Official Title: A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Patients With HER2-Positive Early Breast Cancer

NCT Number: NCT03674112

Document Date: Protocol Version 2: 14-December-2018

PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
PROTOCOL NUMBER:	MO40628
VERSION NUMBER:	2
EUDRACT NUMBER:	2018-002153-30
IND NUMBER:	131009
TEST PRODUCT:	Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 24 July 2018
DATE AMENDED:	Version 2: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	14-Dec-2018 13:59:04

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol MO40628 has been amended to correct minor errors and to provide clarification on several protocol details. Changes to the protocol, along with a rationale for each change, are summarized below:

Sections Affected	Rationale for Change
4.1.1	Hormone receptor status was incorrectly referred to as "hormone receptor-positive status" in the inclusion criteria. This error has been corrected.
4.5.11; Appendix 1 (Schedule of Assessments)	Albumin has been added as part of blood chemistry at Screening, for determination of patient eligibility.
5.2.4.3	Reporting conventions have been added for local infusion reactions.
6, 6.6, 9.4	An interim analysis will now be conducted to support a planned regulatory filing for FDC. The scope of this interim will be a subset of the analyses planned for the primary analysis.
Appendix 1 (Schedule of Assessments)	The timing of pregnancy tests during the Treatment Cross-over and Treatment Continuation Periods has been clarified. It has been clarified that pregnancy testing is only required for women of childbearing potential.
Appendix 1 (Schedule of Assessments)	The Schedule of Assessments has been revised to clarify that adverse events and concomitant medications are collected on an ongoing basis throughout the Treatment Cross-Over Period and the Treatment Continuation Period.
Appendix 1 (Schedule of Assessments)	It has been clarified that, for all protocol-mandated study visits, a time window of ± 3 days is allowed.
Appendix 1 (Schedule of Assessments)	It has been clarified that no specific investigations are required per protocol for Cycles 8-10 and Cycles 12-14 during the Treatment Continuation Period, although the investigator may perform safety laboratory assessments or other tests per institutional practice. Information on treatment administration as well as any new or worsened clinically significant abnormalities will be collected.
Appendix 7	An error in the definition of Grade 4 left ventricular systolic dysfunction (LVSD) has been corrected.

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.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

PROTOCOL TITLE PAGE

VERSION NUMBER:	~~1~~2
DATE FINAL:	~~See electronic date stamp below~~ *Version 1: 24 July 2018*
DATE AMENDED:	*See electronic date stamp below*

FOOTER

SC Fixed-Dose Combination of Pertuzumab and Trastuzumab — F. Hoffmann-La Roche Ltd
Protocol MO40628, Version ~~1~~2

PROTOCOL ACCEPTANCE FORM

VERSION NUMBER:	~~1~~2

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

…

rHuPH20 recombinant human PH20 ~~hylauronidase~~*hyaluronidase*

4.1.1 Inclusion Criteria

…

Disease-specific criteria

…

- Hormone receptor status of the primary tumour determined by local assessment. Hormone receptor ~~positive~~ status may be either positive (i.e. ER-positive and/or PgR-positive) or negative (i.e. ER-negative and PgR-negative)

4.5.11 Laboratory Samples

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

…

- Limited biochemistry: alkaline phosphatase; AST; ALT; lactate dehydrogenase (LDH); total bilirubin; creatinine. *Albumin should be measured at Screening for determining patient eligibility.* Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN.

5.2.4.3 Administration-Related Reactions: Infusion-Related Reactions, Injection-Related Reactions, ~~and~~ Injection-Site Reactions *and Infusion-Site Reactions*

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or injection should be captured as a specific diagnosis (e.g., "infusion-related reaction", "injection-related reaction", "injection-site reaction", *"infusion-site reaction",* "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 Infusion-Related Reaction eCRF or Injection-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Injection-Related Reaction eCRF.

See Table 2 for the reporting conventions for infusion-related reactions, injection-related reactions, ~~and~~ injection-site reactions *and infusion-site reactions*.

Table 2 Reporting Conventions for Administration-Related Reactions

Adverse Event	Term to Be Used on Adverse Event eCRF Form	Symptoms to Be Entered on eCRF Form
…		
Local Infusion Reaction	*"Infusion-site reaction"*	*"Infusion-site reaction"*

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

…

~~An interim safety analysis that includes the study safety endpoints may be conducted. The decision to conduct an interim safety analysis will be based on ongoing review of safety data by the Medical Monitor.~~*An interim analysis will be conducted to support a planned regulatory filing for FDC (see Section 6.6).*

6.6 ~~OPTIONAL~~ INTERIM ANALYSES

~~An interim safety analysis may be conducted. The decision to perform an interim safety analysis will be based on ongoing review of safety data by the Medical Monitor. If conducted, the results of this interim analysis will be evaluated by a Sponsor's Internal Data Monitoring~~

~~Committee.~~ *An interim analysis will be conducted to support a planned regulatory filing for FDC, which will consist of a subset of the analyses planned for the primary analysis. The results of this interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee. Further details will be specified in the Statistical Analysis Plan.*

9.4 ADMINISTRATIVE STRUCTURE

…

~~If an interim safety analysis is conducted, the Sponsor's Internal Data Monitoring Committee will evaluate the results.~~ *The results of the interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee.*

Appendix 1
Schedule of Activities

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
~~Adverse events [p]~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x [p]~~
Adverse events [p]	*x*	*x*	*Collected on an ongoing basis*										*x [p]*
~~Concomitant medication [q]~~		~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x [q]~~
Concomitant medication [q]		*x*	*Collected on an ongoing basis*										*x [q]*

…

Notes Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. *For all protocol-mandated study visits, a time window of ± 3 days is allowed.* If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date.

a. Either pertuzumab and trastuzumab FDC SC or P+H IV will be selected by the patient for study treatment during the Treatment Continuation Period. During this period, pertuzumab and trastuzumab FDC SC or P+H IV will be administered for the number of 3-weekly cycles calculated based on the number of Perjeta and Herceptin cycles received as neoadjuvant treatment prior to study entry and P+H IV and pertuzumab and trastuzumab FDC SC cycles (six total cycles) received during the Treatment Cross-over Period. A total of 18 cycles of anti-HER2 treatment should be administered for EBC treatment unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early cessation of treatment. *No specific investigations are required per protocol for Cycles 8-10 and Cycles 12-14 during the Treatment Continuation Period, although the PI may perform safety laboratory assessments or other tests per institutional practice (these results are not required to be reported in the eCRF). However, information on treatment administration will be collected, and new or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.*

…

n. Haematology: haemoglobin, total WBC, ANC / neutrophils, platelet count. Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. *Albumin should be measured at Screening for determining patient eligibility.* Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN. During the treatment period, bloods for haematology / biochemistry may be taken within three days prior to study treatment administration.

o. *Pregnancy testing is only required for women of childbearing potential:* A woman of childbearing potential is defined as: post-menarchal, has not reached a post-menopausal state (post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. ~~For all women of childbearing potential,~~ *P*~~p~~regnancy tests must be performed via serum β-human chorionic gonadotropin (HCG) at baseline within seven days prior to first study treatment administration. Urine pregnancy tests should be repeated during the Treatment Cross-over and Treatment Continuation Periods ~~within seven days prior to every three treatment cycles starting~~ at Cycle 4, *Cycle 7, Cycle 11 and Cycle 15 (or at last treatment cycle)*, ~~(~~and as clinically indicated~~)~~, with results available prior to study treatment administration, as well as at the End of Treatment Visit and at the Follow-up Visit until seven months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test.

Appendix 7
NYHA Functional Classification System for Heart Failure and LVSD NCI CTCAE V4.0 Grading

…

LVSD NCI CTCAE V4 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~~50~~%	—

…

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf page 109)

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TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
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MEDICAL MONITOR:	Dr. [redacted]
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, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
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PHASE:	II
INDICATION:	HER2-positive Early Breast Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate patient reported preference for a subcutaneously administered fixed-dose combination formulation (FDC SC) of pertuzumab and trastuzumab compared with intravenously (IV) administered Perjeta® and Herceptin® formulations (P+H IV) in patients with HER2-positive (HER2+) early breast cancer (EBC). The study will also evaluate patient reported satisfaction with pertuzumab and trastuzumab FDC SC and health-related quality of life (HRQoL) outcomes; Healthcare professionals (HCPs) perception of time/resource use and convenience of pertuzumab and trastuzumab FDC SC and P+H IV; as well as the safety and efficacy of each study regimen.

Specific objectives and corresponding endpoints for the study are outlined in the following table.

Table of Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate patient preference for pertuzumab and trastuzumab FDC SC	• Proportion of patients who preferred pertuzumab and trastuzumab FDC SC with treatment preference assessed via Question 1 of the PPQ

Secondary Objectives	Corresponding Endpoints
• To evaluate patient assessed satisfaction with route of administration of pertuzumab and trastuzumab FDC SC and route of administration of P+H IV	• Patient responses to Question 1 of the TASQ-SC and TASQ-IV
• To evaluate patients' choice of pertuzumab and trastuzumab FDC SC for the Treatment Continuation Period	• Proportion of patients who select pertuzumab and trastuzumab FDC SC for the study Treatment Continuation Period
• To evaluate HCP perception of time/resource use and convenience with pertuzumab and trastuzumab FDC SC	• HCP responses to the HCPQs, by individual question
• To evaluate HRQoL with pertuzumab and trastuzumab FDC SC and P+H IV	• Change in symptoms and function from baseline and over time as assessed by EORTC QLQ-C30 scores • Mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status / overall QoL scale (items 29 and 30) of the EORTC QLQ-C30.
Secondary Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of pertuzumab and trastuzumab FDC SC and P+H IV during the study Treatment Cross-over Period and the entire adjuvant treatment period (Treatment Cross-over Period + Treatment Continuation Period)	• Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, SAEs and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v4.0 • Incidence of premature withdrawal from study treatment • Targeted vital signs and physical findings • Targeted clinical laboratory test results
• To evaluate the safety of switching from pertuzumab and trastuzumab FDC SC to P+H IV and from P+H IV to pertuzumab and trastuzumab FDC SC	• Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, SAEs and cardiac AEs (including LVEF events) with severity determined according to NCI CTCAE v4.0 during the study Treatment Cross-over Period by treatment arm

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the long-term efficacy of the pertuzumab and trastuzumab FDC SC and P+H IV	• IDFS, defined as the time from randomization to the first occurrence of one of the following events: o Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion) o Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast) o Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer) o Contralateral invasive breast cancer o Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible) Note: Ipsilateral or contralateral *in situ* disease and second primary non-breast cancers (including *in situ* carcinomas and non-melanoma skin cancers) will not be counted as recurrence. • IDFS including second primary non-breast cancer, defined as IDFS with second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and *in situ* carcinoma of any site) included as an event • DDFS, defined as the time from randomization to the date of distant breast cancer recurrence • OS, defined as the time from randomization to death from any cause.

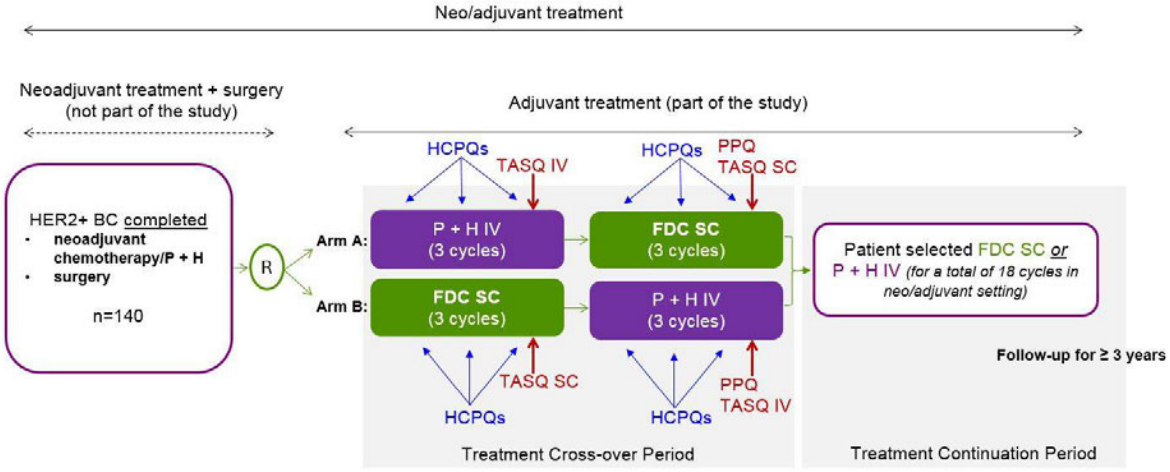
AE: adverse event; DDFS: distant disease-free survival; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; HCP: healthcare professional; HCPQ: Healthcare Professional Questionnaire; HRQoL: health-related quality of life; IDFS: invasive disease-free survival; LVEF: left ventricular ejection fraction; NCI CTCAE v4.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; OS: overall survival; P+H IV: intravenously administered Perjeta and Herceptin formulations; FDC SC: fixed-dose combination of pertuzumab and trastuzumab for subcutaneous use; PPQ: Patient Preference Questionnaire; QoL: quality of life; SAE: serious adverse event; TASQ-IV/SC: Therapy Administration Satisfaction Questionnaire-intravenous/subcutaneous

Study Design

Description of Study

This is a Phase II, randomized, multi-centre, multinational, open-label, cross-over study in adult patients who have completed neoadjuvant chemotherapy with neoadjuvant Perjeta and Herceptin and have undergone surgical treatment of HER2+ EBC. An overview of the study design is provided in the figure below. A Schedule of Activities is provided in Appendix 1.

Study Schema



Abbreviations: IV: intravenous; P+H: Perjeta + Herceptin; FDC SC: subcutaneously administered fixed-dose combination of pertuzumab and trastuzumab; HCPQs: Healthcare Professional Questionnaires; PPQ: Patient Preference Questionnaire; SC subcutaneous; TASQ: Therapy Administration Satisfaction Questionnaire

Eligibility will be assessed within a 28-day screening period. Eligible patients will be enrolled and randomly allocated in a 1:1 ratio to treatment Arm A (P+H IV followed by pertuzumab and trastuzumab FDC SC) or treatment Arm B (FDC SC followed by P+H IV). Patients will be stratified according to neoadjuvant chemotherapy regimen (anthracyclines + taxanes vs. carboplatin + taxanes vs. taxanes only), neoadjuvant treatment response (pathologic complete response [pCR] vs. non-pCR) and hormone receptor status (oestrogen receptor [ER]-positive and/or progesterone receptor [PgR]-positive vs. ER-negative and PgR-negative). Study treatment will be initiated ≥ 2 weeks from breast cancer surgery but ≤ 9 weeks from the last administration of systemic neoadjuvant therapy and will be administered on Day 1 of each 3-week treatment cycle. No adjuvant chemotherapy is allowed after surgery, however, adjuvant hormone and/or radiation therapy are allowed.

Patients randomized to Arm A will receive P+H IV for three treatment cycles followed by pertuzumab and trastuzumab FDC SC for three treatment cycles. Patients randomized to Arm B will receive pertuzumab and trastuzumab FDC SC for three treatment cycles followed by P+H IV for three treatment cycles. This period of 3+3 cycles in both treatment arms constitutes the study Treatment Cross-over Period.

The 6 study treatment cycles of pertuzumab and trastuzumab FDC SC and P+H IV received during the Treatment Cross-over Period and P+H treatment cycles received in the neoadjuvant setting prior to study entry will be considered part of the total 18 anti-HER2 treatment cycles planned for all study patients. Following completion of the Treatment Cross-over Period, patients will enter the Treatment Continuation Period wherein they will receive the remaining anti-HER2 treatment cycles required to complete their 18 planned cycles unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early treatment cessation. Study treatment during this period will be either P+H IV or pertuzumab and trastuzumab FDC SC as selected by the patient at the end of the Treatment Cross-over Period.

Patients who, by the investigator's assessment, cannot tolerate pertuzumab and trastuzumab FDC SC or P+H IV may be allowed to receive P+H IV or pertuzumab and trastuzumab FDC SC, respectively, for their remaining planned anti-HER2 treatment cycles. The investigator must obtain approval from the Medical Monitor to switch study treatment.

Patient preference will be assessed based on the Patient Preference Questionnaire (PPQ) (administered following treatment administration on Day 1, Cycle 6 of the Treatment Cross-over Period). Treatment satisfaction will be assessed based on the Therapy Administration Satisfaction Questionnaire (TASQ) (administered following treatment administration on Day 1 of Cycles 3 and 6 of the Treatment Cross-over Period). Healthcare professionals will record their perception of time/resource use and convenience of treatment administration completing the Healthcare Professional Questionnaires (HCPQs). Perception of time use will be captured during the Treatment Cross-over Period and perception of convenience will be captured after administration of each patient's treatment Cycle 6. Health-related quality of life will be assessed based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30 completed at baseline, Cycle 3, Cycle 6, and the end of study treatment visits as well as at 18 months, 2 years, and 3 years from randomization. The study questionnaires are provided in Appendix 2 and Appendix 3.

Patients will be assessed for safety by regular evaluation of adverse events (AEs), vital signs, routine clinical laboratory tests (haematology, blood chemistry) and left ventricular ejection fraction (LVEF) assessments; and by physical examinations. Adverse events will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). Efficacy will be assessed based on investigator-evaluated disease status determined according to assessments conducted per institutional practice or according to the American Cancer Society / American Society of Clinical Oncology (ACS/ASCO) Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4].

Patients will undergo an End of Treatment Visit approximately 28 days after completing study treatment and will enter the Follow-up Period wherein they will be followed for safety, disease status, survival and HRQoL (via the EORTC QLQ-C30) for three years from the date the last patient is randomized.

Patients who withdraw from the study following randomization will not be replaced. Patients can be screened for the study more than once.

Number of Patients

Approximately 140 patients will be randomized in the study to obtain at least 126 evaluable patients.

Target Population

The target population will consist of adult patients with HER2+ EBC who have received neoadjuvant Perjeta and Herceptin, and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer.

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-specific criteria

- Female or male with histologically confirmed, HER2+ inflammatory, locally advanced or early-stage breast cancer who have received neoadjuvant Perjeta + Herceptin and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer.

  Note: The neoadjuvant chemotherapy regimen (including type and sequencing of selected agents) and the number of neoadjuvant Perjeta and Herceptin treatment cycles are at the discretion of the treating physician and patient. Subcutaneously administered Herceptin may have been used in the neoadjuvant setting. The use of any trastuzumab biosimilars in the neoadjuvant setting is not allowed.

- HER2+ breast cancer assessed at the local laboratory prior to initiation of neoadjuvant therapy. HER2+ status must be determined based on breast biopsy material obtained prior to neoadjuvant treatment and is defined as 3+ by immunohistochemistry (IHC) and/or positive by HER2 amplification by *in situ* hybridization (ISH) with a ratio of ≥ 2 for the number of HER2 gene copies to the number of chromosome 17 copies
- Hormone receptor status of the primary tumour determined by local assessment. Hormone receptor ~~positive~~ status may be either positive (i.e. ER-positive and/or PgR-positive) or negative (i.e. ER-negative and PgR-negative)
- Completed all neoadjuvant chemotherapy and surgery. Adjuvant radiotherapy may be planned or ongoing at study entry and adjuvant hormone therapy is allowed during the study. Note that study treatment cannot be initiated within < 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.
- No evidence of residual, locally recurrent or metastatic disease after completion of surgery. Patients with clinical suspicion of metastases must undergo radiological assessments per institutional practice to rule out distant disease.
- Wound healing after breast cancer surgery adequate per investigator's assessment to allow initiation of study treatment within ≤ 9 weeks of last systemic neoadjuvant therapy
- No adjuvant chemotherapy planned. Note that adjuvant hormonal treatment is allowed during the study.

General criteria

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group performance status 0 or 1
- Intact skin at planned site of subcutaneous (SC) injections (thigh)
- LVEF ≥ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) within 28 days of study randomization
- No major surgical procedure unrelated to breast cancer within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of <1% per year, or 2 effective non-hormonal contraceptive methods during the study treatment periods and for 7 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a post-menopausal state (post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and copper intrauterine devices.

  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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the study treatment periods and for seven months after the last dose of study treatment 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.
- A negative serum pregnancy test must be available prior to randomization for women of childbearing potential (defined as post-menarchal, has not had ≥ 12 continuous months of amenorrhea with no identified cause other than menopause, and has not undergone surgical sterilization [removal of ovaries and/or uterus])

Exclusion Criteria

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

Cancer-specific criteria

- Stage IV (metastatic) breast cancer
- Current or prior history of active malignancy (other than current breast cancer) within the last five years. Appropriately treated non-melanoma skin cancer; *in situ* carcinomas, including cervix, colon, or skin; or Stage I uterine cancer within the last five years are allowed.

  A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than five years.
- Previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective oestrogen receptor modulators, aromatase inhibitors], and antitumor vaccines) for treatment or prevention of breast cancer, except neoadjuvant Perjeta, Herceptin and chemotherapy for current breast cancer

General criteria:

- Investigational treatment within four weeks of enrolment
- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE v4.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class ≥ II
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate ≥ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz II] or third-degree AV-block)
  - Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on electrocardiogram (ECG)
  - Evidence of myocardial infarction within 12 months prior to randomization
  - Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic

testing), clinically significant electrolyte abnormalities (e.g., hypokalaemia, hypomagnesemia, hypocalcaemia), or family history of sudden unexplained death or long QT syndrome

- Inadequate bone marrow function, defined by any of:
  - Absolute neutrophil count < 1.5 x 10^9/L
  - Platelet count < 100 x 10^9/L
  - Haemoglobin < 9 g/dL
- Impaired liver function, defined by any of:
  - Serum (total) bilirubin > 1.25 x upper limit of normal (ULN). In case of Gilbert's syndrome: a total bilirubin of 2 x ULN is permitted.
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 1.25 x ULN
  - Albumin < 25 g/L
- Inadequate renal function with serum creatinine > 1.5 x ULN
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Pregnant or breastfeeding, or intending to become pregnant during the study or within seven months after the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in, and completion of, the study
- Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
- Concurrent, serious, uncontrolled infections, or known infection with human immunodeficiency virus (HIV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

End of Study

The end of the study is defined the Last Patient, Last Visit (LPLV) which will occur three years after the last patient is randomized or the date at which the last data point required for the final statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The study is estimated to last approximately 4 years, based on a recruitment period of up to 10 months and 3 years of follow-up after the last patient is randomized.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are pertuzumab and trastuzumab FDC SC, Perjeta IV, and Herceptin IV.

Test Product (Investigational Drug)

Pertuzumab and trastuzumab FDC SC is given as a fixed dose (i.e. non-weight based). Pertuzumab and trastuzumab FDC SC will be provided in a loading dose configuration and a maintenance dose configuration. The 15 mL loading dose consists of 1200 mg pertuzumab and 600 mg trastuzumab. The 10 mL maintenance dose consists of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Perjeta or Herceptin at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations. All

pertuzumab and trastuzumab FDC SC doses are administered by SC injection over 5 – 8 minutes at a rate of ≤ 2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. Patients should be monitored for 30 minutes after their first pertuzumab and trastuzumab FDC SC dose administration regardless of whether a loading dose is required. Patients should be monitored for 10 - 15 minutes following subsequent administrations. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

Comparator (Active Control)

Perjeta IV is administered at a dose of 840 mg (loading dose) or 420 mg (maintenance dose) on Day 1 of each 3-week treatment cycle and should be administered before Herceptin IV. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Perjeta at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations. Perjeta IV loading dose (if required) will be administered as a 60-minute infusion (± 10 minutes), followed by an observation period of 60 minutes. If the loading dose infusion is well tolerated, subsequent maintenance doses can be administered over a period of 30 minutes (± 10 minutes) with an observation period of 30 minutes. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements. The observation period should be completed prior to the subsequent Herceptin IV infusion.

Herceptin IV is administered at a dose of 8 mg/kg (loading dose) or 6 mg/kg (maintenance dose) on Day 1 of each 3-week treatment cycle. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Herceptin at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations. Herceptin IV loading dose (if required) will be administered as an infusion over approximately 90 (± 10) minutes after which the patient must be observed for 60 minutes. If the loading dose is well tolerated, subsequent maintenance doses can be administered as 30-minute infusions (± 10 minutes) followed by an observation period of 30 minutes. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Primary Analysis

The primary objective of this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC based on the proportion of patients indicating an overall preference for pertuzumab and trastuzumab FDC SC based on Question 1 of the PPQ. Question 1 of the PPQ is as follows: “All things considered, which method of administration did you prefer?”.

The primary endpoint will be analysed for the intent-to-treat (ITT) population and for the modified ITT (mITT) population. The mITT population will include all patients who received at least one dose by both SC and IV routes of administration during the Treatment Cross-over Period and subsequently answered at least Question 1 of the PPQ.

A point estimate with associated 95% confidence interval (CI) for the proportion of patients who preferred pertuzumab and trastuzumab FDC SC will be calculated for the mITT and ITT populations.

Analysis of the primary study endpoint will take place when all patients have completed their last treatment administration during the Treatment Cross-over Period.

Determination of Sample Size

The binary primary endpoint (the proportion of patients who express a preference for pertuzumab and trastuzumab FDC SC) will be estimated with associated two-sided 95% CI.

Assuming a rate of 70% of patients preferring pertuzumab and trastuzumab FDC SC and aiming at a distance from the estimated proportion to the CI limits of approximately ± 8%, a total of 126 patients are needed for the evaluation of preference. Hence, the observed rate of 70% of patients preferring pertuzumab and trastuzumab FDC SC could be estimated to be within 61.9% and 78.4% with a probability of 95%.

To allow for 10% of the patients not providing an evaluable preference assessment, approximately 140 patients are targeted to be randomized into the study.

~~Optional~~ Interim Analysis

~~An interim safety analysis may be conducted. The decision to perform an interim safety analysis will be based on ongoing review of safety data by the Medical Monitor. If conducted, the results of this interim analysis will be evaluated by a Sponsor's Internal Data Monitoring Committee.~~ *An interim analysis will be conducted to support a planned regulatory filing for FDC, which will consist of a subset of the analyses planned for the primary analysis. The results of this interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee. Further details will be specified in the Statistical Analysis Plan.*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ACS/ASCO	American Cancer Society / American Society of Clinical Oncology Breast Cancer
ADA	anti-drug antibody
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ARR	administration-related reactions
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
CHF	congestive heart failure
CI	confidence interval
CRO	contract research organization
C_{trough}	serum trough concentration
DDFS	distant disease-free survival
EBC	early breast cancer
EC	Ethics Committee
ECD	extracellular domain
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
ER	oestrogen receptor
EU	European Union
FDC SC	Fixed-dosed combination formulation for subcutaneous administration
HCG	human chorionic gonadotropin
HCP	healthcare professional
HCPQ	Healthcare Professional Questionnaire
HER2	human epidermal growth factor receptor 2
HER2+	HER2-positive

HER	human epidermal growth factor receptor
Herceptin IV	Herceptin for IV administration
Herceptin SC	Herceptin for SC administration
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IDFS	invasive disease-free survival
Ig	immunoglobulin
IHC	immunohistochemistry
IV	intravenous(ly)
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISH	*in situ* hybridization
ISR	injection site reaction
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web-based response system
LDH	lactate dehydrogenase
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition scan
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
NYHA	New York Heart Association
OS	overall survival
P+H IV	Perjeta IV and Herceptin IV
pCR	pathologic complete response
Perjeta IV	Perjeta for IV administration
PFS	progression–free survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PPQ	Patient Preference Questionnaire
PRO	patient reported outcome
QoL	quality of life

rHuPH20	recombinant human PH20 ~~hylauronidase~~*hyaluronidase*
SAE	serious adverse event
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
TASQ-IV	Therapy Administration Satisfaction Questionnaire – intravenous
TASQ-SC	Therapy Administration Satisfaction Questionnaire – subcutaneous
ULN	upper limit of normal
U.S.	United States
WBC	white blood count

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE EARLY BREAST CANCER

Among developed countries, breast cancer is the most common malignancy and was associated with 198 000 deaths in 2012 alone. Globally, its incidence is exceeded only by lung cancer [Ferlay et al. 2013].

Amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) gene occurs in 20% to 30% of invasive breast cancers and has both prognostic and predictive implications [Slamon et al. 1987, Owens et al. 2004]. HER2 is a member of the family of human epidermal growth factor receptors (HER) that includes HER1 [also known as epidermal growth factor receptor (EGFR)], HER3, and HER4. Each HER receptor consists of an extracellular ligand binding site, a transmembrane lipophilic segment, and an intracellular domain with tyrosine kinase catalytic activity. HER activation initiates a variety of intracellular signalling pathways that are involved in cell proliferation, survival, differentiation, angiogenesis, and invasion. Low levels of HER2 are normally expressed on the surface of epithelial cells and are necessary for the normal development and repair of many tissues, including those of the breast, gastrointestinal tract, central nervous system and myocardium [Ozcelik et al. 2002, Vu and Claret 2012, Iqbal and Iqbal 2014]. When overexpressed in breast tumours, however, HER2 is associated with more aggressive disease characterized by shorter times to relapse and overall survival (OS) [Slamon et al. 1987, Carr et al. 2000].

HER2 activation occurs via autophosphorylation of receptor cytoplasmic domains through homo-dimerization or hetero-dimerization with other ligand-induced HER family members wherein HER2 is the preferred HER family dimerization partner [Graus-Porta et al. 1997, Moasser 2007]. Constitutive HER2 activation and downstream signalling can also occur by proteolytic cleavage of its extracellular domain (ECD), a process known as shedding, to produce a truncated internal domain [Molina et al. 2001].

The benefit of anti-HER2 treatment strategies for HER2-positive (HER2+) breast cancer was first realized with the introduction of the anti-HER2 monoclonal antibody trastuzumab (Herceptin®) into clinical management in 2000 [Cobleigh et al. 1999, Slamon et al. 2001, Bonifazi et al. 2014]. The subsequent development of additional HER2-targeted agents, including pertuzumab (Perjeta®; another HER2-specific monoclonal), trastuzumab emtansine (a trastuzumab-cytotoxic drug conjugate), and lapatinib and neratinib (HER2/HER1 tyrosine kinase inhibitors), has widened the range of available anti-HER2 approaches including the possibility for dual HER2 blockade with Perjeta and Herceptin. Perjeta and Herceptin each bind to distinct epitopes on the HER2 ECD without competing with each other. As described in Sections 1.2.2 and 1.2.3, these molecules have complementary mechanisms for disrupting HER2 signalling. Dual HER2 blockade with Perjeta and Herceptin in HER2+ disease has been shown to improve pathologic complete response (pCR) in the neoadjuvant setting, invasive disease-free survival (IDFS) in the adjuvant setting, and progression-free survival (PFS) and OS in the metastatic setting, and has become standard of care in each of these indications [Swain et al. 2013, Gianni et al. 2016, von Minckwitz et al. 2017, Cardoso et al. 2017, Curigliano et al. 2017, Gradisher et al. 2018].

While improving disease outcomes, the incorporation of intravenously administered (IV) Perjeta and Herceptin IV (P+H IV) into HER2+ breast cancer care results in longer treatment administration schedules due to sequential administration of each monoclonal antibody in addition to IV chemotherapeutics. A recently reported metastatic breast cancer (MBC) study evaluated Herceptin IV and Perjeta IV combined for administration from a single infusion bag compared with Perjeta IV and Herceptin IV administered as sequential infusions. The study found the safety profile in the co-infused treatment group was consistent with the known toxicity profiles of each drug with no unexpected safety signals and no apparent alteration with co-mixing / co-infusion [Andersson et al. 2017].

More recently, Herceptin has been developed in a formulation for subcutaneous (SC) administration (see Section 1.2.3) that can be delivered in under 5 minutes versus the 30-60 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]. Herceptin SC is currently approved in the EU for use in the neoadjuvant, adjuvant and metastatic HER2+ breast cancer settings and is referenced for use with Perjeta IV in this jurisdiction. Initial data from a Phase IIIb single-arm safety study of combined treatment with Herceptin SC and Perjeta IV have shown a safety profile consistent with combined treatment with Herceptin and Perjeta IV formulations [Kummel et al. 2016]. As described in Section 1.2.4, pertuzumab formulated for SC administration and co-administration with Herceptin SC is undergoing development in this study and others.

1.2 BACKGROUND ON STUDY MEDICATIONS

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 pharmacokinetic (PK) properties and when referring to the pertuzumab and trastuzumab fixed-dosed combination formulation for subcutaneous administration (FDC SC).

Other versions of trastuzumab for IV administration may be available in some countries. To distinguish the source of trastuzumab that is an investigational medicinal product (IMP) in this study, as well as in Roche-sponsored clinical studies referenced in support of this study, the trade name (Herceptin) is used throughout the protocol when referring to the commercially available drug product (i.e. trastuzumab plus excipients). For consistency, the trade name (Perjeta) is also used when referring to the commercially available drug product (pertuzumab plus excipients) and IMP in this study.

1.2.2 Background on Perjeta

Perjeta is a recombinant, humanized immunoglobulin (Ig) G1 monoclonal that binds to the subdomain II of the HER2 ECD and sterically hinders HER2 dimerization [Franklin et al. 2004]. Inhibition of homo-dimerization and ligand-activated hetero-dimerization precludes activated intracellular signalling and downstream stimulation of HER-regulated pathways involved in tumorigenesis. *In vitro* studies have also shown that Perjeta can mediate antibody dependent cell-mediated cytotoxicity (ADCC).

Perjeta and Herceptin each bind to distinct epitopes on the HER2 ECD without competing with each other. The molecules have complementary mechanisms for disrupting HER2 signalling (see Section 1.2.3) resulting in augmented *in vitro* and *in vivo* anti-proliferative activity when delivered in combination.

Perjeta is approved in the European Union (EU) and United States (U.S.) for IV administration (Perjeta IV) in combination with Herceptin and chemotherapy for the neoadjuvant and adjuvant (neo/adjuvant) HER2+ EBC at high risk of recurrence and in combination with Herceptin and docetaxel for the treatment of HER2+ MBC.

For further details of non-clinical and clinical studies with Perjeta, please refer to the Perjeta Investigator's Brochure.

1.2.3 Background on Herceptin

Herceptin is a recombinant, humanized IgG1 monoclonal antibody with high affinity for the subdomain IV of the HER2 ECD. Herceptin binding has been shown to prevent access by proteases responsible for cleaving the ECD at the cell surface to produce the constitutively activated truncated form of HER2 [Molina et al. 2011]. In addition to inhibition of HER2 shedding, Herceptin mediates ADCC on HER2-overexpressing cancer cells [Sliwkowski et al. 1999].

The addition of Herceptin to standard chemotherapy in the treatment of HER2+ breast cancer improves pCR rates, disease-free survival and OS in the neoadjuvant and adjuvant settings; and PFS and OS in the metastatic setting [Slamon et al. 2001; Romond et al. 2005, Smith et al. 2007, Gianni et al. 2010, Cameron et al. 2017, Slamon et al. 2011]. Herceptin is indicated for the treatment of patients with HER2+ breast cancer in the neoadjuvant, adjuvant, and metastatic settings.

Herceptin can also be administered SC. Herceptin SC is approved in many countries as treatment for patients with HER2+ EBC and MBC.

For further details of non-clinical and clinical studies with Herceptin, please refer to the Herceptin Investigator's Brochure.

1.2.4 Background on Pertuzumab and Trastuzumab Fixed-dose Combination for Subcutaneous Administration

Pertuzumab and trastuzumab FDC SC represents a combination of both anti-HER2 monoclonal antibodies in a single drug product. A Phase III, randomized, multicentre, open-label, two-arm study comparing the PK, efficacy, and safety of pertuzumab and trastuzumab FDC SC with P+H IV as neo/adjuvant treatment with chemotherapy (doxorubicin and cyclophosphamide followed by a taxane) for EBC is currently underway with 500 patients planned for enrolment (Roche Study WO40324).

As described in Section 1.2.2, Perjeta IV is approved for administration with Herceptin IV and Herceptin SC. Improvement in disease outcomes with combined P+H IV versus Herceptin alone has been shown in neoadjuvant and adjuvant studies in HER2+ EBC. In the randomized Phase II NEOSPHERE (Roche Study WO20697), patients receiving neoadjuvant Perjeta plus Herceptin and standard chemotherapies had a higher pCR rates (39.3%) over patients receiving neoadjuvant Perjeta IV or Herceptin IV with standard

chemotherapy (17.7% or 21.5%, respectively) [Gianni et al. 2012]. In the adjuvant setting, the Phase III APHINITY study (Roche Study BO25126) compared adjuvant P+H IV and standard chemotherapy to adjuvant placebo plus Herceptin IV and standard chemotherapy. The study found a statistically significant improvement in IDFS with a hazard ratio of 0.81 (95% confidence interval [CI], 0.66 to 1.00; p = 0.045) in favour of the Perjeta IV arm [von Minckwitz et al. 2017]. In each of these studies, combined treatment with Perjeta and Herceptin were found to be well tolerated.

Herceptin for SC administration (Herceptin SC, see Section 1.2.3) has been shown to be as safe and effective as Herceptin for IV administration in a Phase III, randomized, open-label, non-inferiority study of neo/adjuvant treatment for HER2+ early EBC (Roche Study BO22227). In that study, Herceptin was administered every 3 weeks at a fixed dose of 600 mg (SC arm) or at an 8 mg/kg loading dose followed by 6 mg/kg maintenance dose (IV arm). Analyses of the co-primary endpoints (pCR and serum trough concentration [C_{trough}]) found Herceptin SC non-inferior to Herceptin IV with respect to both PK profile and efficacy [Ismael et al. 2012]. Immunogenicity evaluations found 53 patients in Herceptin SC arm (n=297) had at least one anti-Herceptin anti-drug antibody (ADA) positive result post-baseline whereas 33 patients in Herceptin IV arm (n=299) had at least one positive ADA result post-baseline. However, exploratory analyses suggested that the occurrence of anti-Herceptin ADAs had no clinical consequences with respect to PK, efficacy (patients with and without ADAs had similar pCR, OS, and event-free survival [EFS] rates), or safety. Analyses of EFS and OS conducted after median follow-ups of approximately 40 and 71 months supported the non-inferiority of Herceptin SC. At 40 months, the unstratified hazard ratios for EFS and OS were 0.95 (95% CI 0.69-1.30) and 0.76 (95% CI 0.44-1.32), respectively. At 71 months, the EFS and OS rates were 65% and 84% in both arms, respectively. During the study treatment period, the overall safety profile and tolerability in the IV and SC arms were consistent with that expected from combination treatment with chemotherapy and Herceptin. Safety findings in the follow-up analyses were also consistent with the known safety profile of Herceptin IV [Jackisch et al. 2016, Herceptin Investigator's Brochure, v18, 2017].

Patient reported preference for Herceptin SC (delivered via single-use injection device or handheld syringe and needle from a vial) over Herceptin IV was evaluated in a Phase II randomized, multi-centre, open-label, crossover study in over 480 patients with HER2+ EBC (Roche Study MO22982). The study found the majority (88.9%) of patients strongly preferred Herceptin SC over Herceptin IV. Results from questionnaires completed by healthcare professionals (HCPs) during the study indicated that HCPs were most satisfied with Herceptin SC administration compared with Herceptin IV administration. Healthcare professionals also reported notable time savings with Herceptin SC administration. Safety and efficacy (3-year EFS) were comparable among the study arms [Herceptin Investigator's Brochure, v18, 2017].

Pertuzumab formulated for SC administration is being tested in an ongoing open-label, two-part, multicentre dose-finding / dose confirmation study (Roche Study BO30185). In part 1 of the study, two pertuzumab formulations were assessed in healthy male volunteers: pertuzumab given as a single-agent SC injection (for eventual use in co-administration with Herceptin SC single-agent injection) and pertuzumab formulated for SC administration co-mixed with Herceptin SC in a single injection. Pertuzumab doses selected for evaluation with

SC administration in this study were based on IV-administered pertuzumab population PK modelling incorporating values of SC-administered trastuzumab PK parameters. In part 1 of Study BO30185, a 600 mg dose of pertuzumab SC was found to provide similar C_{trough} and area under the curve (AUC) as Perjeta IV delivered at a 420 mg dose. Part 2 of Study BO30185 includes confirmation of the 600 mg pertuzumab SC dose when administered with Herceptin SC co-mixed or as FDC in female EBC patients who have completed standard adjuvant treatment. Pertuzumab SC 600 mg (co-mixed and FDC) in EBC patients was confirmed to provide similar C_{trough} and AUC to 420 mg Perjeta IV in healthy male volunteers enrolled in study part 1. Dose proportionality through PK linearity is considered to confirm a pertuzumab 1200 mg SC loading dose [Perjeta Investigator's Brochure, v17, 2018].

Study BO30185 safety data are available for the healthy volunteer cohorts in part 1 and for part 2 EBC cohorts receiving pertuzumab SC co-administered or co-mixed with Herceptin SC. The safety results are generally consistent with prior experience with combined treatment with P+H IV. Treatment in the final study cohort evaluating pertuzumab and trastuzumab FDC SC in EBC is ongoing [Perjeta Investigator's Brochure, v17, 2018].

Herceptin SC, pertuzumab for SC administration, and pertuzumab and trastuzumab FDC SC are each formulated with 2000 U/mL human recombinant PH20 hyaluronidase (rHuPH20). The excipient acts as a permeation enhancer to allow SC administration of higher drug volumes. The concentration of rHuPH20 for these SC formulations was based on preclinical studies in mini-pigs (an animal model selected due to its similarities with human skin structure) and has been tested and found safe in clinical studies [Pivot et al. 2013, Rummel et al. 2017]. Human recombinant PH20 hyaluronidase included in formulations of human immunoglobulin, humanized monoclonals, and insulin has been found to induce only modest immunogenicity with no associated adverse events (AEs) [Rosengren et al. 2015]. Consistent with these findings, anti-rHuPH20 antibodies were detected in Study BO22227 of Herceptin SC, however, exploratory analyses suggest that their occurrence does not affect PK or safety [Herceptin Investigator's Brochure, v18, 2017].

For further details of non-clinical and clinical studies with Herceptin SC, please refer to the Herceptin Investigator's Brochure. For further details of non-clinical and clinical studies with Perjeta SC and pertuzumab and trastuzumab FDC SC, please refer to the Perjeta Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

Treatment with P+H IV has been shown to be efficacious in both early and advanced metastatic HER2+ breast cancer and dual HER2 blockade with these agents has become standard of care in the neoadjuvant, adjuvant and metastatic settings (see Sections 1.1 and 1.2.4). Herceptin SC, which has been shown to have a similar safety profile and non-inferior efficacy to Herceptin IV, can be administered more quickly and without requirement for IV access. The relative appeal of SC administration over IV administration and the reduction in time and resource use with SC administration have been reported by breast cancer patients and HCPs, respectively (see Section 1.2.4).

Given the potential involvement of multiple treatment modalities including repeated IV administration of multiple systemic agents, standard therapy for EBC can be a complex and taxing experience for any patient. The requirements for individual drug preparation, sequential infusion periods and observation periods also result in greater use of limited medical resources. The development of an FDC SC formulation of pertuzumab and trastuzumab provides an opportunity to build on the improvements achieved by Herceptin SC by further reducing the burden associated with treatment for HER2+ breast cancer. By formally assessing, from the patients' perspective, whether FDC SC administration of pertuzumab and trastuzumab is preferable to two separate, consecutive IV administrations, this study will provide patient experience data to supplement the results of the ongoing Roche Phase III WO20324 study comparing the PK, efficacy, and safety of these regimens. This study will also document HCP reported perceptions of resource use with FDC SC administration to evaluate the impact of co-formulation and SC delivery on clinical resources. Study safety analyses will further characterize safety profiles of SC administration of co-formulated pertuzumab and trastuzumab as well as the safety of switching from P+H IV to pertuzumab and trastuzumab FDC SC and vice versa. The measurement of secondary efficacy endpoints in this study will further investigate the potential effects of switching study treatments on disease outcomes.

1.3.2 Benefit-Risk Assessment

As described in Section 1.2.4, the safety and efficacy of Herceptin SC has been shown to be consistent with Herceptin IV with no safety issues attributable to the route of administration or to formulation with rHuPH20. Pertuzumab dosing in the FDC SC formulation has been selected to provide similar PK as approved Perjeta IV dosing. No new safety issues have been seen in clinical evaluation of co-infused Perjeta IV and Herceptin IV preparations (see Section 1.1). Ongoing clinical evaluation of co-administered and co-formulated SC preparations conducted by the Sponsor has also found no safety issues that would not be expected with sequential IV administrations (see Section 1.2.4).

This study is being conducted in HER2+ EBC patients for whom combined treatment with Perjeta IV and Herceptin is indicated. As summarized above, the benefit-risk of incorporating pertuzumab and trastuzumab FDC SC into study participants' anti-HER2 regimen is based on the demonstrated non-inferiority of Herceptin SC PK profile and efficacy (as assessed by pCR rate) with respect to Herceptin IV, the equivalent bioavailability of pertuzumab SC and IV formulations and the consistency of safety profiles among IV, SC, and FDC SC formulations.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate patient reported preference for pertuzumab and trastuzumab FDC SC in HER2+ EBC. The study will also evaluate patient reported satisfaction with pertuzumab and trastuzumab FDC SC; HCP reported perception of time/resource use and convenience of pertuzumab and trastuzumab FDC SC and P+H IV; patient reported health-related quality of life (HRQoL); the safety of each study regimen alone and within the context of the order in which they are administered; as well as efficacy in each treatment arm.

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective for this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC on the basis of the following endpoint:

- Proportion of patients who preferred pertuzumab and trastuzumab FDC SC with treatment preference assessed via Question 1 of the Patient Preference Questionnaire (PPQ).

2.1.2 Secondary Objectives

Secondary objectives for this study are to evaluate:

- Patient assessed satisfaction with pertuzumab and trastuzumab FDC SC and P+H IV based on patient responses to Question 1 of the Therapy Administration Satisfaction Questionnaire – subcutaneous (TASQ-SC) and TASQ – intravenous (TASQ-IV)
- Patients' choice of pertuzumab and trastuzumab FDC SC for the Treatment Continuation Period based on the proportion of patients who select pertuzumab and trastuzumab FDC SC for this study period
- HCP perception of time/resource use and convenience with pertuzumab and trastuzumab FDC SC based on HCP responses to the Healthcare Professional Questionnaires (HCPQs), by individual question
- HRQoL with pertuzumab and trastuzumab FDC SC and P+H IV based on change in symptoms and function from baseline and over time as assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) scores, and mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status / overall quality of life (QoL) scale (items 29 and 30) of the EORTC QLQ-C30.

2.1.2.1 Secondary Safety Objectives

There are two secondary safety objectives for this study. The first is to evaluate the safety and tolerability of pertuzumab and trastuzumab FDC SC and P+H IV during the study Treatment Cross-over Period and the entire adjuvant treatment period (Treatment Cross-over Period + Treatment Continuation Period) based on the following endpoints:

- Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, serious adverse events (SAEs) and cardiac AEs (including left ventricular ejection fraction [LVEF] events)
- Incidence of premature withdrawal from study treatment
- Targeted vital signs and physical findings
- Targeted clinical laboratory test results

The second safety objective for this study is to evaluate the safety of switching from pertuzumab and trastuzumab FDC SC to P+H IV and from P+H IV to pertuzumab and trastuzumab FDC SC based on:

- Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, SAEs and cardiac AEs (including LVEF events) during the study Treatment Cross-over Period by treatment arm.

For all safety endpoints, AE severity will be determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0)

2.1.2.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the long-term efficacy of the pertuzumab and trastuzumab FDC SC and P+H IV based on the following endpoints:

- Invasive disease-free survival, defined as the time from randomization to the first occurrence of one of the following events:
  - Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
  - Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)
  - Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
  - Contralateral invasive breast cancer
  - Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible)

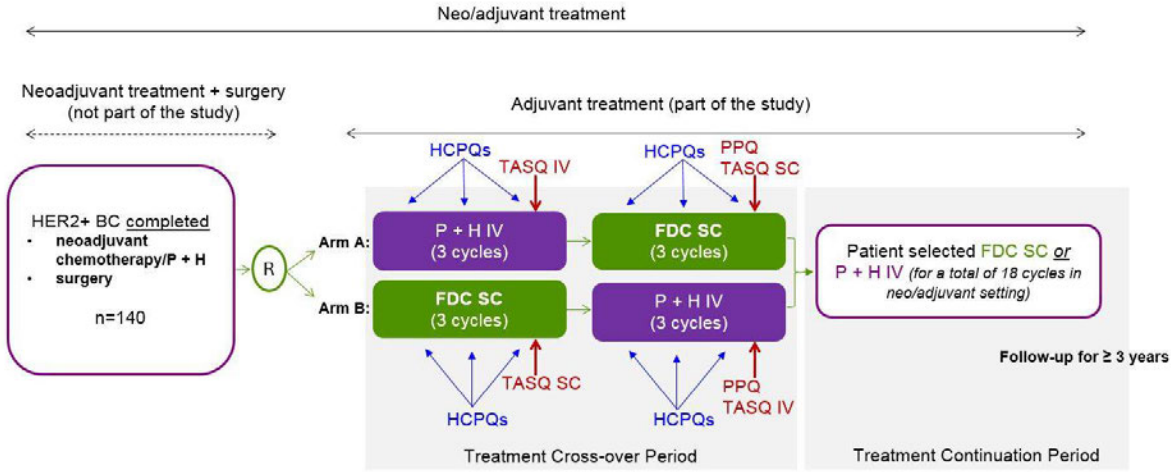
  Note: Ipsilateral or contralateral *in situ* disease and second primary non-breast cancers (including *in situ* carcinomas and non-melanoma skin cancers) will not be counted as recurrence.
- Invasive disease-free survival including second primary non-breast cancer, defined as IDFS with second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and *in situ* carcinoma of any site) included as an event
- Distant disease-free survival (DDFS), defined as the time from randomization to the date of distant breast cancer recurrence
- OS, defined as the time from randomization to death from any cause.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, randomized, multi-centre, multinational, open-label, cross-over study in adult patients who have completed neoadjuvant chemotherapy with neoadjuvant Perjeta and Herceptin and have undergone surgical treatment of HER2+ EBC. An overview of the study design is provided in Figure 1.

Figure 1 Study Schema



Abbreviations: IV: intravenous; P+H: Perjeta + Herceptin; FDC SC: subcutaneously administered fixed-dose combination of pertuzumab and trastuzumab; HCPQ: Healthcare Professional Questionnaires; PPQ: Patient Preference Questionnaire; SC subcutaneous; TASQ: Therapy Administration Satisfaction Questionnaire

Eligibility will be assessed within a 28-day screening period. Eligible patients will be enrolled and randomly allocated in a 1:1 ratio to treatment Arm A (P+H IV followed by pertuzumab and trastuzumab FDC SC) or treatment Arm B (pertuzumab and trastuzumab FDC SC followed by P+H IV). Patients will be stratified according to neoadjuvant chemotherapy regimen (anthracyclines + taxanes vs. carboplatin + taxanes vs. taxanes only), neoadjuvant treatment response (pCR vs. non-pCR), and hormone receptor status (oestrogen receptor [ER]-positive and/or progesterone receptor [PgR]-positive vs. ER-negative and PgR-negative). Study treatment will be initiated ≥ 2 weeks from breast cancer surgery but ≤ 9 weeks from the last administration of systemic neoadjuvant therapy and will be administered on Day 1 of each 3-week treatment cycle. No adjuvant chemotherapy is allowed after surgery, however, adjuvant hormone and/or radiation therapy are allowed.

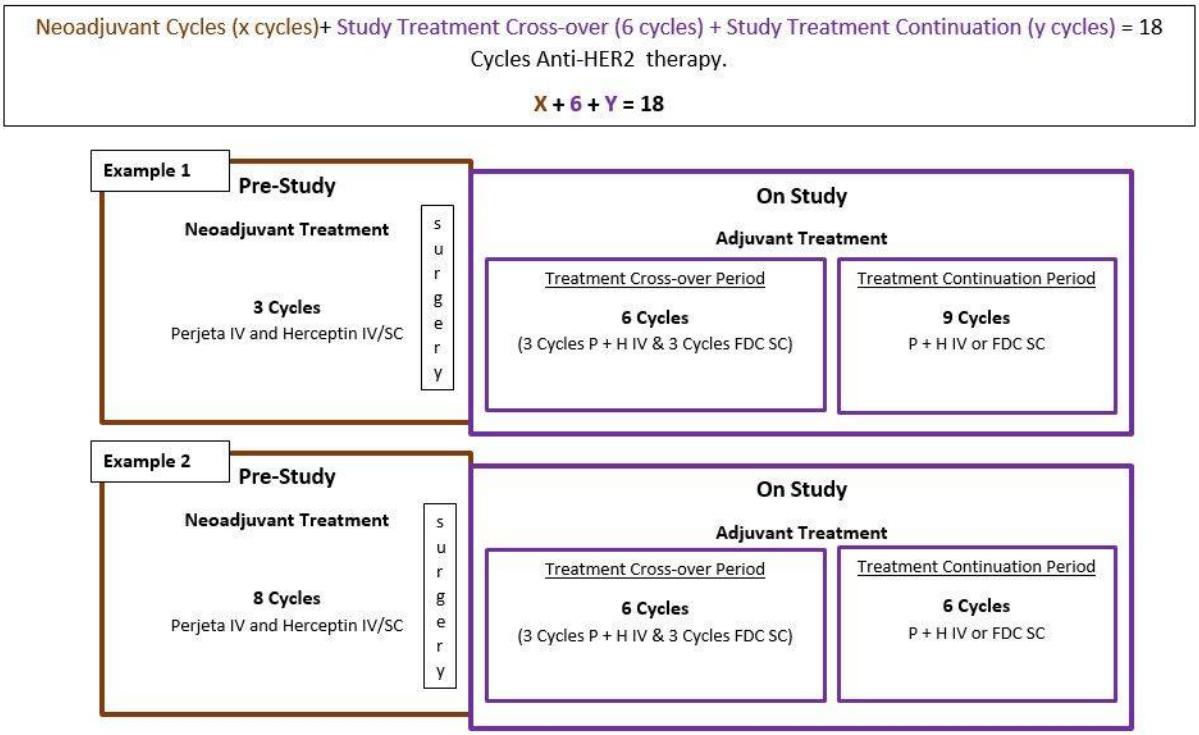
Patients randomized to Arm A will receive P+H IV for three treatment cycles followed by pertuzumab and trastuzumab FDC SC for three treatment cycles. Patients randomized to Arm B will receive pertuzumab and trastuzumab FDC SC for three treatment cycles followed by P+H IV for three treatment cycles. This period of 3+3 cycles in both treatment arms constitutes the study Treatment Cross-over Period.

The 6 study treatment cycles of pertuzumab and trastuzumab FDC SC and P+H IV received during the Treatment Cross-over Period and Perjeta and Herceptin treatment cycles received in the neoadjuvant setting prior to study entry will be considered part of the total 18 anti-HER2 treatment cycles planned for all study patients. Following completion of the Treatment Cross-over Period, patients will enter the Treatment Continuation Period wherein they will receive the remaining anti-HER2 treatment cycles required to complete their 18 planned cycles unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early treatment cessation. Study treatment during this period will be either P+H IV or pertuzumab and trastuzumab FDC SC as selected by the patient at the end of the Treatment Cross-over Period. See Figure 2 for examples of calculating the number of

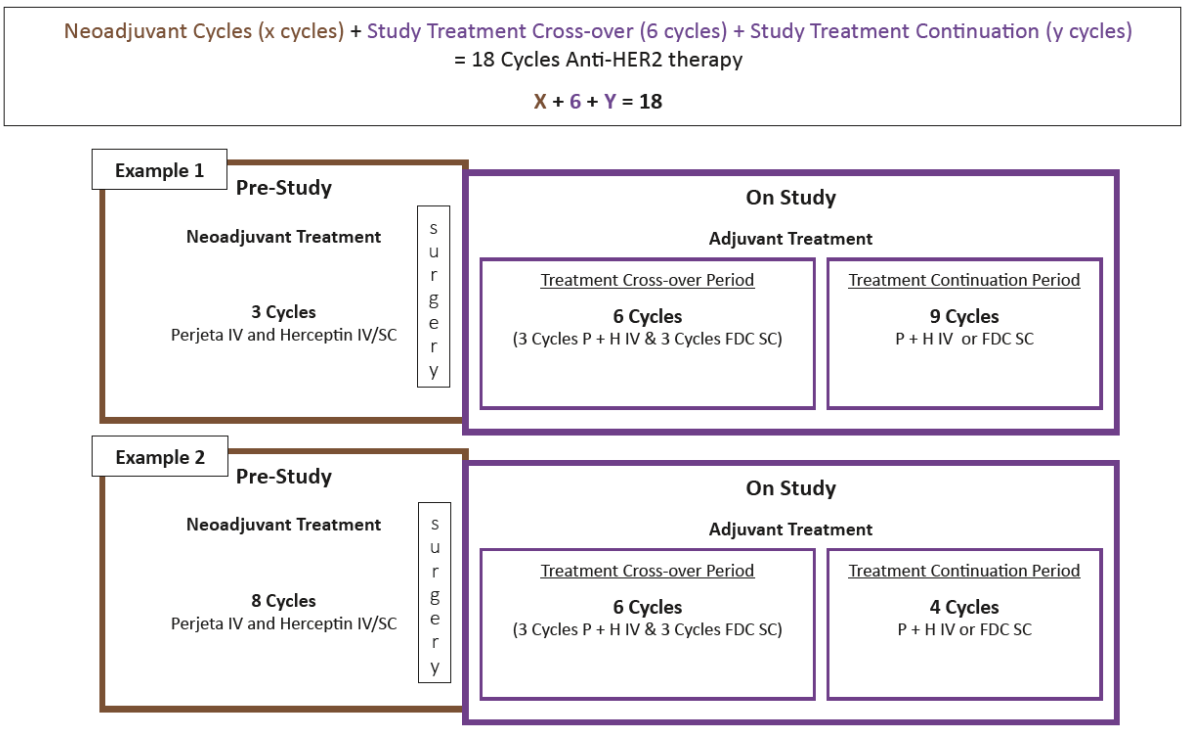
study treatment cycles required during the Treatment Continuation Period. Patients will be followed for at least three years from randomization (the Follow-up Period) during which time they should be assessed at least every six months.

Figure 2 Study Treatment Cycle Calculation

OLD FIGURE



NEW FIGURE



Patients who, by the investigator's assessment, cannot tolerate pertuzumab and trastuzumab FDC SC or P+H IV may be allowed to receive P+H IV or pertuzumab and trastuzumab FDC SC, respectively, for their remaining planned anti-HER2 treatment cycles. The investigator must obtain approval from the Medical Monitor to switch study treatment.

Patient preference will be assessed based on the PPQ (administered following treatment administration on Day 1, Cycle 6 of the Treatment Cross-over Period). Treatment satisfaction will be assessed based on the TASQ (administered following treatment administration on Day 1 of Cycles 3 and 6 of the Treatment Cross-over Period). Healthcare professionals will record their perception of time/resource use and convenience of treatment administration completing the HCPQs. Perception of time use will be captured during the Treatment Cross-over Period and perception of convenience will be captured after administration of each patient's treatment Cycle 6. Health-related quality of life will be assessed based on EORTC QLQ-C30 completed at baseline, Cycle 3, Cycle 6, and the end of study treatment visits, as well as at 18 months, 2 years, and 3 years from randomization. The study questionnaires are provided in Appendix 2 and Appendix 3.

Patients will be assessed for safety by regular evaluation of AEs, vital signs, routine clinical laboratory tests (haematology, blood chemistry) and LVEF assessments; and by physical examinations. Adverse events will be reported and graded according to the NCI CTCAE v4.0. Efficacy will be assessed based on investigator-evaluated disease status determined according to assessments conducted per institutional practice or according to the American Cancer Society / American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4].

Patients will undergo an End of Treatment Visit approximately 28 days after completing study treatment and will enter the Follow-up Period wherein they will be followed for disease status, survival and HRQoL (via the EORTC QLQ-C30) for 3 years from the date the last patient is randomized. The study Schedule of Activities is provided in Appendix 1.

Approximately 140 patients from approximately 42 study sites worldwide will be randomized in the study. Patients who withdraw from the study following randomization will not be replaced. Patients can be screened for the study more than once.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined the Last Patient, Last Visit (LPLV) which will occur three years after the last patient is randomized or the date at which the last data point required for the final statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

In addition, the Sponsor may decide to terminate the study at any time.

The study is estimated to last approximately 4 years, based on a recruitment period of up to 10 months and 3 years of follow-up after the last patient is randomized.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Perjeta IV, Herceptin IV, and Pertuzumab and Trastuzumab FDC SC Doses and Schedules

Perjeta IV and Herceptin IV loading and maintenance doses in the study are the approved doses for the treatment of EBC.

Pertuzumab and trastuzumab FDC SC maintenance and loading doses in the study are based on the approved dose of Herceptin SC (600 mg Herceptin with no loading dose required), clinical studies of pertuzumab showing similar C_{trough} and AUC with pertuzumab SC 600 mg and Perjeta IV 420 mg (Study BO30185), and dose proportionality of pertuzumab 1200 mg SC confirmed through PK linearity (see Section 1.2.4).

Both the loading and maintenance doses of pertuzumab and trastuzumab FDC SC include 2000 U/mL rHuPH20. The concentration of this excipient is the same as in the approved Herceptin SC formulation and has been tested in the aforementioned Study BO30185 (see Section 1.2.4).

The scheduling of all IMPs (every 3 weeks with loading doses required if ≥ 6 weeks since last administration of HER2-targeted therapy) are based on PK studies comparing IV and SC administrations of each molecule (Study BO22227, Study BO30185) and the approved scheduling for Perjeta IV, Herceptin IV and Herceptin SC.

3.3.2 Rationale for Patient Population

Early breast cancer patients who have received neoadjuvant Perjeta IV and Herceptin and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer were selected as the target population for this study since continued dual HER2+ blockade with Perjeta and Herceptin is standard of care in these patients. The completion of chemotherapy prior to study entry limits the influence of chemotherapy administrations and related toxicity on study endpoints. Patients will be allowed to receive adjuvant radiotherapy and/or hormone therapy during the study as these treatments will be indicated in some cases.

3.3.3 Rationale for Randomization Stratification Factors

To include as wide a population as possible while limiting imbalances that may affect study outcomes, randomization will be stratified. Since neoadjuvant treatment selections are associated with varying toxicities and disease outcomes, randomization will be stratified for neoadjuvant chemotherapy regimen (anthracyclines + taxanes vs. carboplatin + taxanes vs. taxanes only).

Randomization will also be stratified for neoadjuvant treatment response (pCR vs. non-pCR) and hormone receptor status (positive vs. negative) due to the associations of these factors with disease outcomes. Complete pathological response to neoadjuvant treatment has been shown to predict for improved disease outcomes in HER2+ EBC [Gianni et al. 2016]. Differences in treatment response with hormone receptor status have also been shown in HER2+ EBC trials of Herceptin and P+H IV [Cameron et al. 2017; Study BO25126 - see Perjeta Investigator's Brochure 2018].

3.3.4 Rationale for Randomized Cross-over Design

The primary objective of this study is to assess patient reported preference for pertuzumab and trastuzumab FDC SC. Patients will be randomized to receive either pertuzumab and trastuzumab FDC SC for three treatment cycles followed by P+H IV for three treatment cycles versus receiving P+H IV first, followed by pertuzumab and trastuzumab FDC SC. Patients in both treatment groups will then choose either IV or SC administered IMPs for their remaining HER2-targeted treatment cycles.

Randomization accommodates potential treatment sequencing-related differences such as in the nature and/or frequency of administration-related reactions (ARRs) with either administration route (e.g. if ARRs to IV formulation occur more frequently following the treatment break for surgery and/or with a loading dose) or in AEs attributable to switching administration routes. At the same time, the cross-over design provides exposure to both study regimens allowing each patient to act as their own control for patient reported outcomes (PROs) measured after study Cycle 3 and study Cycle 6.

3.3.5 Rationale for Patient Reported Outcome Assessments

Early breast cancer is often asymptomatic, especially after tumour removal, thus it is important to assess treatment impact and tolerability to inform the benefit-risk ratio for a patient on adjuvant therapy. The PPQ used to assess the primary study endpoint has been developed in clinical trials assessing patient preference for SC administered monoclonal antibodies. An interview-based assessment was first developed to assess patient preference for Herceptin SC in a clinical trial of adjuvant Herceptin SC and IV in HER2+ EBC [Study MO22982, Pivot et al. 2013]. Interview questions were based on input from experienced clinicians, chemotherapy nurses and psychologists and were tested with patient volunteers prior to use in the study. The three interview questions identified as most informative in the Herceptin MO22982 study were then administered as the patient-completed PPQ in a subsequent lymphoma study evaluating preference for SC or IV administered rituximab [PrefMab study, Rummel et al. 2017]. Notably, PPQ endpoints collected in this study were considered adequate evidence for preference claims included in rituximab SC product labelling [Rituxan Hycela™ Package Insert 2017]. The TASQ questionnaires used in this study have been adapted from administration satisfaction questionnaires used in the aforementioned PrefMab study.

Health-related quality of life evaluations in this study will contextualize a patient's experience on trial, elucidating symptom and treatment burden between P+H IV and pertuzumab and trastuzumab FDC SC. Because treatment-related side effects have the potential to affect patient functioning and HRQoL, it is crucial to characterize not only the incidence of these side effects but also the associated trends and burden from the patient's perspective, which would contribute to a more comprehensive understanding of treatment impact and tolerability. The EORTC QLQ-C30, is a well-known and commonly used questionnaire with strong demonstrated psychometric properties of both reliability and validity.

4. MATERIALS AND METHODS

4.1 PATIENTS

Adult patients with HER2+ EBC who have received neoadjuvant Perjeta and Herceptin, and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer will be enrolled in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-specific criteria

- Female or male with histologically confirmed, HER2+ inflammatory, locally advanced or early-stage breast cancer who have received neoadjuvant Perjeta + Herceptin and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer.

  Note: The neoadjuvant chemotherapy regimen (including type and sequencing of selected agents) and the number of neoadjuvant Perjeta and Herceptin treatment cycles are at the discretion of the treating physician and patient. Subcutaneously administered Herceptin may have been used in the neoadjuvant setting. The use of any trastuzumab biosimilars in the neoadjuvant setting is not allowed.
- HER2+ breast cancer assessed at the local laboratory prior to initiation of neoadjuvant therapy. HER2+ status must be determined based on breast biopsy material obtained prior to neoadjuvant treatment and is defined as 3+ by immunohistochemistry (IHC) and/or positive by HER2 amplification by *in situ* hybridization (ISH) with a ratio of ≥ 2 for the number of HER2 gene copies to the number of chromosome 17 copies
- Hormone receptor status of the primary tumour determined by local assessment. Hormone receptor ~~positive~~ status may be either positive (i.e. ER-positive and/or PgR-positive) or negative (i.e. ER-negative and PgR-negative)
- Completed all neoadjuvant chemotherapy and surgery. Adjuvant radiotherapy may be planned or ongoing at study entry and adjuvant hormone therapy is allowed during the study. Note that study treatment cannot be initiated within < 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.
- No evidence of residual, locally recurrent or metastatic disease after completion of surgery. Patients with clinical suspicion of metastases must undergo radiological assessments per institutional practice to rule out distant disease.
- Wound healing after breast cancer surgery adequate per investigator's assessment to allow initiation of study treatment within ≤ 9 weeks of last systemic neoadjuvant therapy
- No adjuvant chemotherapy planned. Note that adjuvant hormonal treatment is allowed during the study.

General criteria

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form

- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG; see Appendix 5) performance status 0 or 1
- Intact skin at planned site of subcutaneous injections (thigh)
- LVEF ≥ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within 28 days of study randomization
- No major surgical procedure unrelated to breast cancer within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year, or 2 effective non-hormonal contraceptive methods during the study treatment periods and for 7 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a post-menopausal state (post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and copper intrauterine devices (IUDs).

  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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the study treatment periods and for seven months after the last dose of study treatment 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.
- A negative serum pregnancy test must be available prior to randomization for women of childbearing potential (defined as post-menarchal, has not had ≥ 12 continuous months

of amenorrhea with no identified cause other than menopause, and has not undergone surgical sterilization [removal of ovaries and/or uterus])

4.1.2 Exclusion Criteria

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

Cancer-specific criteria

- Stage IV (metastatic) breast cancer
- Current or prior history of active malignancy (other than current breast cancer) within the last five years. Appropriately treated non-melanoma skin cancer; *in situ* carcinomas, including cervix, colon, or skin; or Stage I uterine cancer within the last five years are allowed.

  A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than five years.
- Previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective oestrogen receptor modulators, aromatase inhibitors], and antitumor vaccines) for treatment or prevention of breast cancer, except neoadjuvant Perjeta, Herceptin and chemotherapy for current breast cancer

General criteria:

- Investigational treatment within four weeks of enrolment
- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE v4.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class ≥ II
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate ≥ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz II] or third-degree AV-block)
  - Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication
  - Angina pectoris requiring anti-angina medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on electrocardiogram (ECG)
  - Evidence of myocardial infarction within 12 months prior to randomization
  - Poorly controlled hypertension (e.g., systolic > 180 mm Hg or diastolic > 100 mmHg)
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalaemia, hypomagnesemia, hypocalcaemia), or family history of sudden unexplained death or long QT syndrome

- Inadequate bone marrow function, defined by any of:
  - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
  - Platelet count < 100 x 10^9/L
  - Haemoglobin < 9 g/dL
- Impaired liver function, defined by any of:
  - Serum (total) bilirubin > 1.25 x upper limit of normal (ULN). In case of Gilbert's syndrome: a total bilirubin of 2 x ULN is permitted.
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 1.25 x ULN
  - Albumin < 25 g/L
- Inadequate renal function with serum creatinine > 1.5 x ULN
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Pregnant or breastfeeding, or intending to become pregnant during the study or within seven months after the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in, and completion of, the study
- Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
- Concurrent, serious, uncontrolled infections, or known infection with human immunodeficiency virus (HIV)
- Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

4.2 METHOD OF TREATMENT ASSIGNMENT

Eligible patients will be randomly allocated at study entry to either Arm A (P+H IV followed by pertuzumab and trastuzumab FDC SC) or Arm B (pertuzumab and trastuzumab FDC SC followed by P+H IV).

Randomization will occur via a web-based response system (IWRS) in a 1:1 ratio. Randomization will be stratified according to neoadjuvant chemotherapy regimen (anthracyclines + taxanes vs. carboplatin + taxanes vs. taxanes only), neoadjuvant treatment response (pCR vs. non-pCR), and hormone receptor status (positive [ER-positive and/or PgR-positive) or negative [ER-negative and PgR-negative]).

4.3 STUDY TREATMENT

The IMPs for this study are pertuzumab and trastuzumab FDC SC (loading dose configuration and maintenance dose configuration), Perjeta IV and Herceptin IV. All study drugs will be provided by the Sponsor free of charge.

Study drug supplies will be labelled in accordance with applicable legal requirements and will be printed in the local language. The storage conditions for each study drug will be described on the medication label. Study drug supplies should not be used beyond the expiration date provided by the manufacturer.

Please refer to the Pharmacy Manual for all instructions pertaining to study drug supply and management.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Pertuzumab and Trastuzumab FDC SC

A loading and maintenance dose of pertuzumab and trastuzumab FDC SC will be provided in the following configurations as single vials:

- Loading dose: a sterile solution for injection containing L-histidine hydrochloride, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each single use 20 mL glass colourless vial contains 1200 mg of pertuzumab and 600 mg of trastuzumab in 15 mL of solution.
- Maintenance dose: a sterile solution for injection containing L-histidine hydrochloride, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each single use 15 mL colourless glass vial contains 600 mg of pertuzumab and 600 mg of trastuzumab in 10 mL of solution.

For information on the packaging, handling and storage of pertuzumab and trastuzumab FDC SC, see the Pharmacy Manual and Perjeta Investigator's Brochure.

4.3.1.2 Perjeta IV

Perjeta IV is provided as a sterile, preservative-free, single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate, 120 mM sucrose, and 0.02% (w/v) polysorbate 20 at pH 6.0. Each 20 mL vial contains 420 mg of pertuzumab (14.0 mL/vial).

For information on the packaging, storage and dispensing of Perjeta IV, see the current Perjeta Investigator's Brochure and Summary of Product Characteristics (SmPC).

4.3.1.3 Herceptin IV

Herceptin IV is provided in single or multi-dose freeze-dried preparations containing nominal trastuzumab amounts of 150 mg/vial or 440 mg/vial, respectively. The drug is formulated in histidine/histidine-HCl; α, α-trehalose dehydrate; and polysorbate 20.

For information on the packaging, storage, and dispensing of Herceptin IV, see the current Herceptin Investigator's Brochure and SmPC.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1 and below.

With the exception Herceptin IV dosing which should be modified for changes in body weight > 10%, study treatment doses should not be modified. No dose reductions are allowed for Perjeta IV, Herceptin IV or pertuzumab and trastuzumab FDC SC. If an accidental overdose or medication error occurs, it should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated AEs, should also be reported as described in Section 5.4.4.

Guidelines for treatment interruption or discontinuation for patients who experience AEs are provided in Section 5.1.

4.3.2.1 Pertuzumab and Trastuzumab FDC SC

Pertuzumab and trastuzumab FDC SC is given as a fixed dose (i.e. non-weight based). Two doses of pertuzumab and trastuzumab FDC SC may be administered in the study: a 15 mL loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab and a 10 mL maintenance dose consisting of 600 mg pertuzumab and 600 mg trastuzumab. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Perjeta IV and Herceptin (IV or SC) at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

All pertuzumab and trastuzumab FDC SC doses are administered by SC injection by the investigator or their designee over 5 – 8 minutes at a rate of ≤ 2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. Patients should be monitored for 30 minutes after their first pertuzumab and trastuzumab FDC SC dose administration regardless of whether a loading dose is required. Patients should be monitored for 10 – 15 minutes following subsequent administrations. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

4.3.2.2 Perjeta IV

Perjeta IV is administered at a dose of 840 mg (loading dose) or 420 mg (maintenance dose) on Day 1 of each 3-week treatment cycle and should be administered prior to Herceptin IV. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Perjeta IV at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

Perjeta IV loading dose (if required) will be administered as a 60-minute infusion (± 10 minutes), followed by an observation period of 60 minutes. If the loading dose infusion is well tolerated, subsequent maintenance doses can be administered over a period of 30 minutes (± 10 minutes) with an observation period of 30 minutes. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements. The observation period should be completed prior to the subsequent Herceptin IV infusion.

4.3.2.3 Herceptin IV

Herceptin IV is administered at a dose of 8 mg/kg (loading dose) or 6 mg/kg (maintenance dose) on Day 1 of each 3-week treatment cycle and should be administered Perjeta IV

infusion and observation period are complete. Patients who have had ≥ 6 weeks since their last neoadjuvant dose of Herceptin IV or Herceptin SC at study entry, or have had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose before continuing with maintenance doses for subsequent administrations.

Herceptin IV loading dose (if required) will be administered as an infusion over approximately 90 (± 10) minutes after which the patient must be observed for 60 minutes. If the loading dose is well tolerated, subsequent maintenance doses can be administered as 30-minute infusions (± 10 minutes) followed by an observation period of 30 minutes. Patients can be observed for longer periods at the discretion of the investigator or if necessary, as per local requirements.

If variation in the patient's weight of ≥ ± 10% compared with study baseline occurs, the Herceptin IV dose will be recalculated. Weight at the time the dose is recalculated will be considered as baseline for subsequent evaluations of degree of weight change with respect to Herceptin IV dose modification requirements.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (pertuzumab and trastuzumab FDC SC, Perjeta IV, Herceptin IV) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor. Any damaged shipments will be replaced.

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 for destruction. 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 Inventory Log.

4.3.4 Continued Access to Pertuzumab and Trastuzumab FDC SC, Perjeta IV and Herceptin IV

Due to the completion of the standard neo/adjuvant course of Herceptin plus Perjeta (18 cycles) within the trial, the Sponsor does not plan to provide the Roche IMPs (pertuzumab and trastuzumab FDC SC, Perjeta IV, Herceptin IV) or any other study treatments or interventions to patients who have completed the study.

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from seven days prior to initiation of study drug until the End of Treatment Visit. After the End of Treatment Visit and until the end of the study, only medications used for the treatment of cancer will be reported. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Adjuvant hormone therapy for breast cancer
- Adjuvant radiotherapy for breast cancer
- Contraception: acceptable methods of contraception must be used when the female patient is of childbearing potential (i.e. is post-menarchal, has not reached a post-menopausal state [post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause], and has not undergone surgical sterilization [removal of ovaries and/or uterus]). Acceptable methods of contraception are described in Section 5.1.3.
- H_1-receptor or H_2-receptor antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics, beta blockers, calcium channel blockers, digoxin, thrombocyte aggregation inhibitors
- Analgesics / anti-inflammatories (e.g., paracetamol / acetaminophen, meperidine, opioids)
- Short-term use of corticosteroids to treat or prevent allergic or infusion reactions are allowed, however, the dose must not exceed > 20 mg/day of dexamethasone (or equivalent) for > 7 consecutive days.
- Standard therapies for pre-existing medical conditions and medical or surgical complications
- Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) at the investigator's discretion
- Blood transfusions at the investigator's discretion
- Gonadotropin-releasing hormone agonists for fertility preservation
- Vitamin and mineral supplements
- Bone density modifying agents (to be used in accordance with the approved labelled indication and/or nationally recognized treatment guidelines)
- Any other medication not included in the list of prohibited medications

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per institutional standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional standard practice. Serious infusion-associated events manifested by dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not

intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Any investigational therapy or agent (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment
- Any anti-cancer treatment other than adjuvant hormone treatment, adjuvant radiotherapy or bone density modifying treatment
- Regular systemic treatment with steroids

  Short-term corticosteroid to treat and prevent allergic or infusion reactions are allowed however the dose must not exceed > 20 mg/day of dexamethasone (or equivalent) for > 7 consecutive days.
- Any systemically active oral, injected, or implanted hormonal method of contraception (see Section 5.1.3 for acceptable contraception methods) except for progesterone-coated IUDs that had been previously implanted
- Hormone-replacement therapy
- Use of erythropoiesis-stimulating agents (e.g., erythropoietin)
- Herbal remedies initiated for cancer treatment. Other herbal remedies are discouraged but permitted and must be reported on the appropriate eCRF.
- Topical oestrogens (including any intra-vaginal preparations), megestrol acetate, and selective ER modulators used with prophylactic intent are prohibited

  Postmenopausal women with significant vaginal discomfort associated with anti-oestrogen therapy may be considered for intermittent use of low-dose topical oestrogens if non-prescription methods are unsuccessful at ameliorating symptoms.

4.5 STUDY ASSESSMENTS

The Schedule of Activities describing study assessments and collection procedures is provided in Appendix 1. Please refer to the Schedule of Activities for frequency and timing of study activities. All study activities must be documented and must be performed as outlined in the Schedule of Activities.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each study treatment; dosing will occur only if clinical assessments and local laboratory test values are acceptable.

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. Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 or 7 days of randomization (as indicated) may be used; such tests do not need to be repeated for screening. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrolment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history will be recorded at baseline and will include: clinically significant diseases within the past five years, surgeries, breast and other cancer history (including prior cancer therapies and procedures), complete cardiovascular history, cardiac risk factors, and reproductive status. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within seven days prior to initiation of study treatment will be recorded.

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

4.5.3 Pathology

Pathology reports from the initial breast cancer diagnosis and from breast cancer surgery will be collected prior to randomization. The report from breast surgery will be used to determine pathological response status for randomization stratification.

Results of HER2 and hormone receptor testing conducted by a local laboratory based on breast tumour tissue obtained prior to initiation of neoadjuvant treatment will be collected to assure study eligibility (HER2) and for randomization stratification (hormone receptor status).

4.5.4 Physical Examinations

A complete physical examination, performed during Screening and other specified visits, should include physical measurements (body weight in kilograms and, at screening only, height in centimetres) and evaluation of the head; eyes; ears; nose; throat; and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations including weight, should be performed at specified post-baseline visits and as clinically indicated. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

During the study Follow-up Period, physical examinations should be completed per institutional practice or the ACS / ASCO Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4].

4.5.5 Vital Signs

Vital signs will include temperature and, with the patient in a seated position, heart rate, respiration rate, and systolic and diastolic blood pressure.

4.5.6 ECOG Performance status

Performance status will be assessed according to ECOG definitions provided in Appendix 5.

4.5.7 Clinical Breast Examination

Clinical breast examinations must be performed prior to study entry to assess post-surgery wound healing, eligibility for adjuvant treatment initiation, and to detect residual / recurrent disease. During the study treatment periods clinical breast examinations must be conducted to detect signs of locoregional relapse during the study treatment periods. The examination should be conducted per institutional practice and include examination of the breast, axilla, and supraclavicular fossa. If the patient shows disease progression post-baseline, this should be recorded on the Disease Status eCRF.

During the study Follow-up Period, assessments should be completed per institutional practice or the ACS / ASCO Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4].

4.5.8 Mammograms

Mammograms conducted at the time of diagnosis (before initiation of the neoadjuvant treatment) as well as pre-surgery (if performed) will be collected. Mammograms collected and/or conducted for the study (including pre-neoadjuvant treatment, pre-surgery, and Follow-up Period evaluations) can be replaced by another conventional imaging method such as magnetic resonance imaging (MRI) or ultrasound per institutional practice, at the investigator's discretion, but the same method of assessment must be used for each evaluation for an individual patient. If a mammogram (or acceptable alternative breast imaging evaluation) has been conducted as part of routine care within four months prior to the End of Treatment Visit, it may be used in lieu of the End of Treatment Visit evaluation.

4.5.9 Diagnosis of Breast Cancer Recurrence or Second Primary Cancer

All patients must be followed to assess disease recurrence and second primary cancers. The designation of disease recurrence whether local, regional or distant, or a diagnosis of second primary cancer will be conducted per institutional practice or according to ACS / ASCO Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016; see Appendix 4] but can be made only when clinical, laboratory, radiological and/or histological findings support the diagnosis.

The diagnosis of a breast cancer progression, recurrence or a second primary tumour should be confirmed histologically whenever clinically possible. The earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence. The date of disease recurrence should be reported as the date of first diagnosis of a lesion (i.e. an objective finding), not the date of occurrence of the first symptom.

Recurrent disease includes local, regional, and distant recurrence and contralateral invasive breast cancer. Patients who are diagnosed with *in situ* breast disease or second (non-breast) malignancies should be maintained in regular follow-up wherever possible to fully capture any subsequent recurrent breast cancer events. In cases of diagnostic doubt (e.g. ill-defined, palpable mass in an irradiated breast), histologic or cytologic confirmation of recurrence should be obtained whenever possible.

Some patients may develop a suspicious recurrence that leads quickly to death without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such patients.

4.5.10 Cardiac Function

Prior to study enrolment, patients must have an assessment for history of cardiac events, a physical examination, an ECG (per standard institutional methods), and an LVEF assessment (by ECHO or MUGA) to exclude any cardiac condition that would render them ineligible for participation in this trial. Cardiac function will be assessed locally according to the schedule of activities (see Appendix 1).

All patients must have an LVEF ≥ 55% by ECHO or MUGA scan in order to be eligible for the study. The same LVEF evaluation method should be used throughout the study for each patient and should be performed and assessed by the same assessor if possible. Results of LVEF assessments must be reviewed prior to study treatment administration on the scheduled visit day.

Investigators must be aware of local institutional regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories, and patients in this study require LVEF assessment on more than four occasions within one year.

4.5.11 Laboratory Samples

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

- Haematology: haemoglobin, total white blood count (WBC), ANC / neutrophil count, platelet count.
- Limited biochemistry: alkaline phosphatase; AST; ALT; lactate dehydrogenase (LDH); total bilirubin; creatinine. *Albumin should be measured at Screening for determining patient eligibility.* Bilirubin fractions (direct and indirect) must be included if total bilirubin is greater than ULN.
- Pregnancy test

  For all women of childbearing potential (see Section 4.1.1), pregnancy tests must be performed via serum β-human chorionic gonadotropin (HCG) at baseline and via urine tests thereafter according to Appendix 1 until seven months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. During the study treatment periods, pregnancy test results must be available prior to study treatment administration.

  For women who are not of childbearing potential, documentation must be present in medical history confirming that the patient is not of childbearing potential.

4.5.12 Patient Reported Outcomes

Patient reported outcomes will be collected via paper questionnaires. All questionnaires must be completed in their entirety at the specified timepoints during the study (Appendix 1). The questionnaires will be translated into the local language as appropriate.

4.5.12.1 Patient Preference Questionnaire

The PPQ will be completed by each patient immediately after completion of treatment administration at the scheduled timepoint. Please refer to Appendix 1 for instructions regarding when patients who prematurely discontinue study treatment should complete the PPQ.

4.5.12.2 Therapy Administration Satisfaction Questionnaires

Patient assessed satisfaction with P+H IV and pertuzumab and trastuzumab FDC SC will be evaluated using the TASQ-IV and TASQ-SC, respectively. Each TASQ will be completed by the patient immediately after completion of treatment administration at the scheduled timepoint. Please refer to Appendix 1 for instructions regarding when patients who switch study treatment due to lack of tolerance should complete each TASQ.

4.5.12.3 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

Patient reported HRQoL will be assessed via the EORTC QLQ-C30 administered at specified timepoints throughout the study including during the Follow-up Period.

To ensure instrument validity and that data standards meet health authority requirements, the EORTC QLQ-C30 will be self-administered before the patient and clinician receives any information on disease status and prior to treatment administration on the scheduled visit day.

4.5.13 Healthcare Professional Reported Outcomes

4.5.13.1 Healthcare Professional Questionnaire

Healthcare professional reported perception of time and resource use associated with pertuzumab and trastuzumab FDC SC will be assessed via two HCPQs (see Appendix 3). One HCPQ (HCPQ-Treatment Room) will be completed by an HCP involved in treatment preparation and/or administration in the treatment room where study drugs are administered. The other HCPQ (HCPQ-Drug Preparation Area) will be completed by an HCP involved in study drug preparation. Please refer to each HCPQ in Appendix 3 for personnel qualifying as HCPs for each questionnaire. The HCPQs will be completed by the HCP after preparation and/or administration of the study treatment at each scheduled time point (see Appendix 1).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

- Heart failure (NYHA class III or IV)
- Anaphylaxis associated any of the study drugs
- Patients who experience disease recurrence will be withdrawn from study treatment and treated as clinically indicated, according to local clinical practice

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients who discontinue study treatment prematurely will return to the clinic for an End of Treatment Visit 28 days (± 7 days) of the administration of the last dose of study drug and will continue in the Follow-up Period (see Appendix 1 for additional details). Anti-cancer treatment for patients who have prematurely discontinued study treatment is at the discretion of the investigator as clinically indicated.

4.6.2 Patient Discontinuation from Study

Patients 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 patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source to obtain information about survival status.

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 AEs in this or other studies indicates a potential health hazard to patients
- Patient enrolment 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 study 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 patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Pertuzumab and trastuzumab drug substances in the FDC SC are identical to the drug substances in Perjeta IV, Herceptin IV and Herceptin SC. As described in Section 1.2.4, the safety profiles and tolerability of Herceptin SC and Herceptin IV have been shown to be consistent. As also described in Section 1.2.4, preliminary safety data from healthy volunteers and EBC patients treated with pertuzumab SC co-administered or co-mixed with Herceptin SC are consistent with prior experience with combined treatment with Perjeta IV and Herceptin IV. The safety plans for this study, as well as for the ongoing Phase III Roche Study WO40324 (see Section 1.2.4) comparing pertuzumab and trastuzumab FDC SC with P+H IV, are therefore based on the anticipated safety risks of Herceptin IV and Perjeta IV, alone and in combination, described in the Perjeta and Herceptin Investigator's Brochures.

Measures taken to ensure the safety of patients participating in this study include eligibility criteria designed to exclude patients at higher risk for toxicities and ongoing safety monitoring. Safety monitoring includes assessment of the nature, frequency, and severity of AEs and cardiac function evaluations.

The anticipated important safety risks for pertuzumab and trastuzumab are outlined below. Please refer to the Perjeta and Herceptin Investigator's Brochures for complete summaries of safety information.

5.1.1 Risks Associated with Pertuzumab

5.1.1.1 Hypersensitivity Reactions / Anaphylaxis and Administration-Related Reactions

Like other monoclonal antibodies, Perjeta IV has been associated with ARRs. These include:

- Infusion-related reactions (i.e., a systemic reaction with symptoms such as chills, diarrhoea, fatigue, headache, nausea and pyrexia).

  Such reactions are likely to be due to cytokine release and typically occur during, or very shortly after, the administration of monoclonal antibodies, but they may also show a delayed onset. In general, infusion-related AEs are more frequent and severe with the first infusion, and decrease in number and severity over time. The majority of AEs resolve fully.
- Injection-related reactions with SC administration may manifest themselves as:
  - Systemic reactions, similar to the infusion-related reactions

- Local injection site reactions (ISRs) with signs and symptoms such as erythema, induration, swelling, pain, hypoaesthesia and discomfort

Hypersensitivity reactions / anaphylaxis are systemic reactions caused activation of mast cells and basophils by antigen-bound IgE that results in degranulation and release of inflammatory mediators. Hypersensitivity reactions / anaphylaxis events are likely to start mildly and increase in number and severity over time. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of Perjeta IV. Patients in this study who experience a Grade 4 allergic reaction or acute respiratory distress syndrome (ARDS) should be discontinued from study treatment. Since there is a potential for delayed onset, patients should be instructed to contact the treating physician with any concerns, signs or symptoms subsequent to treatment administration. Administration-related reactions may be difficult to distinguish from hypersensitivity reactions.

In this study, if a loading dose of Perjeta IV is required, it will be given over 60 (± 10) minutes, followed by an observation period of 60 minutes. If the loading dose infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes (± 10) with an observation period of 30 minutes. If symptoms occur, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. The observation period should be completed prior to the subsequent Herceptin IV infusion. Premedication with antipyretics, antihistamines, or corticosteroids may be administered before Perjeta IV administration.

For pertuzumab and trastuzumab FDC SC administration, patients should be monitored for 30 minutes after their first dose regardless of whether a loading dose is required. Patients should be monitored for 10 - 15 minutes following subsequent administrations unless a loading dose is required. If a patient requires a loading dose after their first pertuzumab and trastuzumab FDC SC treatment, they should be monitored for 30 minutes after dosing. If ARRs occur, patients must be monitored until complete resolution of signs and symptoms.

Perjeta IV and pertuzumab and trastuzumab FDC SC will be administered by staff who have immediate access to emergency equipment and are trained to monitor for, and respond to, medical emergencies.

Please refer to the Perjeta Investigator's Brochure for the most recent data related to the risk of hypersensitivity reactions.

5.1.1.2 Symptomatic Left Ventricular Systolic Dysfunction

Similar to trastuzumab, pertuzumab's interaction with HER2 may be associated with a risk of symptomatic LVSD. Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE, Grade 1 and Grade 2) or as a symptomatic decreased in LVEF / CHF (NCI CTCAE, Grade ≥ 3; NYHA Class III or IV). Please refer to Appendix 6 for management of patients with decreased LVEF.

In the Roche pivotal trial WO20698/TOC4129g (CLEOPATRA) in MBC patients, treatment with P+H IV and docetaxel was not associated with increases in the incidence of symptomatic LVSD or LVEF declines compared with placebo in combination with Herceptin IV and docetaxel. The incidence of symptomatic LVSD was 1.5% (6/408) for patients receiving P+H IV and docetaxel (events in the treatment period only) and 1.5% (7/396) in the

placebo arm. Regardless of treatment arm, patients who had received prior anthracyclines or prior radiotherapy to the chest area were at higher risk of decreased LVEF. In the Roche Phase II WO209697 study (NEOSPHERE) of neoadjuvant P+H IV and docetaxel, the incidence of left ventricular dysfunction defined as LVEF decline ≥ 10% to below 50% was higher in the Perjeta IV plus docetaxel-treated groups (7.4% with Perjeta IV plus docetaxel, 8.4% P+H IV plus docetaxel) than the Herceptin IV plus docetaxel treated group (1.9%). An increased incidence of LVEF declines was observed in patients treated in the Perjeta IV plus Herceptin IV and docetaxel. Left ventricular ejection fraction recovered to ≥ 50% in all patients. In the ongoing Roche Phase II WO29217 study (BERENICE; neoadjuvant anthracycline / taxane based regimens given in combination with P+H IV), the overall incidence of LVEF declines and symptomatic LVD in the neoadjuvant period is consistent with previous data in the neoadjuvant setting.

Perjeta has not been studied in patients with the following: a pre-treatment LVEF value of ≤ 50%; a prior history of CHF; decreases in LVEF to < 50% during prior Herceptin adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment, or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

Subjects with significant cardiac disease or baseline LVEF < 55% are not eligible for this study. As in all Perjeta trials, study patients must undergo routine cardiac monitoring by ECHO or MUGA scan. During the screening / baseline period, complete medical history information will be collected from all patients to explore possible risk factors for treatment-associated CHF. Monitoring of LVEF is required while patients are receiving study treatment and up to 24 months following discontinuation of study treatment (see Appendix 1). If symptomatic LVSD (heart failure; SAE of NCI CTCAE v4.0 Grade 3 or 4; NYHA Class III or IV) develops, the patient must be monitored carefully with repeat LVEF assessments. Symptomatic LVSD should be treated and followed according to standard medical practice. Refer to the algorithm in Appendix 6 for decisions regarding the continuation or discontinuation of study treatment based on LVEF assessment in asymptomatic patients.

Please refer to the Perjeta Investigator's Brochure for the most recent data relating to risk of LVSD and CHF.

5.1.1.3 Epidermal Growth Factor Receptor (HER1)-Related Toxicities

Pertuzumab inhibits HER2 heterodimerization with other members of the HER family including HER1/EGFR. As a result, pertuzumab may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors such as diarrhoea, rash and other dermatologic toxicities (e.g., dry skin, pruritus, nail disorders, mucositis).

The most recent data relating to the risk of EGFR-related toxicities are found in the Perjeta Investigator's Brochure.

5.1.1.3.1 Diarrhoea

Diarrhoea has been observed in approximately 60% of patients (treatment-related diarrhoea in 50% of patients) being treated with Perjeta IV in Phase II single-agent studies, and in up to 90% of patients in combination therapy studies. Diarrhoea was NCI CTCAE Grade 1 or 2 in the majority of cases. To prevent dehydration, early treatment of diarrhoea with anti-

diarrheal medication should be considered and patients treated with fluids and electrolyte replacement, as clinically indicated.

5.1.1.3.2 Rash / Skin Reactions

Rash / skin reactions have been observed in approximately 17% of patients treated with Perjeta IV in the Phase II single-agent studies and in up to 73% of patients in combination studies. The rash was generally mild to moderate in intensity and NCI CTCAE Grade 1 or 2.

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

5.1.1.3.3 Mucositis

Mucositis has been observed in approximately 15% of patients treated with Perjeta IV in Phase II single-agent studies and in up to 50% of patients in combination studies. The most common preferred terms reported were mucosal inflammation and stomatitis.

5.1.1.3.4 Interstitial Lung Disease

Interstitial lung disease is associated with the use of EGFR inhibitors and therefore could occur with pertuzumab. The few reports of interstitial lung disease in Perjeta IV-treated patients received to date also had evidence of alternative causes (e.g., concomitant medication, preceding / concurrent neutropenia with potential infection or other relevant medical history).

In the pivotal study WO20698/TOC4129g (CLEOPATRA; Herceptin IV and docetaxel with Perjeta IV or placebo), respiratory events (i.e., dyspnoea, cough), which are unspecific symptoms of various conditions, including infusion-related reaction or hypersensitivity / anaphylaxis, cardiac dysfunction, and respiratory disease, were reported in > 10% of Perjeta IV-treated patients.

5.1.2 Risks Associated with Trastuzumab

Serious adverse reactions, including LVSD, ARRs, hypersensitivity, allergic-like reactions, and pulmonary events, have been observed in patients receiving Herceptin IV and/or SC.

5.1.2.1 Administration-Related Reactions, Allergic-Like Reactions, and Hypersensitivity

Herceptin IV and SC have been associated with ARRs. ARRs are defined as systemic ‘infusion-related reactions’ associated with Herceptin IV and systemic reactions associated with Herceptin SC. In some studies, local ISRs were excluded from the ARR definitions. A revised definition of ARRs potentially associated with IV and SC administration of Herceptin was used in Study BO22227 (see Section 1.2.4) and is applicable to all future and ongoing Herceptin IV and SC studies. This definition is based on a modified version of the anaphylactic reaction Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (as modified by the addition of the following four MedDRA Preferred Terms: hypersensitivity, drug hypersensitivity, infusion-related reaction, and injection-site hypersensitivity). The revised definition of ARRs differs from that in previous studies in the metastatic and early breast cancer settings which reported only ‘infusion reactions’ or

‘infusion-related reactions’ associated with Herceptin administration and makes comparison of the rates of ARRs between studies difficult.

Serious adverse reactions to Herceptin IV that have been reported infrequently include dyspnoea, hypotension, wheezing, bronchospasm, asthma, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. Fatalities have occurred within hours and up to one week following Herceptin IV administration. On very rare occasions, patients have experienced the onset of administration-related symptoms or pulmonary symptoms more than six hours after the start of the Herceptin administration. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who have dyspnoea at rest due to comorbidities may be at increased risk of a fatal ARR therefore should not be treated with trastuzumab. Although such events were not reported in clinical trials with Herceptin SC, caution should be exercised, as these events have been associated with the IV formulation.

These reactions were usually associated with the first administration of Herceptin IV and generally occurred during or immediately following administration. In this study, all patients will be pre-treated with Perjeta IV and Herceptin IV or SC in neoadjuvant phase of their treatment. Due treatment delays necessary for breast cancer surgery, a loading dose of Herceptin IV may be required. If required, the loading dose must be administered over 90 (± 10) minutes, after which the patient must be observed for 60 minutes. If the loading dose infusion is well tolerated, subsequent maintenance doses may be administered over 30 (± 10) minutes, followed by an observation period of 30 minutes. Premedication with antipyretics, antihistamines, or corticosteroids may be administered before Perjeta IV administration (which will occur before Herceptin IV administration).

In Study BO22227, the overall incidence of ARRs in the Herceptin IV arm was 37.2% (111/298) compared with 47.8% (142/297) in the Herceptin SC arm. Most of the ARRs occurred in the neoadjuvant treatment phase, with an incidence of 32.6% in the Herceptin IV arm and 38.4% in the Herceptin SC arm. Fewer ARRs were reported during the adjuvant treatment phase of the study. All but one of the ARRs was Grade 1 or Grade 2 in intensity and the distribution was balanced between the study phases in terms of the most common AEs and MedDRA System Organ Class. There was a higher rate of Herceptin SC injection-site reactions compared with the Herceptin IV infusion (11.1% in Herceptin SC vs. 0.3% in Herceptin IV). With few exceptions, all of these events were of Grade 1 intensity. Serious reactions to Herceptin IV have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids.

In this study, patients should be monitored for 30 minutes after their first pertuzumab and trastuzumab FDC SC dose administration regardless of whether a loading dose is required. Patients should be monitored for 10 - 15 minutes following subsequent administrations unless a loading dose is required. If a patient requires a loading dose sometime after their first pertuzumab and trastuzumab FDC SC dose, they should be monitored for 30 minutes following administration. If ARRs occur, patients must be monitored until complete resolution of signs and symptoms.

Herceptin IV and pertuzumab and trastuzumab FDC SC will be administered by staff with immediate access to emergency equipment who are trained to monitor for, and respond to, medical emergencies.

Please refer to the Herceptin Investigator's Brochure for the most recent data related to the risk of ARRs, allergic-like reactions, and hypersensitivity reactions.

5.1.2.2 Pulmonary Events

Severe pulmonary events have been reported with the use of the Herceptin IV formulation in the post-marketing setting. These events have occasionally been fatal. They may occur as part of an ARR or with delayed onset. In addition, cases of interstitial lung disease, including lung infiltrates, ARDS, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema, and respiratory insufficiency have been reported with Herceptin IV. These events have been most common with the first infusion, and their severity has decreased with subsequent infusions. Serious reactions have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids. Acute respiratory distress syndrome has been reported with a fatal outcome.

Please refer to the Herceptin Investigator's Brochure for the most recent data related to the risk of pulmonary events.

5.1.2.3 Symptomatic Left Ventricular Systolic Dysfunction

Heart failure (NYHA Class II - IV) has been observed in patients who have received Herceptin IV and/or SC alone or in combination with docetaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This event may be moderate to severe and has been associated with death. Risk factors for Herceptin-associated LVSD include increased age, concomitant administration with anthracyclines, and declining LVEF while on Herceptin treatment. If symptomatic cardiac failure develops during treatment, it should be treated with standard medications for this purpose.

The rates of cardiac dysfunction observed in large Herceptin adjuvant trials in EBC are < 4% with event rates comparable across the studies. In Study BO22227 (see Section 1.2.4), the proportion of patients who experienced a significant decrease in LVEF (defined as a drop in LVEF ≥ 10 percentage points to a value of < 50%) was similar in each treatment arm (12 [4.2%] patients in Herceptin IV and 11 [3.8%] patients in Herceptin SC).

Because the half-life of Herceptin IV is approximately 28 - 38 days, Herceptin may persist in the circulation for up to 7 months after the last dose of Herceptin. Patients who receive anthracyclines after the last dose of Herceptin may possibly be at increased risk of LVSD. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks (7 months) after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Most patients who developed heart failure in the Phase III trials of Herceptin IV or SC in MBC and EBC improved with standard medical treatment. This treatment included diuretics, cardiac glycosides, and/or ACE inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on weekly therapy with Herceptin without experiencing additional clinical cardiac events.

Please refer to the Herceptin Investigator's Brochure for the most recent data related to the risk of LVSD.

5.1.3 Reproductive Risks Associated with Pertuzumab and Trastuzumab

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-foetal deaths. However, reproductive toxicity studies with trastuzumab conducted in female cynomolgus monkeys revealed no trastuzumab-related embryotoxicity or effects on foetal development. There are no clinical studies of trastuzumab or pertuzumab in pregnant women. IgGs are known to cross the placental barrier. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Therefore, neither pertuzumab or trastuzumab should be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

Due to these risks, female participants of childbearing potential in this study are tested for pregnancy prior to study entry and must undergo pregnancy testing during the study and, guided be the half-life of Herceptin IV, up to seven months after their last study treatment. Pregnancies in female participants or partners of male participants will be monitored. Further, participants of childbearing potential (defined as post-menarchal, has not reached a post-menopausal state [post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause], and has not undergone surgical sterilization [removal of ovaries and/or uterus]), must remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods with a failure rate of <1% per year, or two effective non-hormonal contraceptive methods during the study treatment periods and for 7 months after the last dose of study treatment and must refrain from donating eggs during the same period. Women who have had a tubal ligation do not require additional contraception. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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 treatment periods and for seven months after the last dose of study treatment to avoid exposing the embryo. All male participants must also refrain from donating sperm during this same period.

Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and copper IUDs.

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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Alternatively, two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal IUD or intrauterine system

- Consideration should be given to the type of device being used, as there are higher failure rates quoted for certain types (e.g., steel or copper wire).
- Condom with spermicidal foam / gel / film / cream / suppository
- Occlusive cap (diaphragm or cervical / vault caps) with spermicidal foam / gel / film / cream / suppository

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical / vault caps) with spermicidal foam / gel / film / cream / suppository.

5.1.3.1 Breastfeeding

It is not known whether trastuzumab or pertuzumab are excreted in human milk. Since maternal IgG is excreted in milk and either trastuzumab or pertuzumab could harm infant growth and development, women must discontinue nursing during study treatment and should not breastfeed for at least seven months following the last study treatment.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications for Perjeta IV, Herceptin IV, and Pertuzumab and Trastuzumab FDC SC

Dose modifications of study treatment are not permitted.

5.1.4.2 Dose Delays and Treatment Interruption for Perjeta IV, Herceptin IV, and Pertuzumab and Trastuzumab FDC SC

The administration of study treatment may be delayed to assess or treat AEs, such as cardiac AEs.

During the study treatment period, a dose delay of up to (and including) six weeks (i.e., up to and including nine weeks between doses) will be permitted to allow AE recovery to baseline. Following a dose delay of less than 3 weeks (i.e., < 6 weeks between doses), study treatment does not need to be reloaded (only the maintenance doses needs to be given).

Patients receiving pertuzumab and trastuzumab FDC SC with ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose consisting of 1200 mg pertuzumab and 600 mg trastuzumab FDC SC before continuing with maintenance doses for subsequent administrations. Patients should be monitored for 30 minutes after their first pertuzumab and trastuzumab FDC SC dose administration in the study (regardless of whether a loading dose is required) and if a loading dose is required during the study. Patients should be monitored for 10 - 15 minutes following maintenance dose administrations.

Patients receiving Perjeta IV with ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose of 840 mg before continuing with maintenance doses for subsequent administrations. Perjeta IV loading dose (if required) will be administered as a 60-minute infusion (± 10 minutes), followed by an observation period of 60 minutes. If the loading dose infusion is well tolerated, subsequent maintenance doses can be administered over a period of 30 minutes (± 10 minutes) with an observation period of 30 minutes. The observation period should be completed prior to the subsequent Herceptin IV infusion.

Patients receiving Herceptin IV with had ≥ 6 weeks since their last study treatment during the study treatment periods, must receive a loading dose of 8 mg/kg before continuing with maintenance doses for subsequent administrations. Herceptin IV loading dose (if required) will be administered as an infusion over approximately 90 (± 10) minutes after which the patient must be observed for 60 minutes. If the loading dose is well tolerated, subsequent maintenance doses can be administered as 30-minute infusions (± 10 minutes) followed by an observation period of 30 minutes.

If study treatment is withheld for more than two cycles (> 9 weeks) because of toxicity, the patient should be discontinued from study treatment, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Patients who are permanently discontinued from study treatment should be treated at the discretion of the investigator as clinically indicated. The patient will continue to be followed post-treatment as described in Section 4.6.1.

5.1.4.3 Management Guidelines

Supportive care and medical management of AEs are at the discretion of the investigator, unless specifically listed below.

5.1.4.3.1 Symptomatic LVSD and/or LVEF Decline

All patients 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 AE may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within three weeks.

Symptomatic LVSD (CHF) should be assessed as “heart failure” on the basis of NCI CTCAE v4.0 and NYHA classification (see Appendix 7). Symptomatic LVSD (CHF) should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist.

Appendix 6 summarizes the management of study medication in patients who develop an asymptomatic decrease in LVEF. The decision to initiate study treatment and whether to continue or stop therapy should be based on two factors: measured LVEF and changes in LVEF from baseline. If a significant LVEF decrease occurs, this decrease should be

confirmed by a second assessment within approximately three weeks showing also a significant decrease.

Heart failure and asymptomatic LVEF decline AEs must be graded per NCI CTCAE v4.0 (see Appendix 7) and reported in the eCRF as described in Table 1.

5.1.4.3.2 Hypersensitivity / Anaphylaxis and Administration-Related Reactions (Infusion or Injection)

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

Patients who experience any of the following events will be discontinued from study treatment:

- Grade 4 allergic reaction
- Grade 3 or 4 hypersensitivity reaction
- ARDS
- Bronchospasm

Patients who experience ARRs may be managed by:

- Slowing or stopping Perjeta IV or Herceptin IV infusion
- Stopping the injection of pertuzumab and trastuzumab FDC SC
- Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion, as per institutional practice
- Subsequently pre-medicating with analgesia and antihistamines as per institutional practice

Patients 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 AEs 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 5.2.4.3.

5.1.4.3.3 EGFR-Related Toxicities

Diarrhoea

To prevent dehydration, early treatment of diarrhoea with anti-diarrheal medication (e.g. loperamide) should be considered, and patients 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 patients 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 AEs (including SAEs and AEs 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 AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavourable 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 5.3.5.8 and 5.3.5.9 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 AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any AE 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 AE results in substantial disruption of the patient'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 patient 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 AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v4.0; 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 AE 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 study treatment
- 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 5.3.5.6)
- 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 patient 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 selected AEs described below.

5.2.4.1 Heart Failure

Symptomatic LVSD (referred to as heart failure) should be reported as an SAE. If the diagnosis is heart failure, it should be reported as such, and not as individual signs and symptoms of heart failure. Heart failure should be graded according to both NCI CTCAE and NYHA Class (see Appendix 7). Left ventricular ejection fraction results must also be reported.

Heart failure occurring during the study (including the Follow-up Period) must be reported irrespective of causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

5.2.4.2 Asymptomatic Declines in Left Ventricular Ejection Fraction

Asymptomatic declines in LVEF should not be reported as AEs because LVEF data are collected separately in the eCRF. 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 AE with the term of "ejection fraction decreased", as per NCI CTCAE v4.0 (see Appendix 7). In addition, a comment in the AEs 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 AE of special interest and must be reported in an expedited manner (see Section 5.4.2). The event must be reported as an AE with the term of "ejection fraction decreased", as per NCI CTCAE v4.0 (see Appendix 7) and a comment should be added to the AEs 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 eCRF.	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline to an LVEF of < 50%	AE [a] (eCRF 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 (eCRF AE eForm) and report as a non-serious AEs of special interest on an SAE form	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure / CHF (symptomatic LVSD) [b]	AE (eCRF AE eForm) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; CHF = congestive heart failure; eCRF = electronic Case Report Form; 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. Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.
b. Any symptomatic LVSD event must be reported as "heart failure."

5.2.4.3 Administration-Related Reactions: Infusion-Related Reactions, Injection-Related Reactions, ~~and~~ Injection-Site Reactions *and Infusion-Site Reactions*

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or injection should be captured as a specific

diagnosis (e.g., "infusion-related reaction", "injection-related reaction", "injection-site reaction", *"infusion-site reaction",* "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 Infusion-Related Reaction eCRF or Injection-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Injection-Related Reaction eCRF.

See Table 2 for the reporting conventions for infusion-related reactions, injection-related reactions, ~~and~~ injection-site reactions *and infusion-site reactions*.

Table 2 Reporting Conventions for Administration-Related Reactions

Adverse Event	Term to Be Used on Adverse Event eCRF Form	Symptoms to Be Entered on eCRF Form
Systemic Infusion Reaction	"Infusion-related reaction"	Infusion-related reaction
Systemic Injection Reaction	"Injection-related reaction"	Injection-related reaction
Local Injection Reaction	"Injection-site reaction"	Injection-site reaction
Local Infusion Reaction	*"Infusion-site reaction"*	*"Infusion-site reaction"*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (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 Section 5.4–5.6.

For each AE 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 AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only SAEs 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 SAEs).

After initiation of study treatment, all AEs regardless of relationship to study drug will be reported until 28 days after the last dose of study drug. Between 28 days and 7 months from the last study dose the following AEs will be reported:

- study drug-related SAEs
- AEs of special interest, heart failure, pregnancies, non−breast-related second primary malignancies and deaths, irrespective of causal relationship

Instructions for reporting AEs 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 AE information at all patient 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 AE severity grading scale for the NCI CTCAE v4.0 will be used for assessing AE severity. Table 3 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 3 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 v4.0, 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 patients who are not bedridden.

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

d. Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of an SAE in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient 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

Table 4 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 patient'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 fulfils the criteria specified below. Evidence exists that the adverse event has an aetiology other than the study drug (e.g., pre-existing 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 AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

Refer to Section 5.2.4 for procedures for recording heart failure, asymptomatic decreases in LVEF and ARRs.

5.3.5.1 Diagnosis versus Signs and Symptoms

For AEs other than heart failure and ARRs (see Section 5.2.4), 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 AEs 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.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, AEs 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 AE 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 haemorrhage 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 AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient 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 AE 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 SAEs.

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

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE 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 hypokalaemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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 AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalaemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent AEs).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE 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 AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., 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 5.3.5.3 for details on recording persistent AEs).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline) in combination with either an elevated total bilirubin (> 2 × 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 AE the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 x baseline value 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 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an AE of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to recurrence of breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, 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 be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.

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

5.3.5.8 Pre-existing Medical Conditions

A pre-existing 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 pre-existing medical condition should be recorded as an AE 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Recurrence of Breast Cancer

Events that are clearly consistent with breast cancer recurrence should not be recorded as AEs. These data will be captured as efficacy assessment data only. Disease recurrence will be determined based on the investigator's assessment as per institutional practice or the ACS / ASCO Breast Cancer Survivorship Care Guideline (see Appendix 4). Though a determination of clinical recurrence could be based on symptomatic deterioration, every effort should be made to document recurrence through use of objective criteria. If there is any uncertainty as to whether an event is due to disease recurrence, it should be reported as an AE.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE 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 AE or an SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a pre-existing 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 pre-existing condition
  - The patient has not experienced an AE
- Hospitalization due solely to recurrence of breast cancer

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

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

5.3.5.11 Patient Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Because the data collection processes and intent of interpretation of investigator-assessed AEs and patient-completed questionnaires are inherently different, these data sets will not be reconciled by the Sponsor and should not be used as source documents for AE reporting by the investigator.

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)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events 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 SAEs to the local health authority and Institutional Review Board (IRB) / Ethics Committee (EC).

5.4.1 Emergency Medical Call Centre

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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 SAEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event / Adverse Event of special interest Reporting 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 and until 28 days from the last study treatment dose all SAEs and AEs of special interest will be reported.

After 28 days from the last study treatment, SAEs related to study treatment and all AEs of special interest will be reported until 7 months after the last study treatment. Additional events that will be reported during this period are described in Section 5.3.1.

After seven months from the last study treatment until the end of the study, SAEs related to study treatment will be reported. Additional events that will be reported during this period are described in Section 5.6.

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 Serious Adverse Event / Adverse Event of special interest Reporting 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 SAEs that occur after the end of the study are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

In addition to the reporting requirements described below, other information will be requested by Roche / Genentech Drug Safety in order to learn more about the effects of pertuzumab and trastuzumab on pregnancy. This information will be requested on any pregnancy or infant exposed to Perjeta IV, Herceptin IV or pertuzumab and trastuzumab FDC SC at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). In case of a report of congenital abnormality, a guided questionnaire will be sent out by Roche / Genentech Drug Safety.

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within seven months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted 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. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel

the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the foetus, an event in the mother during or after the pregnancy, or a congenital anomaly / birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within seven months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted 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 patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for 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 when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), 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).

5.4.3.4 Congenital Anomalies / Birth Defects

Any congenital anomaly / birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as an SAE, 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 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 AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated AE fulfils seriousness criteria, 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). Adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with study treatment, regardless of whether they result in an AE, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded 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 the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For SAEs, AEs 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

After the end of the adverse event reporting period (defined as seven months after the last dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of:

- an SAE that is believed to be related to prior exposure to study drug
- heart failure, AEs of special interest, or non-breast-related second primary malignancies, regardless of causality

  the event 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 Serious Adverse Event / Adverse Event of Special Interest Reporting 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 SAEs and AEs 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 AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Perjeta Investigator's Brochure (source for Perjeta IV and for pertuzumab and trastuzumab FDC SC)
- Herceptin Investigator’s Brochure (source for Herceptin IV)

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 primary study analysis will take place when all study patients have completed their last study treatment administration in the Treatment Cross-over Period. Summaries of secondary study endpoints, including patient reported TASQ and EORTC QLQ-C30 responses, selection of treatment administration method for the Treatment Continuation Period, HCP reported HCPQ responses and safety endpoints will be included in the primary analysis.

~~An interim safety analysis that includes the study safety endpoints may be conducted. The decision to conduct an interim safety analysis will be based on ongoing review of safety data by the Medical Monitor.~~*An interim analysis will be conducted to support a planned regulatory filing for FDC (see Section 6.6).*

The final study analysis that includes all secondary endpoints including safety and efficacy endpoints will be conducted after the end of the study.

The Intent-to-Treat (ITT) population will include all patients randomized into the study, allocated to their randomized treatment arm. Summaries of patient and HCP reported outcomes and efficacy endpoints will be based on the ITT population.

The modified ITT (mITT) population will include all patients who received at least one dose of pertuzumab and trastuzumab FDC SC and one dose of P+H IV during the Treatment Cross-over Period and subsequently answered at least Question 1 of the PPQ. A sensitivity analysis of PROs, including the primary endpoint, and HCP reported outcomes will be based on the mITT population.

The Safety population will include all patients who received at least one dose of any study drug categorized according to the study drug administered. All safety analyses will be based on the Safety population.

Continuous variables will be summarised by the mean, standard deviation, median and range (minimum and maximum). Categorical variables will be summarised by number / percentage of patients.

Further details about the planned analyses will be presented in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The primary study objective is to estimate the proportion of patients who express a preference for pertuzumab and trastuzumab FDC SC.

The planned total sample size of 140 patients is based on an assumed rate of 70% of patients preferring pertuzumab and trastuzumab FDC SC. To achieve a distance of approximately
± 8% from the estimated proportion to 95% CI limits, a total of 126 patients are needed for the evaluation of preference. The final target sample size was increased to approximately 140 patients to allow for 10% of the patients not providing an evaluable preference assessment.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, eligibility violations and patient disposition will be summarized for patients by treatment arm. Reasons for patient's study treatment discontinuation and patient's reasons for study discontinuation will be listed by patient and summarized. Major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

Median follow-up on treatment and on study, estimated with corresponding 95% CI by the reverse Kaplan-Meier approach, will be presented.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables and other baseline and disease characteristics will be summarized overall, by treatment arm using descriptive statistics.

6.4 PRIMARY ENDPOINT ANALYSIS

The primary objective of this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC based on the proportion of patients indicating an overall preference for pertuzumab and trastuzumab FDC SC in Question 1 of the PPQ. Question 1 of the PPQ is as follows: "All things considered, which method of administration did you prefer?".

A point estimate with associated 95% CI for the proportion of patients who preferred pertuzumab and trastuzumab FDC SC will be calculated for the mITT and ITT populations.

The primary endpoint will also be presented by neoadjuvant chemotherapy regimen (anthracyclines + taxanes / carboplatin + taxanes / taxanes only), neoadjuvant treatment response (pCR / non-pCR) and hormone receptor status (positive / negative).

6.5 SECONDARY ENDPOINT ANALYSES

Patient assessed satisfaction with pertuzumab and trastuzumab FDC SC and P+H IV will be based on patient responses to Question 1 of the TASQ-SC and TASQ-IV respectively. In addition, responses of the TASQ-SC and TASQ-IV will be summarized by domain (physical impact, psychological impact, impact on activities of daily living, convenience and satisfaction) over time.

The proportion of patients who select each treatment administration route for the Treatment Continuation Period will be summarized for all patients who complete the Treatment Cross-over Period.

EORTC QLQ-C30 scores including change from baseline, will be summarised by treatment arm and by time.

Healthcare professional perception of time/resource use and convenience with pertuzumab and trastuzumab FDC SC will be assessed by summarizing responses to individual questions of the HCPQs.

6.5.1 Safety Analyses

Safety analyses will be conducted based on the Safety Population.

Analyses will include summaries of the following safety endpoints:

- Incidence, nature and severity of all AEs, ≥ Grade 3 AEs, SAEs and cardiac AEs (including LVEF events). Cardiac AE analyses will focus on the incidence of patients with heart failure (NYHA, NCI-CTCAE [heart failure] Grades 2, 3, 4, and 5). Left ventricular ejection fraction data summaries will include the incidence of patients with LVEF decreases with an absolute decrease of at least 10 percentage points from baseline and to below 50%.
- Incidence of premature withdrawal from study treatment
- Targeted vital signs and physical findings
- Targeted clinical laboratory test results

The analysis of AEs will focus on treatment-emergent AEs, i.e. AEs occurring on or after the day of first study drug administration. Non-treatment emergent AEs (i.e. those occurring before start of study treatment) will be listed (with a flag to identify those AEs that continued into on-study treatment cycles). Adverse events will be coded using MedDRA. All AEs and laboratory abnormalities will be graded according to NCI CTCAE version 4.0.

The incidence of all AEs, AEs leading to premature discontinuation or interruption of study treatment, SAEs, AEs of grade ≥ 3 and cardiac AEs will be summarized according to the primary system-organ class and by preferred term. The incidence of deaths and cause of deaths will be listed and summarized by treatment arm and overall.

Adverse events will be summarised by treatment arm for the Treatment Cross-over Period, Treatment Continuation Period and overall.

Vital signs and targeted physical examination variables will be summarized by treatment arm over time.

Clinical laboratory parameters will be presented in shift tables of NCI CTCAE grade at baseline against worst grade recorded during each treatment period and overall. Laboratory parameters will be summarized by absolute value and change from baseline.

Concomitant medication will be coded and tabulated in summary tables.

Exposure to study treatment, including the number of cycles administered, duration of treatment (calculated from date of first treatment date to the last treatment date) and dosing information (e.g. dose interruptions, modifications and delays) will be summarized for each treatment arm.

To evaluate the safety of switching from pertuzumab and trastuzumab FDC SC to P+H IV and from P+H IV to pertuzumab and trastuzumab FDC SC, AE summaries will also by produced for the Treatment Cross-over Period by treatment arm and actual treatment. An AE will be allocated to the treatment received on or before the AE start date.

Adverse events that started during the first three cycles of the Treatment Cross-over Period and continued into subsequent cycles (even if the AE changed severity grade) will be summarized by the route of administration during which it first occurred. These AEs will be flagged in listings.

6.5.2 Efficacy Analyses

Secondary efficacy endpoints include IDFS, IDFS including second primary non-breast cancer, DDFS and OS.

IDFS is defined as the time from randomization to the first occurrence of one of the following events:

- Ipsilateral invasive breast tumour recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion),
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast),
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer),
- Contralateral invasive breast cancer,
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible).

  Note: Ipsilateral or contralateral *in situ* disease and second primary non-breast cancers (including *in situ* carcinomas and non-melanoma skin cancers) will not be counted as recurrence.

IDFS including second primary non-breast cancer is defined as IDFS with second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and *in situ* carcinoma of any site) included as an event.

DDFS is defined as the time from randomization to the date of distant breast cancer recurrence.

OS is defined as the time from randomization to death from any cause.

The time-to-event endpoints IDFS, IDFS including second primary non-breast cancer, DDFS and OS will be summarized by treatment arm using the Kaplan Meier approach. The median and the corresponding 95% CI will be reported. Patients who have experienced none of these events at the time of analysis (clinical-cut off) and patients who are lost to follow up will be censored at their last clinical assessment date. A frequency table will also be provided for type of IDFS event.

Descriptive analyses will be provided for sub-groups of interest, including neoadjuvant chemotherapy regimen (anthracyclines + taxanes / carboplatin + taxanes / taxanes only), neoadjuvant treatment response (pCR / non-pCR), and hormone receptor status (positive / negative).

6.6 ~~OPTIONAL~~ INTERIM ANALYSES

~~An interim safety analysis may be conducted. The decision to perform an interim safety analysis will be based on ongoing review of safety data by the Medical Monitor. If conducted, the results of this interim analysis will be evaluated by a Sponsor's Internal Data Monitoring~~

~~Committee.~~ *An interim analysis will be conducted to support a planned regulatory filing for FDC, which will consist of a subset of the analyses planned for the primary analysis. The results of this interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee. Further details will be specified in the Statistical Analysis Plan.*

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data.

Electronic CRFs 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.

PRO and HCP reported outcomes data will be collected on paper questionnaires. Study site staff will enter these data into the EDC system. Paper copies of each questionnaire are source documents (see Section 7.3) and will be maintained at the study site.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic CRFs 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. Electronic CRFs 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. 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 patient 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, paper PRO and HCP reported outcome data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the EU or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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 patient the objectives, methods, and potential risks associated with each optional procedure. Patients 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 patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient 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 patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information / findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient 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 patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health

Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, 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 patient 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 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs 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

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

Patient 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 patient, unless permitted or required by law.

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

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 other summary reports will be provided upon request.

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 one 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 patient 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 patient 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 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' 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.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd.

A CRO will provide clinical operations management, medical monitoring and pharmacovigilance support. Data Management will be provided by the sponsor’s Data Management provider.

This is a multi-centre, multinational study that will enrol approximately 140 patients. Enrolment will occur through an IWRS.

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

~~If an interim safety analysis is conducted, the Sponsor's Internal Data Monitoring Committee will evaluate the results.~~ *The results of the interim analysis will be evaluated by a Sponsor's Internal Monitoring Committee.*

9.5 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 HCPs and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, 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, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients 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 six months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients 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 multicentre trials only in their entirety and not as individual centre 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 patents, 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.

9.6 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 patients 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	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
Informed consent [f]	x												
Medical history and demographics	x												
Collection of pathology reports [g]	x												
Complete physical examination [h, i]	x					x			x				x [i]
Limited physical examination [h, i]			x	x	x		x	x		x	x	x	
Vital signs [j]	x		x			x			x			x	
ECOG Performance Status [h]		x	x			x			x	x	x	x	
Weight [h, k]	x		x	x	x	x	x	x	x	x	x	x	
Height	x												

Appendix 1: Schedule of Activities (cont'd)

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
Investigator assessment to exclude residual / recurrent or metastatic disease as per institutional practice	x												
Clinical breast examination [l]	x		x			x			x	x	x	x	x [l]
Electrocardiogram	x												
LVEF [m]	x					x			x	x		x	x [m]
Haematology / limited biochemistry [n]	x		x			x			x	x	x	x	
Pregnancy test [o]		x				x			x [o]	x [o]	x [o]	x	x [o]
~~Adverse events [p]~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x [p]~~
Adverse events [p]	*x*	*x*	*Collected on an ongoing basis*										*x [p]*
~~Concomitant medication [q]~~		~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	~~x [q]~~
Concomitant medication [q]		*x*	*Collected on an ongoing basis*										*x [q]*
PPQ [r]								x					
TASQ-IV [s]					***Arm A*** *only*			***Arm B*** *only*					

Appendix 1: Schedule of Activities (cont'd)

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
TASQ-SC [s]					***Arm B*** *only*			***Arm A*** *only*					
EORTC QLQ-C30 [t]			x		x			x			x		x [t]
HCPQ-Treatment Room [u]			x	x	x	x	x	x					
HCPQ-Drug Preparation Area [u]			x	x	x	x	x	x					
Bilateral mammogram (or other breast imaging method per institutional practice) [v]												x	
Assessments for breast cancer recurrence			Per institutional practice or the ACS / ASCO Breast Cancer Survivorship Care Guideline [see Appendix 4]										
Assessments for non-breast primary cancers			Per institutional practice										
Survival													x
P+H IV			***Arm A*** *only*	***Arm A*** *only*	***Arm A*** *only*	***Arm B*** *only*	***Arm B*** *only*	***Arm B*** *only*					
Pertuzumab and trastuzumab FDC SC			***Arm B*** *only*	***Arm B*** *only*	***Arm B*** *only*	***Arm A*** *only*	***Arm A*** *only*	***Arm A*** *only*					

Appendix 1: Schedule of Activities (cont'd)

	Screening	Baseline	Treatment Cross-over Period						Treatment Continuation Period [a]			End of Treatment Visit [b]	Follow-up Period [c]
Study Cycle			1	2	3	4	5	6	7	11 [d]	15 (or last treatment cycle) [e]		
Day	–28 to –1	–7 to –1	1	1	1	1	1	1	1	1	1	≤ 28 days from last study dose	
P+H IV or pertuzumab and trastuzumab FDC SC									every cycle from C7 until the end of EBC treatment [w]				

ALT = alanine aminotransferase; ANC = absolute neutrophil count; ACS/ASCO: American Cancer Society / American Society of Clinical Oncology; AST = aspartate aminotransferase; EBC= early breast cancer ; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FDC SC = fixed-dose combination for subcutaneous administration; FU = follow-up; HCPQ = Healthcare Professional Questionnaire; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MUGA = multi-gated acquisition; PPQ = Patient Preference Questionnaire; P+H IV = Perjeta intravenous + Herceptin intravenous; TASQ-IV/SC = Therapy Administration Satisfaction Questionnaire for Intravenous Administration / Subcutaneous Administration; WBC = white blood cell.

Notes Unless otherwise specified, assessments should be performed within three days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. *For all protocol-mandated study visits, a time window of ± 3 days is allowed.* If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date.

a. Either pertuzumab and trastuzumab FDC SC or P+H IV will be selected by the patient for study treatment during the Treatment Continuation Period. During this period, pertuzumab and trastuzumab FDC SC or P+H IV will be administered for the number of 3-weekly cycles calculated based on the number of Perjeta and Herceptin cycles received as neoadjuvant treatment prior to study entry and P+H IV and pertuzumab and trastuzumab FDC SC cycles (six total cycles) received during the Treatment Cross-over Period. A total of 18 cycles of anti-HER2 treatment should be administered for EBC treatment unless disease recurrence, unacceptable toxicity or patient withdrawal from treatment necessitates early cessation of treatment. *No specific investigations are required per protocol for Cycles 8-10 and Cycles 12-14 during the Treatment Continuation Period, although the PI may perform safety laboratory assessments or other tests per institutional practice (these results are not required to be reported in the eCRF). However, information on treatment administration will be collected, and new or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.*

b. End of Treatment Visit to be performed within 28 days (± 7 days) of the administration of the last dose of any study drug.

c. Study patients will be followed for at least three years from randomization. A follow-up visit should occur at least every six months during this period.

d. If study treatment Cycle 12 is planned as last study treatment cycle (i.e. corresponding to Cycle 18 of neo/adjuvant anti-HER2 treatment), all planned assessments may be delayed to study treatment Cycle 12

e. The number of the last treatment cycle in Treatment Continuation Period will depend on number of neoadjuvant cycles with Perjeta and Herceptin. A total of 18 cycles of HER2-targeted therapy should be administered over neo/adjuvant treatment (i.e. neoadjuvant cycles + Treatment Cross-over Period Cycles + Treatment Continuation Period cycles = 18 neo/adjuvant cycles).

f. Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within 28 or 7 days of randomization (as indicated) may be used; such tests do not need to be repeated for screening.

g. Pathology reports from initial breast cancer diagnosis and from breast cancer surgery will be collected. Results of local HER2 and hormone receptor testing conducted prior to neoadjuvant therapy will also be collected.

h. Must be performed pre-dose on study treatment dosing days

i. Complete physical examinations should include physical measurements (body weight in kilograms and height in centimetres) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited physical examinations are symptom-directed and, in addition to the scheduled examinations indicated, may be conducted as clinically indicated. New or worsened clinically significant abnormalities observed post-baseline should be recorded as AEs on the Adverse Event eCRF. During the Follow-up Period, physical examinations should be conducted in accordance with institutional practice or the American Cancer Society/American Society of Clinical Oncology Breast Cancer (ACS/ASCO) Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4].

j. Vital signs (heart rate, blood pressure, temperature, respiration rate) will be taken before and after study treatment administration. Heart rate, blood pressure, and respiration rate should be obtained while the patient is seated.

k. Weight will be measured during screening and on Day 1 of each cycle prior to treatment administration. If variation of ≥ ± 10% compared with baseline occurs, Herceptin IV dosing should be recalculated. Weight at the time the Herceptin IV dose is recalculated will be considered as baseline for subsequent evaluations of degree of weight change with respect to Herceptin IV dose modification requirements.

l. Clinical breast examination should be performed to detect signs of residual disease / local recurrence prior to study entry and to detect locoregional relapse during the Treatment Cross-over and Treatment Continuation Periods, and at the End of Treatment Visit. During the Follow-up Period, clinical breast exams should be conducted in accordance with institutional practice or the ACS/ASCO Breast Cancer Survivorship Care Guideline [Runowicz et al. 2016, see Appendix 4].

m. LVEF may be assessed by ECHO or MUGA however the same method should be used throughout the study for each patient and should be performed and assessed by the same assessor where possible. During the study treatment periods, results of LVEF assessments must be reviewed prior to study treatment administration on the scheduled visit day. During the Follow-up Period, LVEF should be assessed at 6, 12, and 24 months after last study treatment or per institutional practice.

n. Haematology: haemoglobin, total WBC, ANC / neutrophils, platelet count. Limited biochemistry: alkaline phosphatase; AST; ALT; LDH; total bilirubin; creatinine. *Albumin should be measured at Screening for determining patient eligibility.* Bilirubin fractions (direct and indirect) must be included if total bilirubin

is greater than ULN. During the treatment period, bloods for haematology / biochemistry may be taken within three days prior to study treatment administration.

o. *Pregnancy testing is only required for women of childbearing potential:* A woman of childbearing potential is defined as: post-menarchal, has not reached a post-menopausal state (post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements. ~~For all women of childbearing potential,~~ *P*~~p~~regnancy tests must be performed via serum β-human chorionic gonadotropin (HCG) at baseline within seven days prior to first study treatment administration. Urine pregnancy tests should be repeated during the Treatment Cross-over and Treatment Continuation Periods ~~within seven days prior to every three treatment cycles starting~~ at Cycle 4, *Cycle 7, Cycle 11 and Cycle 15 (or at last treatment cycle)*, ~~(~~and as clinically indicated~~)~~, with results available prior to study treatment administration, as well as at the End of Treatment Visit and at the Follow-up Visit until seven months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test.

p. Adverse event reporting period will continue up to seven months after the last dose of study drug. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected. After initiation of study treatment, all AEs regardless of relationship to study drug will be reported until 28 days after the last dose of study drug. Between 28 days and 7 months after the last dose of study drug, drug-related SAEs, AEs of special interest, heart failure, pregnancies, non−breast-related second primary malignancies and deaths, should continue to be collected. After the end of the adverse event reporting period (defined as seven months after the last dose of study drug), drug-related SAEs, AEs of special interest, heart failure, non−breast-related second primary malignancies and deaths, should continue to be collected should be collected.

q. All concomitant medications used by the patient from seven days prior to initiation of study drug until the End of Treatment Visit should be reported. After the End of Treatment Visit and until the end of the study, only medications used for the treatment of cancer will be reported.

r. The Patient Preference Questionnaire (PPQ) must be completed following study treatment administration on Day 1 of Cross-over Treatment Period Cycle 6. Patients who discontinued study treatment prior to study treatment Cycle 6 should complete the questionnaire at the time of discontinuation as long as they have received at least one dose of pertuzumab and trastuzumab FDC SC, Perjeta IV and Herceptin IV post-randomization.

s. Patients in Arm A will complete the Therapy Administration Satisfaction Questionnaire for IV administration (TASQ-IV) immediately following study treatment administration on Day 1 of Cycle 3 of the Treatment Cross-over Period and the Therapy Administration Satisfaction Questionnaire for SC administration (TASQ-SC) immediately following study treatment administration on Day 1 of Cycle 6 of the Treatment Cross-over Period. Patients in Arm B will complete the TASQ-SC and TASQ-IV immediately following study treatment administration on Day 1 of Cycle 3 and 6 of the Treatment Cross-over Period respectively. Patients who switch study treatment due to investigator-assessed lack of tolerance should complete the TASQ corresponding to the study treatment they cannot tolerate prior to switching treatment (i.e. after the decision to change study treatment has been approved by the Medical Monitor and before receiving the next study treatment).

t. During the study treatment periods, patients must complete the EORTC QLQ-30 before the patient and clinician receives any information on disease status and prior to treatment administration on the scheduled visit day. During the Follow-up Period, the EORTC QLQ-30 must be completed at 18 months, 2 years, and 3 years from randomization.

u. Each Healthcare Professional Questionnaire (HCPQ) will be completed by the applicable HCP after each study treatment preparation and/or administration for each patient. Applicable HCPs are described in each of the questionnaires (HCPQ-Treatment Room, HCPQ-Drug Preparation Area). Instructions for which questions should be completed in each questionnaire at each timepoint are indicated in the introduction to each questionnaire.

v. Mammograms conducted at the time of diagnosis (before initiation of the neoadjuvant treatment) as well as pre-surgery (if performed) will be collected. Mammograms collected and/or conducted for the study (including pre-neoadjuvant treatment, pre-surgery, and study Follow-up Period evaluations) can be replaced by another conventional imaging method such as magnetic resonance imaging (MRI) or ultrasound per institutional practice at the investigator's discretion, but the same method of assessment must be used for each evaluation for an individual patient. If a mammogram (or acceptable alternative breast imaging evaluation) has been conducted as part of routine care within four months prior to the End of Treatment Visit, it may be used in lieu of the End of Treatment Visit evaluation.

w. After completion of the Treatment Cross-over Period, participating patients will select the study treatment formulation (P+H IV or pertuzumab and trastuzumab FDC SC) to complete their 18 cycles of neo/adjuvant HER2-targeted treatment. The number of study treatment cycles administered during the Treatment Continuation Period required to complete a total of 18 of neo/adjuvant HER2-targeted treatment will be calculated based on the sum of number of P+H cycles received in neoadjuvant treatment (before study entry) plus 6 cycles administered in the Treatment Cross-over Period.

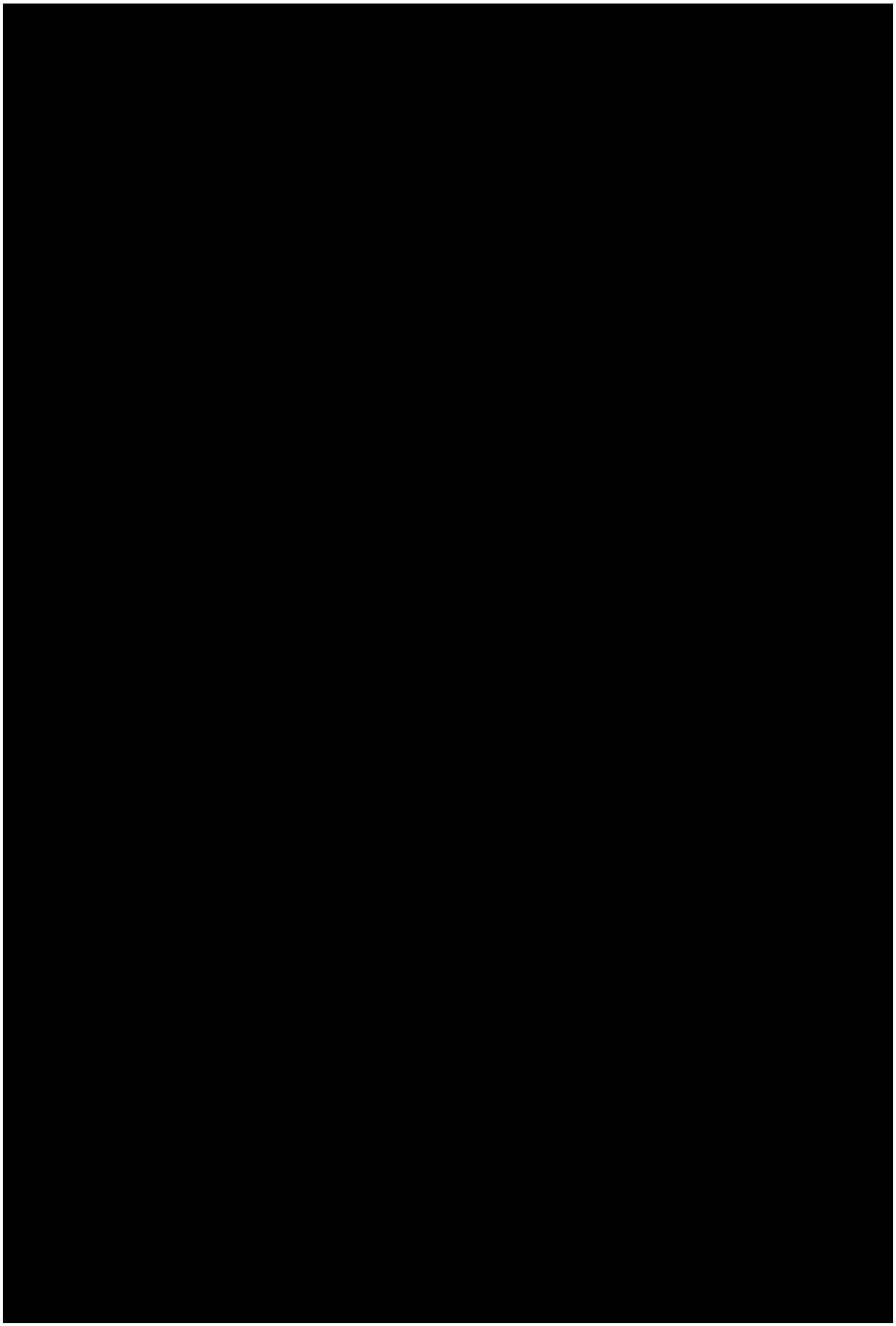
Appendix 2
Patient Reported Outcome Measures

[redacted]

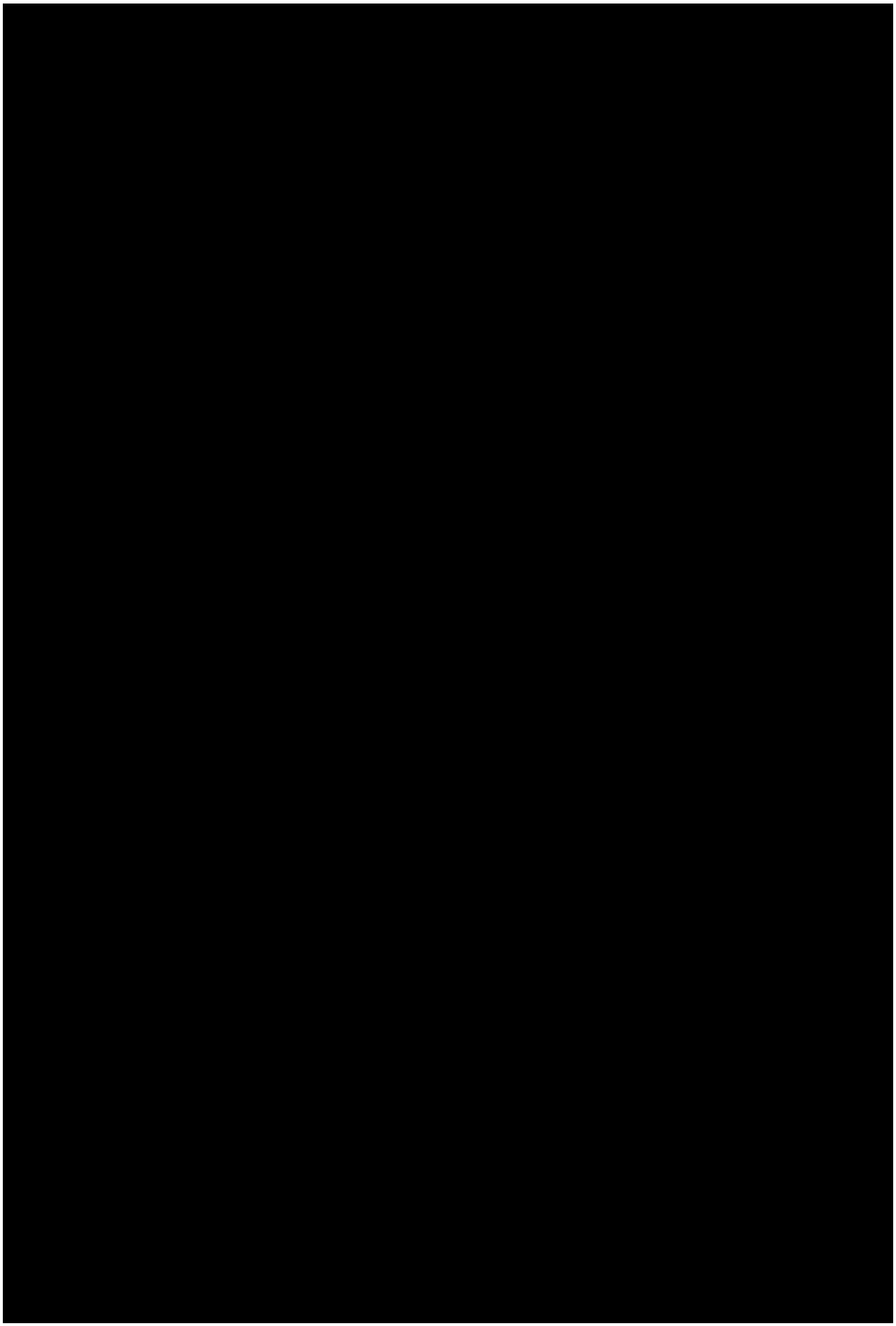
Appendix 2: Patient Reported Outcome Measures (cont'd)

[redacted]

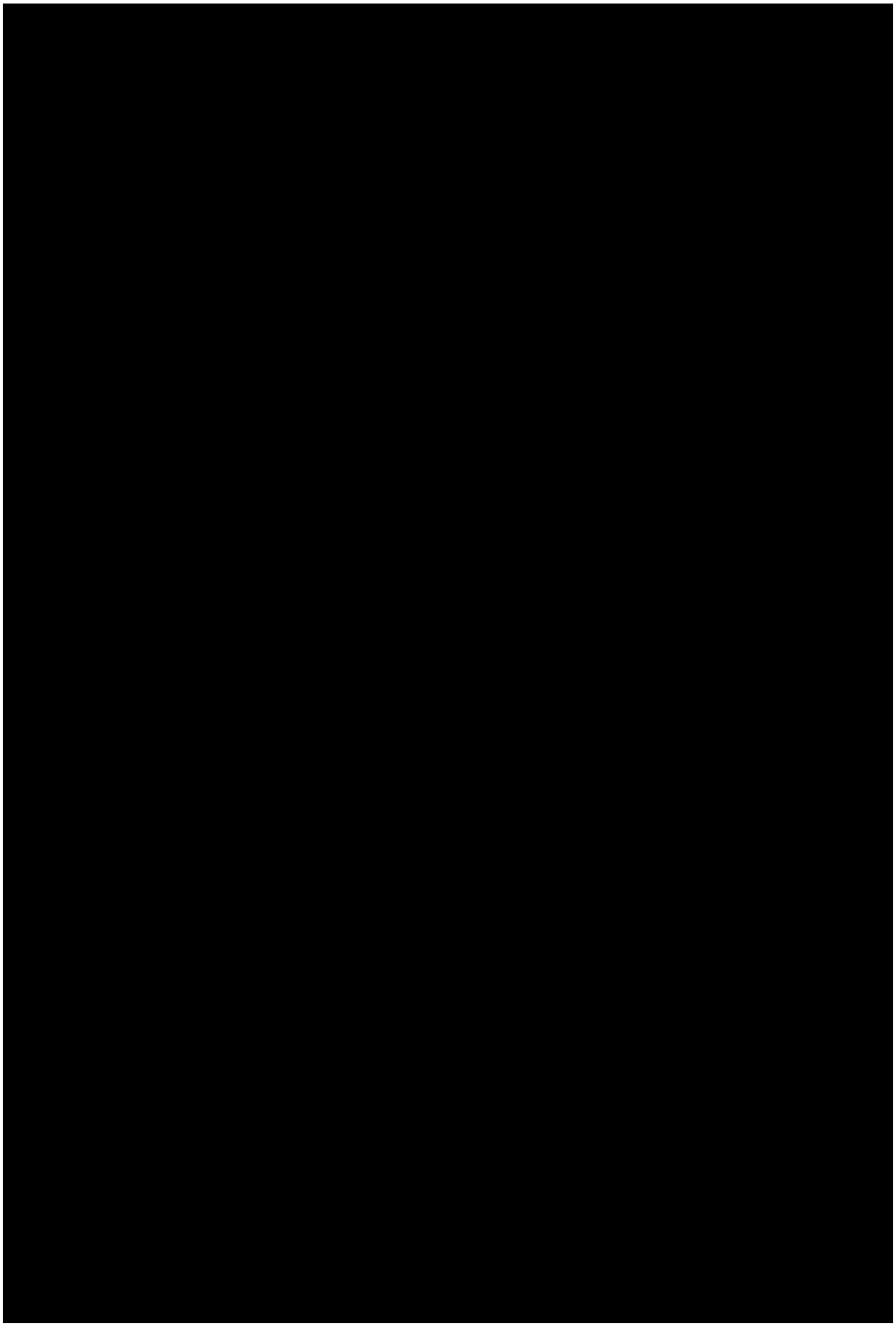
Appendix 2: Patient Reported Outcome Measures (cont'd)



Appendix 2: Patient Reported Outcome Measures (cont'd)



Appendix 2: Patient Reported Outcome Measures (cont'd)



European Organization European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

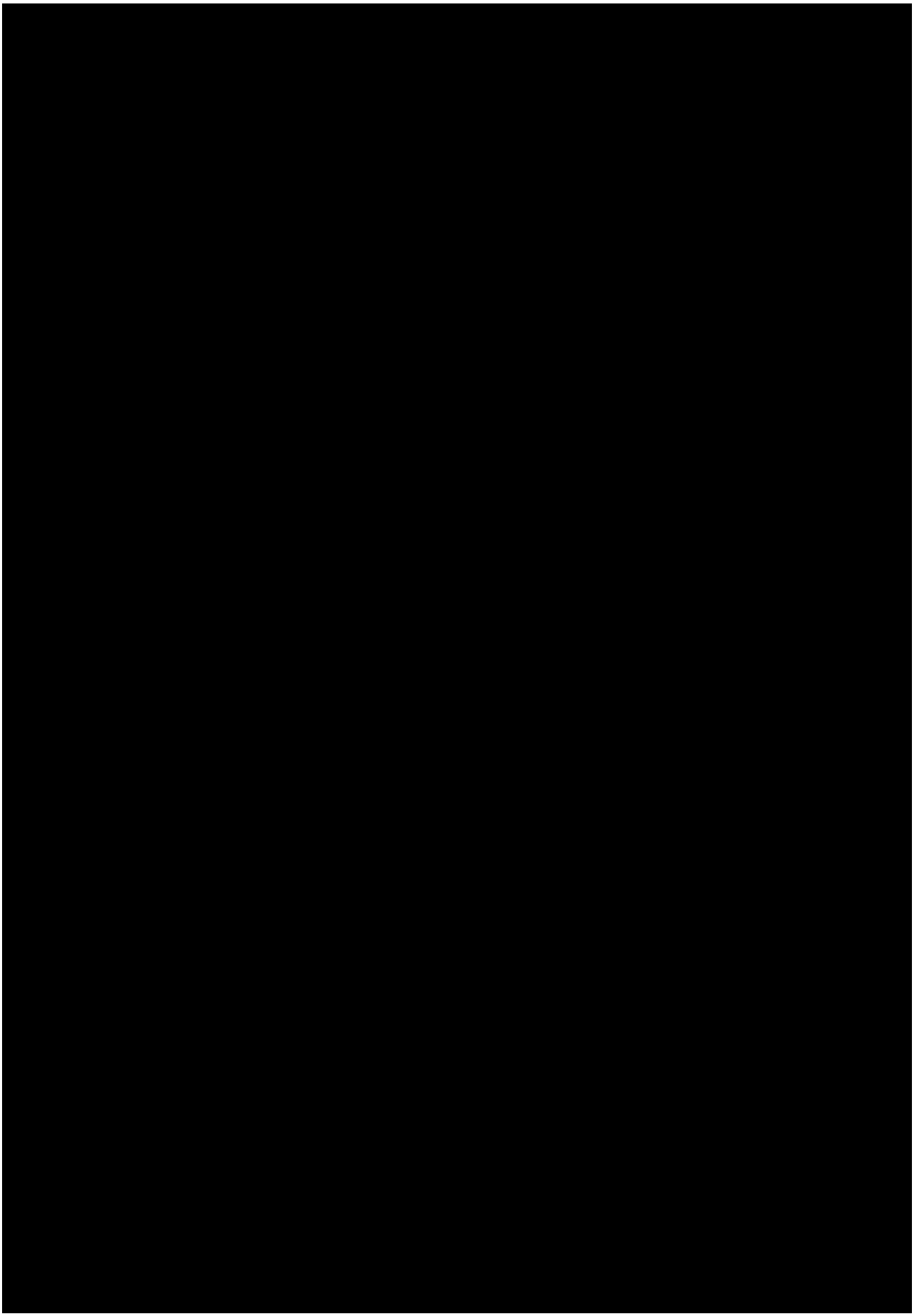
30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

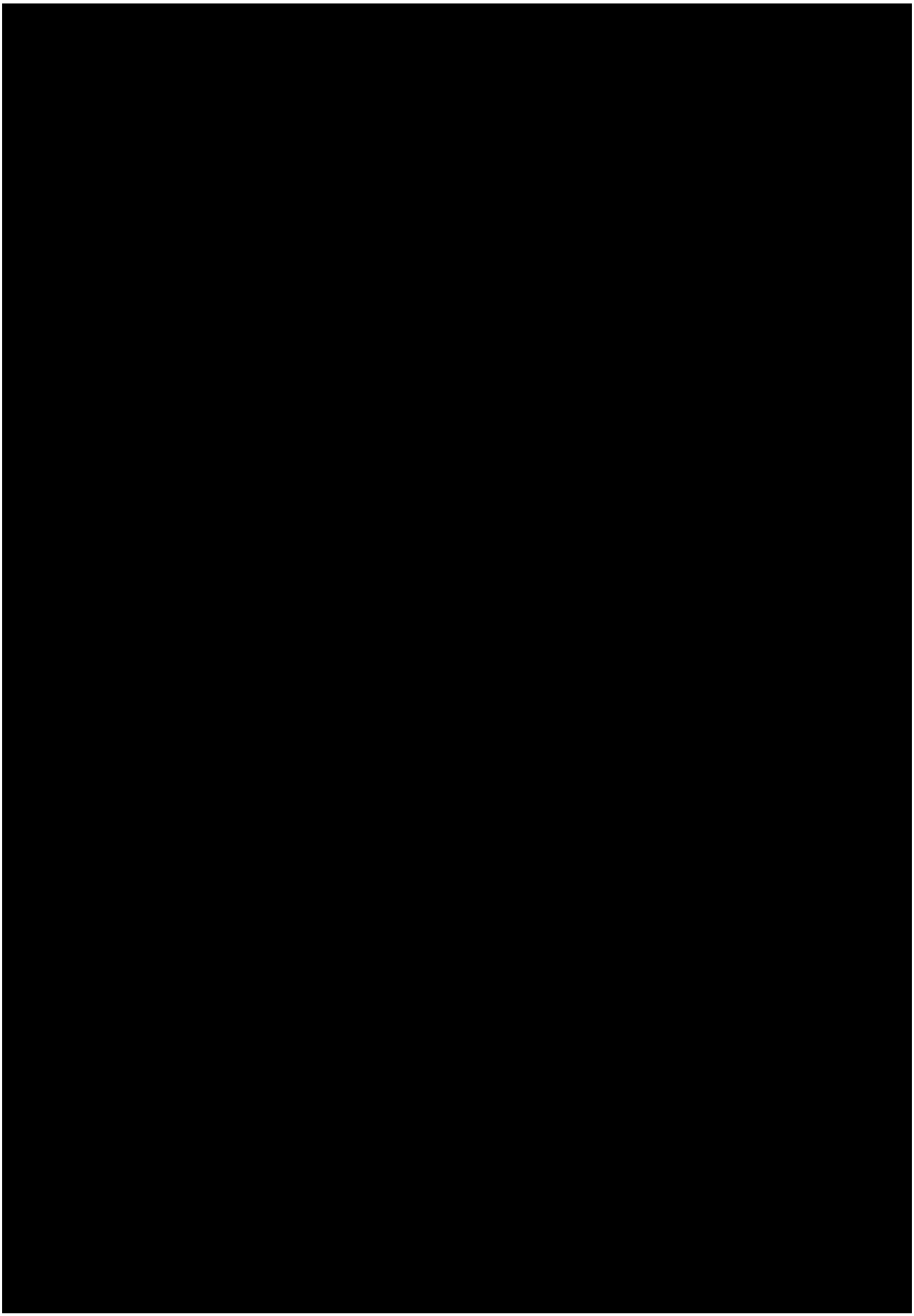
Appendix 3
Healthcare Professional Reported Outcome Measures

[redacted]

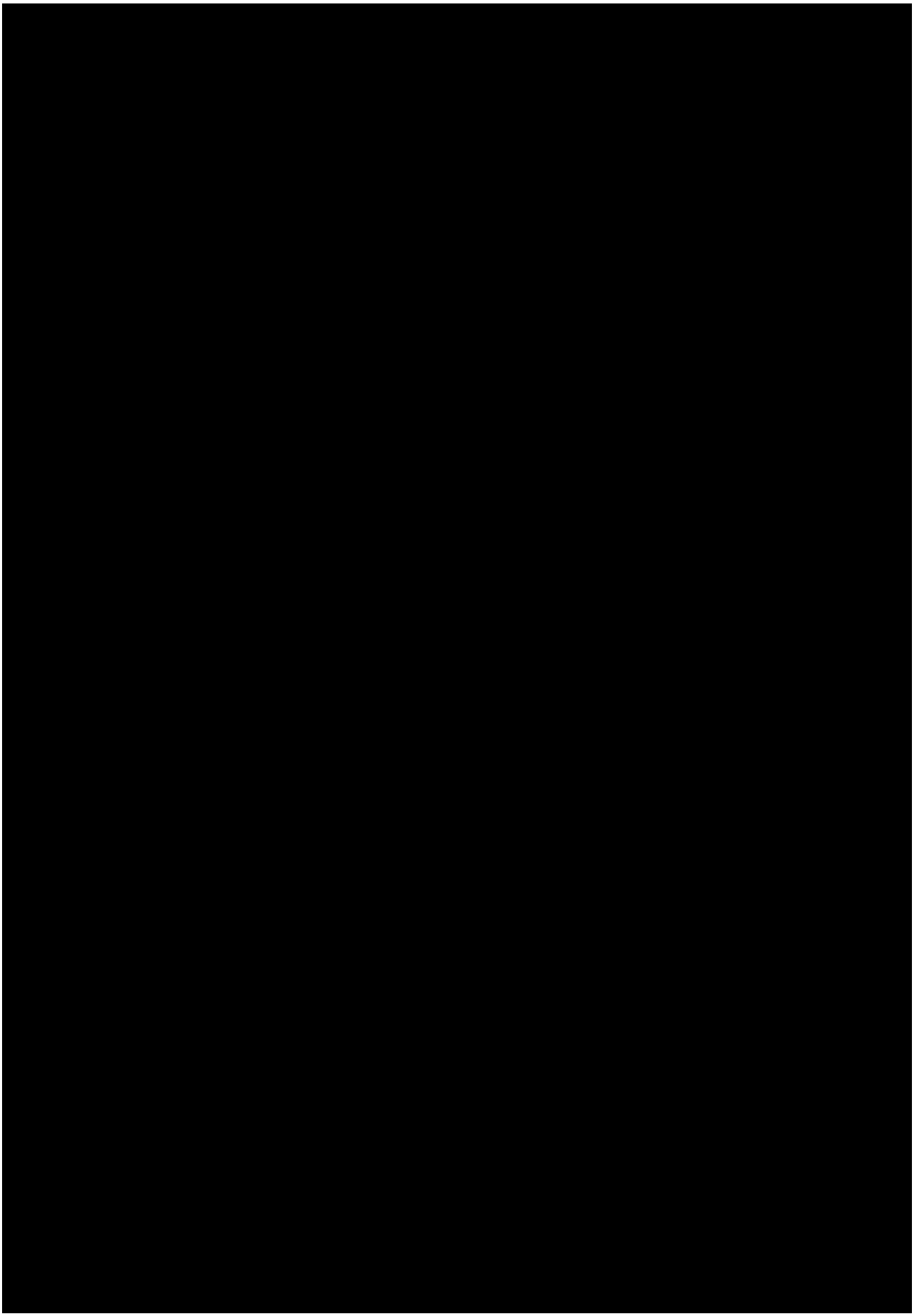
Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)



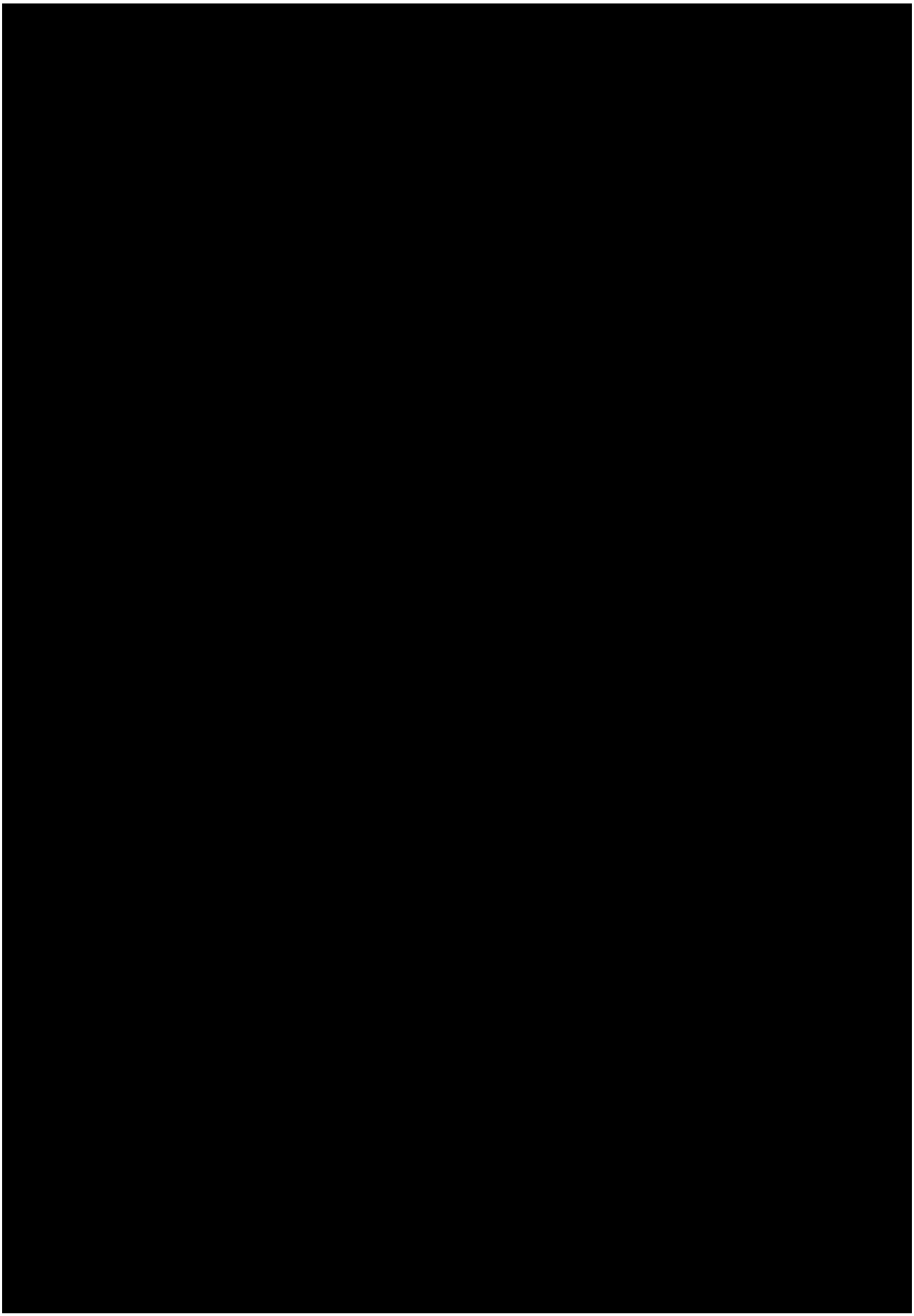
Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)



Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)



Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)



Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)

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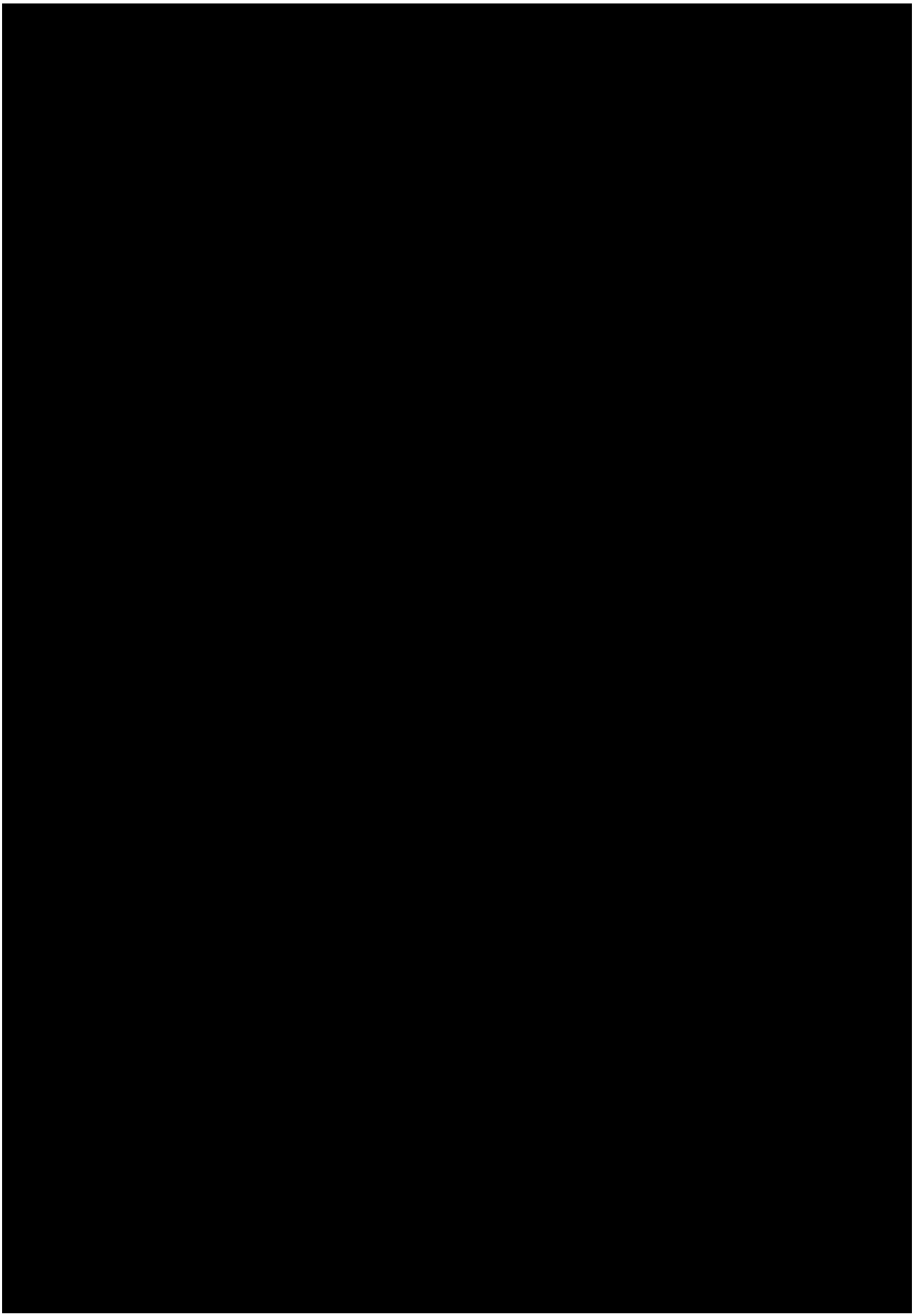
Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)



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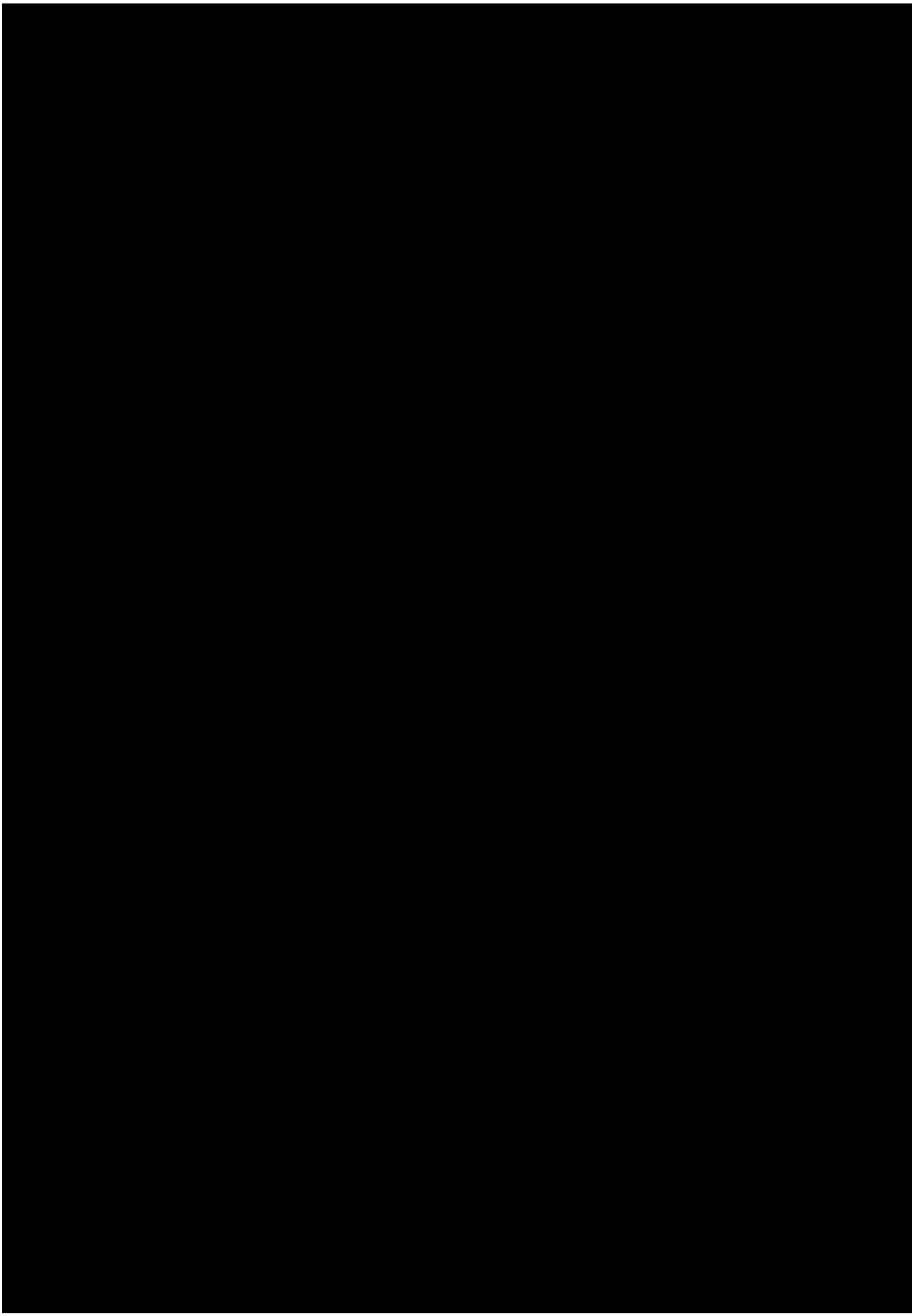

Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)

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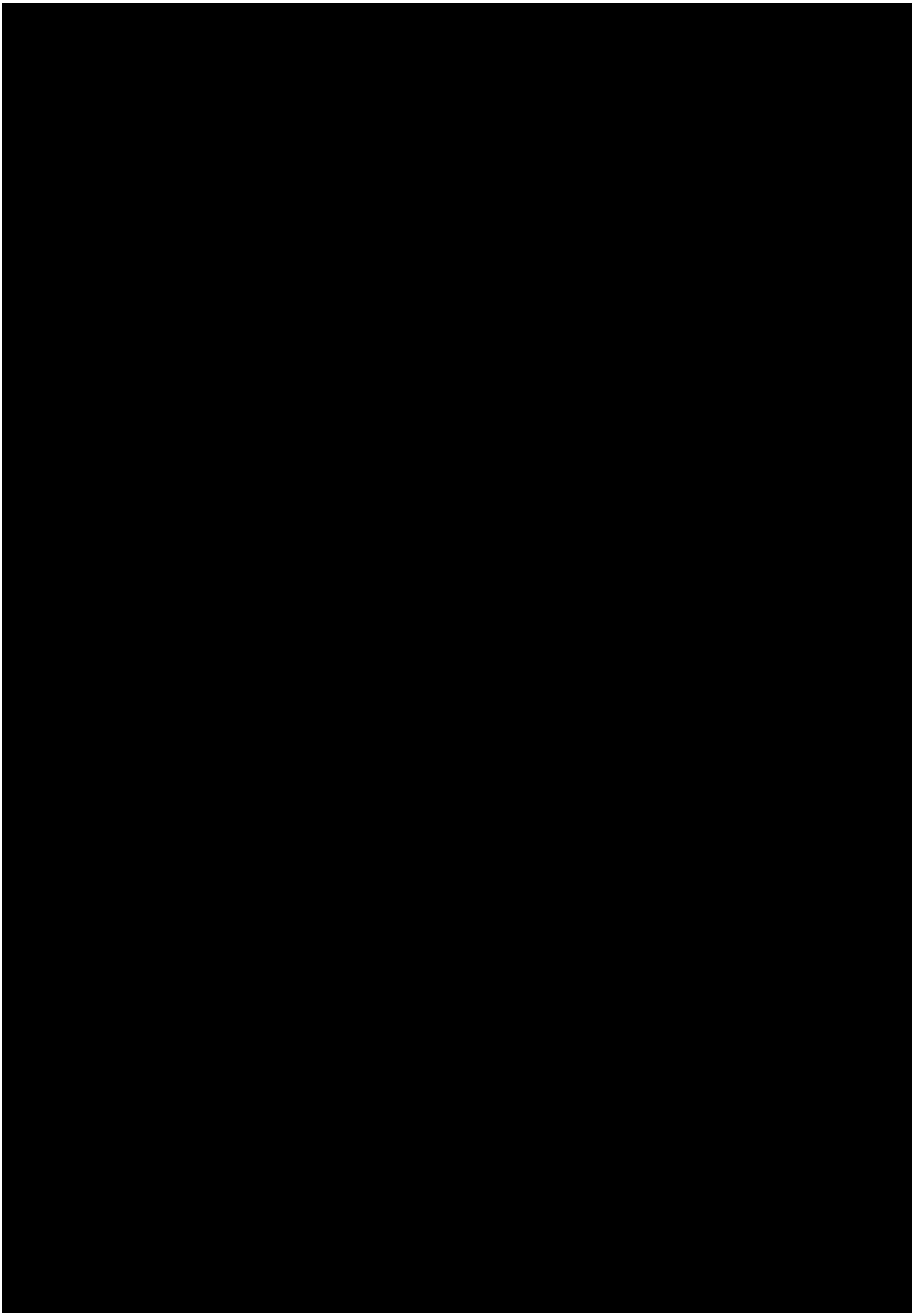
Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)



Appendix 3: Healthcare Professional Reported Outcome Measures (cont'd)

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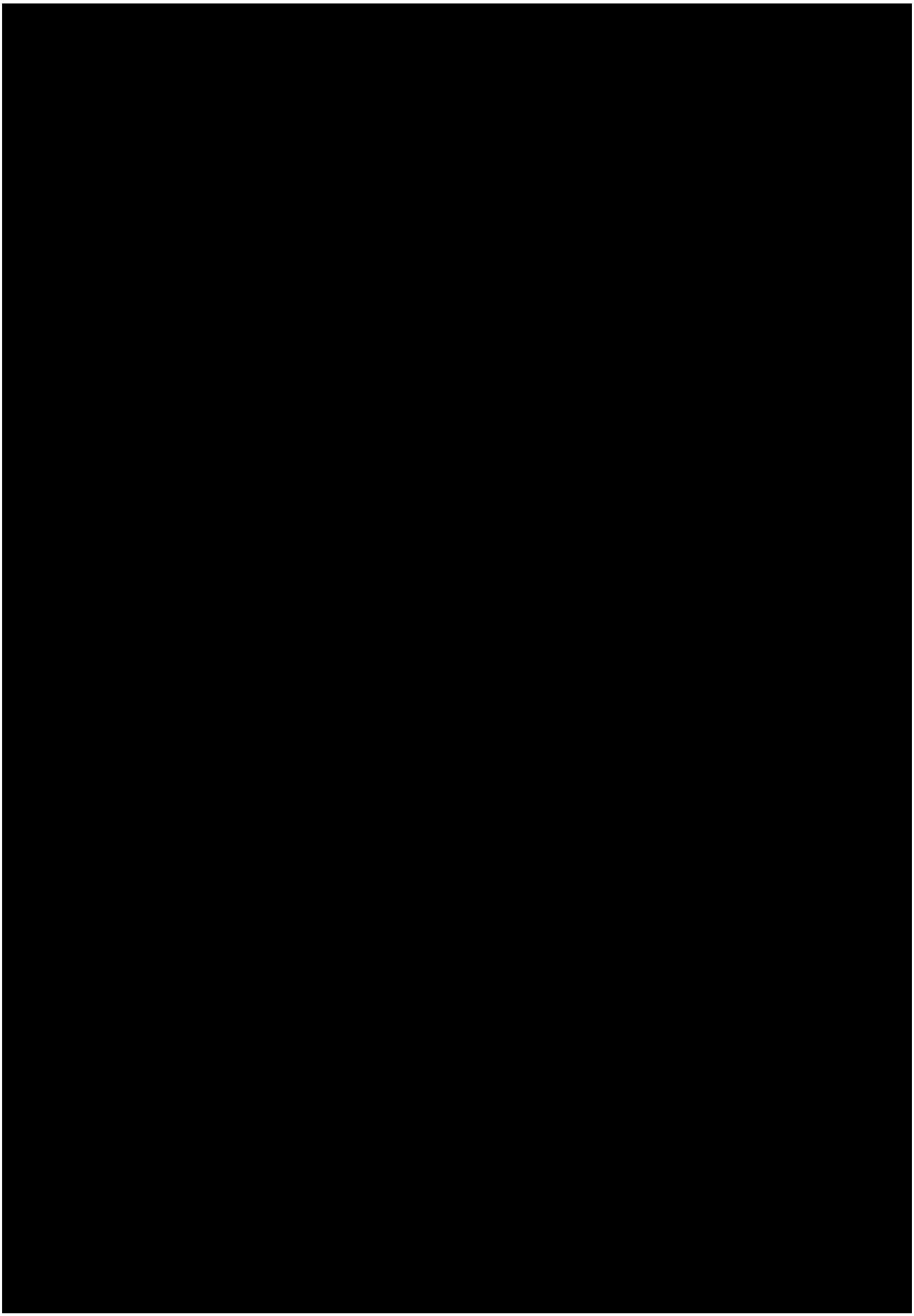


Appendix 4
American Cancer Society / American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

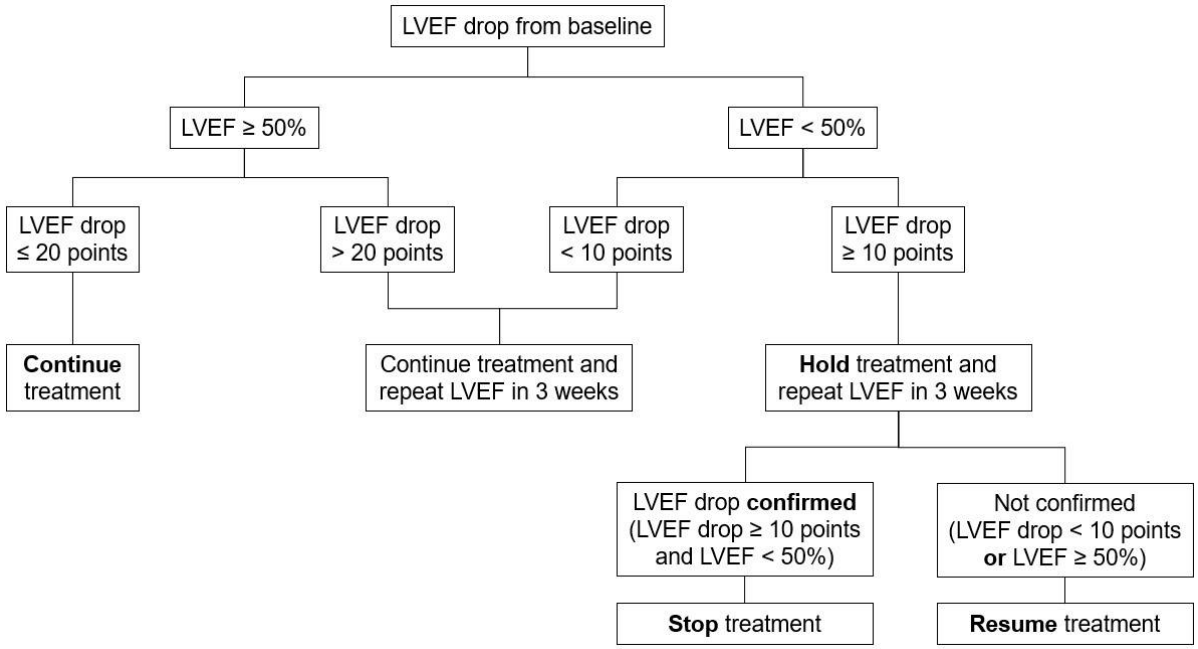
Available at:

http://ascopubs.org/doi/abs/10.1200/JCO.2015.64.3809?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Appendix 5
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 6
Asymptomatic Decline in LVEF: Algorithm for Continuation and Discontinuation of Study Treatment



LVEF = left ventricular ejection fraction

Patients must have an LVEF ≥ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) to be eligible for the study.

Appendix 7
NYHA Functional Classification System for Heart Failure and LVSD NCI CTCAE V4.0 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 V4 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~~50~~%	—
Cardiac Disorders					
	Grade				
	1	2	3	4	5
Heart failure [b]	Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities	Symptoms with mild to moderate exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	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.

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 only at an elevation in the filling pressure.

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf page 109)