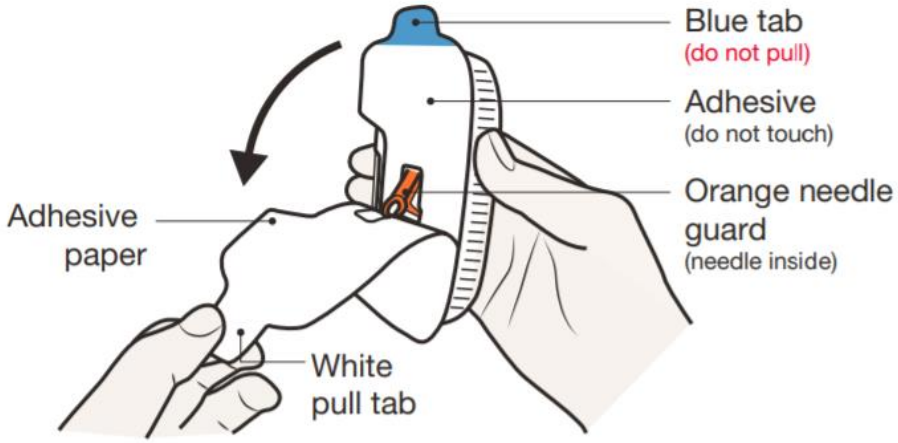
  Scars or stretch marks

  If the subject has a skin condition such as psoriasis, try to avoid any raised, thick, red, or scaly skin patches or lesions

Injecting PH FDC SC using the OBDS subcutaneously

- Clean an area on the skin at least 2 inches larger than the injector with an alcohol swab.
- Allow the alcohol to dry thoroughly before applying the device. Maintain sterility while preparing the device to be placed on the skin.
- Pick up the OBDS and without touching the blue tab, completely peel away the adhesive paper to expose the sticky adhesive (Figure 1). Retain the adhesive paper to weigh with the device after the injection.

Figure 1 Preparation of the OBDS



- With the blue tab facing the stomach, place the injector on the cleaned injection site. The status light will continue to flash blue until you press the start button. With the injector flat against the thigh, run a finger around the adhesive edges to secure the injector to the skin.

Appendix 5
Subcutaneous Injection Using On-Body Delivery system (cont.)

- Firmly press the start button until it clicks, then release. A flashing green status light and three quick beeps signal the injection has started. Make sure you see a continuous flashing green status light. Once the injection has started, watch the PHESGO window. The white plunger in the cartridge will begin to move in the window as PHESGO is injected.
- The injection takes about 5 to 10 minutes to complete. Three quick beeps and a solid green status light signal the injection is completed.

Removal of the OBDS

- When the injection is complete, grab the blue tab. Carefully lift and remove the injector off the skin.
- Once removed, you will hear three quick beeps, and the solid green status light will turn off. Use a gauze pad to wipe away fluid or apply a bandage. Do not touch the orange needle guard.
- Check to see that the white plunger has completely filled the PHESGO window. If the white plunger does not completely fill the PHESGO window, this means the subject may not have received the complete dose.
- Weigh the device together with the adhesive paper using the same balance used to weigh the device before the injection and record the weight on the eCRF.
- Place the device back into the packaging for return to the Sponsor. Refer to the pharmacy manual for details.

Appendix 6
NYHA Functional Classification System for Heart Failure and LVSD NCI CTCAE Version 5.0 Grading

NYHA Functional Classification System for Heart Failure

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

LVSD NCI CTCAE V5 Grading

Investigations					
	Grade				
	1	**2**	**3**	**4**	**5**
EF decreased [a]		Resting EF 50%–40%; 10%–19% drop from baseline	Resting EF 39%–20%; ≥20% drop from baseline	Resting EF <20%	
Cardiac Disorders					
	Grade				
	1	**2**	**3**	**4**	**5**
Heart failure [b]	Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities	Symptoms with moderate exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death

BNP = B-natriuretic peptide; EF = ejection fraction; LVSD = left ventricular systolic dysfunction; NYHA = New York Heart Association.

[a] Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.

[b] Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or the ability to do so only at an elevation in the filling pressure.

Appendix 7 Correction Formulas for QTc Intervals

Bazett's correction for QTc Measurement - QTcB

$$\text{QTcB (msec)} = \frac{\text{QT (msec)}}{\sqrt{\text{RR(msec)}/1000}}$$

Example: QTcB of a subject with a QT of 386 msec and a RR of 848 msec

QT (msec) = 386
RR (msec) = 848

$$\frac{\text{QT (msec)}}{\sqrt{\text{RR(msec)}/1000}} = 419 \text{ msec}$$

Fridericia's correction for QTc Measurement - QTcF

$$\text{QTcF (msec)} = \frac{\text{QT (ms)}}{\sqrt[3]{\text{RR(ms)}/1000}}$$

Example: QTcF of a subject with a QT of 386 msec and a RR of 848 msec

QT (msec) = 386
RR (msec) = 848

$$\frac{\text{QT (msec)}}{\sqrt[3]{\text{RR(msec)}/1000}} = 408 \text{ msec}$$

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Approval Task	[redacted] Company Signatory 13-Dec-2022 12:39:15 GMT+0000