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: SAP Version 3: 12-May-2023

STATISTICAL ANALYSIS PLAN

STUDY 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**
STUDY NUMBER:	WP42873
VERSION NUMBER:	3
ROCHE COMPOUND(S):	Fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	Not Applicable
NCT NUMBER:	To be determined
PLAN PREPARED BY:	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL DATE:	See electronic date stamp on the final page of this document.

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on the Roche SAP model document v2.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	24 November 2021	v1, 27 April 2021
2	1 0October 2022	v2, 21 April 2022
3	See electronic date stamp on the final page of this document.	v4, 13 December 2022

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) for Study WP42873 has been amended primarily to align with Protocol WP42873, Version 4. Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
	SAP v3	
1.1	Combined secondary PK objectives serum concentration at Day 22 (C_{Day21}), serum concentration at Day 63 (C_{Day62}), ($AUC_{0-\infty}$), 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) as one objective.	The Pharmacokinetics (PK) analysis plan for C_{Day21} and C_{Day62} will be the same as the rest of PK parameters and no hypothesis test will be performed for these two PK parameters.
4	• For analysis of $AUC_{0\text{-}62\ days}$, 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.	Per protocol amendment v4.
	Additional minor changes have been made to improve clarity and consistency.	
	SAP v2	
1.2.1	PK data removed from the list of data containing Treatment Assignment Information.	
3	Updated to state that 'approximately 144 subjects' will be enrolled instead of 'a total of 144 subjects.'	Per protocol amendment.
4	- PK analysis population further defined for C_{max} and $AUC_{0\text{-}62}$ for pertuzumab and trastuzumab. - Text added to allow for the possibility of PK non-evaluable subjects to be replaced at the discretion of Sponsor.	Per protocol.
	Additional minor changes have been made to improve clarity and consistency.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AEGTs	adverse event grouped terms
AESI	adverse event of special interest
ARR	administration related reaction
AUC	Area under the time−concentration curve
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
CSR	Clinical Study Report
CL/F	apparent drug clearance
CV	coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
FDC	Fixed dose combination
GMR	Geometric mean ratio
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IRF	Independent Review Facility
ITT	intent to treat
IxRS	interactive voice/web-based response system
LLoQ	lower limit of quantification
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OBDS	on-body delivery system
OBI	on-body injector
PFS	progression-free survival
PRO	patient-reported outcomes
PT	preferred term
PD	pharmacodynamic

PK	pharmacokinetic
rHuPH20	recombinant human PH20 hyaluronidase
SAE	serious adverse events
SAP	Statistical Analysis Plan
SMQs	standardized MedDRA queries
SC	Subcutaneous
VAS	Visual Analog Scale;
Vd/F	apparent volume of distribution

1. INTRODUCTION

Study WP42873 is a Phase I, single dose, multi-center study to investigate the comparability of pharmacokinetics of the fixed-dose combination (FDC) of pertuzumab and trastuzumab administered subcutaneously in healthy male subjects using a handheld syringe or using the on-body delivery system (OBDS), also referred to as on-body injector (OBI). The terminology OBDS will be used in the Statistical Analysis Plan (SAP), this will be referred to as OBI in the outputs.

This SAP provides details of the planned analyses and statistical methods for Study WP42873. For detailed background information on the study, refer to the Study WP42873 protocol.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics and safety of the FDC of pertuzumab and trastuzumab for subcutaneous administration (PH FDC SC) given by the OBDS compared to hypodermic needle and syringe in healthy male subjects. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Objectives	**Corresponding Endpoints**
• To demonstrate comparability of single-dose area under the time-concentration curve from the start of dosing to 63 days ($AUC_{0\rightarrow 62days}$) 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	• serum pertuzumab $AUC_{0\rightarrow 62days}$ and C_{max} • serum trastuzumab $AUC_{0\rightarrow 62days}$ and C_{max}
Secondary Objectives	**Corresponding Endpoints**
• 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	• *serum concentration at Day 22* (C_{Day21}) • *serum concentration at Day 63* (C_{Day62}) • 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)

Table 1 Objectives and Corresponding Endpoints (cont.)

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 v 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
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 Objectives	**Exploratory 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; $AUC_{0\rightarrow 62days}$ = area under the time−concentration curve from the start of dosing to Day 63; $AUC_{0-\infty}$ = 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; Cmax = 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.

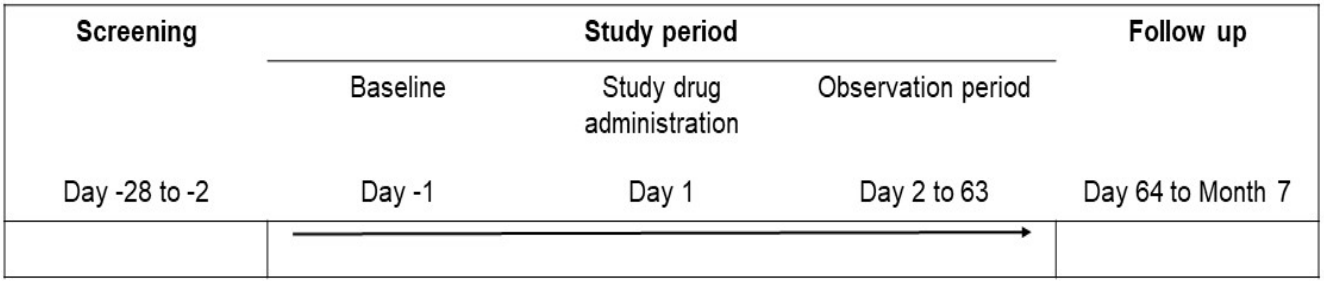
1.2 STUDY DESIGN

Study WP42873 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. The study will be conducted at two clinical research facilities in New Zealand.

The study schema is shown in Figure 1.

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 2). 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

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.

Endpoints and objectives are listed in Section 1.1. For additional details, see the schedule of activities in Appendix 2.

The analysis of primary, secondary, and exploratory 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.

1.2.1 Treatment Assignment and Blinding

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 (600 mg pertuzumab/600 mg trastuzumab/ 20,000U rHuPH20) 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 by weight ($\leq$75 kg, $>$75 kg) at Day $-$1.

A subject may only be randomized once in this trial. Subjects randomized into the study will not be replaced. Subjects who choose to withdraw after screening but before randomization will be replaced. *PK non-evaluable subjects may be replaced at the discretion of the Sponsor, as specified in Section 4.*

Review of dummy randomization lists along with User Acceptance Testing (UAT) within the IxRS system will be performed to ensure the randomization procedure is set up and performed correctly.

For additional details of administration of PH FDC SC using the OBDS or handheld syringe and needle, see the Study WP42873 protocol.

The Study Management Team is, by definition, unblinded given the open-label nature of this study. However, to further protect the integrity of the study, any treatment assignment information, such as the randomization file from the IxRS, will be withheld from the Sponsor until the primary analysis.

1.2.2 Independent Review Facility

Given the nature of the study and objective, the Independent Review Facility (IRF) or Reading Center is not applicable.

1.2.3 Data Monitoring

Given the nature of study design and shorter study duration, no independent Data Monitoring Committee (iDMC)/Internal Monitoring Committee (IMC) is used to monitor the safety data during the study. Review of data for safety purposes will not be reviewed at an aggregate level prior to the primary analysis.

2. STATISTICAL HYPOTHESES

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

- H0: 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
- H1: 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])

3. SAMPLE SIZE DETERMINATION

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 $AUC_{0\rightarrow 62days}$ 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 $AUC_{0\rightarrow 62days}$ and C_{max} values for pertuzumab and trastuzumab administered as PH FDC SC, either by the OBDS or by handheld syringe.

4. ANALYSIS POPULATIONS

The primary and secondary PK endpoints analysis will be performed using a per protocol PK population which would include all subjects randomized and adherent to the pre-specified protocol criteria specified later in this section.

The following populations are defined:

Population	Definition
ITT (intent to treat)	All randomized participants, independent of whether the participant received the assigned treatment.
Safety-evaluable	All randomized participants who received at least one dose of study treatment.
PK analysis (PAP)	A per protocol PK analysis population (PAP) which would include all randomized *participants who were treated* and *adhered* to the *pre-specified protocol criteria (listed separately below i, ii, iii).
PPAP1 (Per protocol PK analysis population for pertuzumab $AUC_{0\rightarrow 62}$)	This population is a subset of PAP. For the analysis of $AUC_{0\rightarrow 62days}$, subjects from PAP with missing Day 63 PK pertuzumab concentration data or with a Day 63 PK sample time deviation outside a $\pm 120\text{-}hour$ window of planned sampling time will be excluded.
PPAP2 (Per protocol PK analysis population for pertuzumab C_{max})	This population is a subset of PAP. For analysis of C_{max}, subjects from PAP with *two or more* missing PK pertuzumab concentration data on any of Days 3, 5, 7, 9 or 11 will be excluded.
TPAP1 (Per protocol PK analysis population for trastuzumab $AUC_{0\rightarrow 62}$)	This population is a subset of PAP. For analysis of $AUC_{0\rightarrow 62days}$, subjects from PAP with missing Day 63 PK trastuzumab concentration data or with a Day 63 PK sample time deviation outside a $\pm 120\text{-}hour$ window of planned sampling time will be excluded.
TPAP2 (Per protocol PK analysis population for trastuzumab C_{max})	This population is a subset of PAP. For analysis of C_{max}, subjects from PAP with *two or more* missing PK trastuzumab concentration data on any of Days 3, 5, 7, 9 or 11 will be excluded.
Immunogenicity analysis	The immunogenicity analysis population will consist of all participants with at least one ADA assessment.

ITT = intent to treat, PK = pharmacokinetic.

*List of pre specified protocol criteria is listed below. Participants will be excluded from the Per Protocol Pharmacokinetic Population (PAP) for the following reasons:

1. The subject violates the following inclusion or exclusion criteria:
    - A body mass index (BMI) between 18 and 32 kg/m2, 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

2. A subcutaneous injection site other than thigh is used
3. Any subject whose injection is not successfully performed (see the Study WP42873 protocol, Appendices 4 and 5) will be considered as non-evaluable for the PK analysis; however, all data including PK and ADA samples will be collected

Subjects who deviate significantly from the PK collection schedule, as *defined in PPAP1, PPAP2, TPAP1, and TPAP2* are therefore PK non-evaluable, will be replaced at the discretion of the Sponsor.

5. STATISTICAL ANALYSES

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

5.1 GENERAL CONSIDERATION

All primary and secondary PK endpoints analyses will be performed in one of the pre-defined per protocol PK analysis population (defined in section 4), unless otherwise specified. Participants will be assigned to treatment groups according to the treatment they actually received.

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

All safety analyses will be performed in the safety-evaluable population, unless otherwise specified. Participants will be assigned to treatment groups according to the treatment they actually received.

The evaluation of comparability between the arms will include summaries of demographic and baseline characteristics, medical history demographics, medical history, concomitant medication and a summary of the randomization stratification factors will be done based on the ITT population. Participants will be assigned to treatment groups as randomized by the IxRS. Listing of randomization assignments at IxRS will be generated. Continuous variables will be summarized using means, standard deviations, medians and ranges. Categorical variables will be summarized by counts and proportions. Summaries will be presented by treatment groups.

5.2 PARTICIPANT DISPOSITION

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

5.3 PRIMARY ENDPOINT(S) ANALYSIS

The co-primary endpoints of this study are single-dose $AUC_{0\rightarrow 62days}$ 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 one of the pre-defined per protocol PK analysis population (PPAP1, PPAP2, TPAP1, TPAP2). Subjects will be excluded from the pharmacokinetic analysis population as per the specified criteria listed in section 4.

5.3.1 Definition of Primary Endpoint(s)

To demonstrate comparability single-dose area under the time−concentration curve from the start of dosing to 63 days $AUC_{(0\rightarrow 62days)}$ 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 $AUC_{0\rightarrow 62days}$ and C_{max}
- serum trastuzumab $AUC_{0\rightarrow 62days}$ and C_{max}

5.3.2 Main Analytical Approach for Primary Endpoint(s)

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 $AUC_{0\rightarrow 62days}$ and C_{max} values.

The null hypothesis will be rejected and bioequivalence will be concluded if the bounds of the 90% CI of the geometric mean ratio of $AUC_{0\text{-}62days}$ 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 $AUC_{0\rightarrow 62days}$ and C_{max}.

The GMR together with the two-sided 90% CI will be estimated using analysis of variance method with log-transformed $AUC_{0\rightarrow 62days}$ and C_{max} values as the dependent variables and treatment arm as a covariate for pertuzumab and trastuzumab.

Serum concentrations of pertuzumab and trastuzumab at each sampling time point will be presented by listings. Serum concentration plots over the time for pertuzumab and trastuzumab will be generated. Summary statistics of PK parameter values including means, geometric means, medians, ranges, standard deviations and coefficients of variations will be presented. All excluded subjects will be presented by listings with the reason for exclusion.

5.4 SECONDARY ENDPOINTS ANALYSES

The secondary pharmacokinetic, safety and device-related endpoints are detailed in Section 1.1.

5.4.1 Pharmacokinetic Analyses

PK parameters including C_{Day21}, C_{Day62}, $AUC_{0-\infty}$, $t_{1/2}$, CL/F, and Vd/F will be analyzed on pre-defined per protocol PK population for pertuzumab $AUC_{(0-62)}$ (PPAP1) and trastuzumab $AUC_{(0-62)}$ (TPAP1). t_{max} will be analyzed on the pre-defined per protocol PK population for pertuzumab C_{max} (PPAP2) and trastuzumab C_{max} (TPAP2). All secondary pharmacokinetic parameter values will be presented by listings and descriptive summary statistics (such as mean, median, min, max, standard deviation, %CV) separately by treatment groups. *Subjects will be analyzed according to the treatment received.*

5.4.2 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. 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 events of special interest that are related to study drug will be reported until 7 months follow up.

Safety will be assessed using reporting of adverse events, severity of adverse events, changes in clinical laboratory test results, including vital signs, LVEF, 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.

5.4.2.1 Adverse Events

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 Version 5.0. For adverse events for which the CTCAE 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.

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

Additionally, for this study the following will be used to characterize cardiac adverse events and will be summarized by mapped term, appropriate thesaurus level, and severity grade as appropriate.

Investigator-assessed cardiac adverse event, based on:

- LVEF using preferred term ‘Ejection fraction decreased’
- Heart failure/CHF (symptomatic LVSD) Preferred term ‘Heart failure’

Standardized MedDRA Queries (SMQs) are used when available because this constitutes a globally recognized and consistent set of preferred terms (PTs) by regulatory authorities. Where no SMQs are available baskets of Roche Standard MedDRA Adverse Event Grouped Terms (AEGTs) will be used.

For this study the following will be used to characterize reactions related to the administration of study drug(s) and will be summarized by mapped term, appropriate thesaurus level, and severity grade as appropriate.

Investigator-assessed Administration Related Reactions (ARRs), including:

- Injection-related reactions (Systemic), defined as any systemic reaction in response to the SC injection of study drug
- Injection-site reactions (Local), defined as any local morphological or physiological change at or near the SC injection site

Additionally, ARRs potentially associated with SC administration of study drug(s), defined as adverse events in the SMQ “Anaphylactic Reaction (wide)”, Roche Standard AEGT “Anaphylaxis and Hypersensitivity” and “Infusion-Related Reactions and Hypersensitivity”, or the dictionary-derived term “Cytokine Release Syndrome” occurring during injection or within 24 hours of the end of administration, should be assessed as to whether considered related or unrelated to study drug by the investigator (see the Study WP42873 protocol for additional information about ARRs).

Standard Perjeta SMQ search criteria will be used to summarize adverse events to monitor (includes ARRs, hypersensitivity and anaphylaxis, diarrhoea, rash, neutropenia or febrile neutropenia, mucositis, interstitial lung disease, and reproductive risks) by treatment regimen.

5.4.2.2 Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Laboratory abnormalities will be defined based on local laboratory normal ranges and NCI CTCAE Version 5.0. Relevant laboratory parameters and change from baseline will be displayed by time. Roche Standard Reference Ranges will be implemented before any data is summarized for reporting and analysis.

5.4.2.3 Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, and body temperature) will be summarized by time. Changes from baseline will also be summarized. The mean, standard deviation, median, minimum, and maximum values will be presented by treatment groups.

5.4.2.4 ECGs

ECG data will be displayed by time, with abnormality identified where appropriate. Changes from baseline in ECG will be also listed. Summary of ECG abnormality will be displayed by count and proportion.

5.4.2.5 LVEF

LVEF (%) descriptive summary (mean, standard deviation, median, and minimum and maximum values) will be displayed and changes in LVEF will be also summarized by treatment groups.

5.4.3 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. Appropriate listings will be produced.

Skin irritation and sensitization reactions to the OBDS will be assessed on a scale between 0 to 7 using the Device (OBDS) Monitoring Assessment eCRF page in two sub-categories: 1) dermal effects and 2) other effects. Summaries of device monitoring assessments will be listed for both sub-categories.

Injection site preparation, injection device preparation, body positioning of the device compliance, cartridge inspection (before, during, and after injection), issues with the attachment of the device to the body, any device failure, needle insertion, and other device usage will be summarized by counts and proportions for OBDS. Appropriate listings will be generated.

Comparability of evaluation of pain assessment in the syringe and the OBDS group will include descriptive summaries and listings. Pain intensity scores will be assessed using the Visual Analog Scale (VAS) on a line measuring between 0mm ("no pain") and 100mm ("unbearable pain"). Pain will be assessed at baseline prior to injection, during injection, immediately post-injection while removing the injection material and 2h after injection.

5.5 EXPLORATORY ENDPOINT(S) ANALYSIS

The exploratory Immunogenicity endpoints are detailed in Section 1.1**.**

5.5.1 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 analysis will be done for anti-pertuzumab antibodies, anti-trastuzumab antibodies, and anti-rHuPH20 antibodies. Listings will also be generated as appropriate.

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 and 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 will be analyzed and reported via descriptive statistics (as data allow).

5.6 OTHER 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.

5.6.1 Extent of Exposure

Study treatment exposure (such as total dose received) will be summarized with descriptive statistics. Actual dose delivered will be calculated based on the weight difference of the syringe or OBDS before and after administration.

5.6.2 Adverse Events

Adverse events to monitor, cardiac adverse events and administration-related reactions will be summarized separately**.**

5.6.3 Concomitant Medications

All concomitant medications will be summarized by treatment groups.

5.7 OTHER ANALYSES

5.7.1 Optional Sensitivity Analyses

An optional sensitivity analysis will be performed for bioequivalence establishment of the two methods for both pertuzumab and trastuzumab $AUC_{0\rightarrow 62days}$ and C_{max} by including the baseline weight ($\leq$75 kg, $>$75 kg). The GMR together with the two-sided 90% CI will be estimated using analysis of variance method with log-transformed $AUC_{0\rightarrow 62days}$ and C_{max} values as the dependent variables and treatment arm, weight as a covariates for pertuzumab and trastuzumab.

5.8 INTERIM ANALYSES

No Interim analysis is planned.

6. REFERENCES

1) International Conference on Harmonization, 1998. Statistical Principles for Clinical Trials - ICH Harmonised Tripartite Guideline. Guidance for Industry, E9, FDA federal register. 1998;63:p49583. Available at: http://www.fda.govieder/guidance .

2) U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Statistical Approaches to Establishing Bioequivalence. 2001. Available at: https://www.fda.gov/media/70958/download .

Appendix 1
Changes to Protocol-Planned Analyses

No change from the protocol planned analysis.

Appendix 2
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 2: 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 2: Schedule of Activities (cont.)

ADA = anti-drug antibody; CTCAE v5.0 = Common Toxicity Criteria for Adverse Events; D = day; 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), 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: hemoglobin, hematocrit, erythrocytes (RBC), platelets, total leukocytes (WBC), and WBC differential count.

[h] Blood chemistry: 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 laboratory for microscopy and culture.

[j] Serology: 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.

[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.

Appendix 2: Schedule of Activities (cont.)

[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 NCI 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 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.

Notes: 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 samples 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
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 Version 5 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 5
Correction Formulas for QT_C 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

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

Signature Page for Statistical Analysis Plan - WP42873
System identifier: RIM-CLIN-487133

Approval Task	[redacted] Company Signatory 12-May-2023 08:10:38 GMT+0000