# 1. TITLE PAGE

**De-Escalation of adjuvant ChemotheRapy in HER2-positive, EStrogen reCEptor-negative, Node-negative early breast cancer patients who achieved pathological complete response after neoadjuvant chemotherapy and Dual HER2 blOckade**

**DECRESCENDO - Protocol version 3.0, dated 01 SEP 2022**

**EudraCT Number:** 2020-002918-41

**Sponsor Protocol Number:** IJB-EBC-Decrescendo-2020

**ClinicalTrials.gov Number:** NCT04675827

**BIG Protocol Number:** BIG 19-02

**Sponsor:** Institut Jules Bordet
Rue Meylemeersch 90, 1070 Anderlecht, Belgium

**Co-Lead:** Breast International Group (BIG)
Rue de Bretagne 20, 1200 Brussels, Belgium

**Report version:** 1.0

**Document type:** Clinical Study Report

**Report date:** 01 December 2025

**Investigational Medicinal Products:**
Neoadjuvant phase: Pertuzumab and trastuzumab FDC SC, paclitaxel (or docetaxel)
Adjuvant phase: Pertuzumab and trastuzumab FDC SC, trastuzumab emtansine

DECRESCENDO is a multicenter, open-label, dual-phase single-arm phase II de-escalation trial, evaluating an anthracycline-free strategy in subjects with HER2-positive/ER-negative/PR-negative, node-negative early breast cancer considered to be highly sensitive to dual HER2 blockade with the monoclonal antibodies pertuzumab and trastuzumab.

The first subject visit was on 17 January 2022, and the last subject's last visit on 26 November 2024. DECRESCENDO was terminated early due to low recruitment, on 26/11/2024.

The protocol original version was finalized on 22 January 2021. The protocol amendments are shown in Appendix 16.1.1.

The study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents. Numbering of sections in this document follows the notation used in *International Conference on Harmonisation (ICH) guidance, E3: Structure and Content of Clinical Study Reports* and *Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications*.



## SIGNATURES

I have read this abbreviated report and confirm that, to the best of my knowledge, it accurately describes the main features of the conduct and results of the study.

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## 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Sponsor:** Institut Jules Bordet and Breast International Group (BIG) | **Individual Study Table Referring to Part of the Dossier** | **(For National Authority Use only)** |
| **Name of finished products:** Phesgo®; Kadcyla®; paclitaxel; docetaxel | **Volume:** | |
| **Name of active ingredients:** Pertuzumab and trastuzumab fixed-dose combination; trastuzumab emtansine; paclitaxel; and docetaxel | **Page:** | |

**Title of Study:** De-Escalation of adjuvant ChemotheRapy in HER2-positive, EStrogen reCEptor-negative, Node-negative early breast cancer patients who achieved pathological complete response after neoadjuvant chemotherapy and Dual HER2 blOckade (DECRESCENDO)

**Investigators:**

**Study Chair:** Prof. Martine Piccart, MD, PhD – Institut Jules Bordet and Breast International Group (BIG)

**Study Co-Chair:** Prof. Gabriele Zoppoli, MD, PhD – IRCCS Ospedale Policlinico San Martino, Genova, Italy.

**Study centres:**

A total of 51 sites enrolled patients in six countries: Australia (n=14 sites), Belgium (n=7), France (n=22), Israel (n=1), South Korea (n=4), and Switzerland (n=3).

**Publication (reference):**

Agostinetto E, et al: De-escalation of chemotherapy in patients with HER2-positive, hormone receptor negative, node negative early breast cancer: primary results of the phase II DECRESCENDO trial, Poster Presentation, SABCS 2024. Clin Cancer Res (2025) 31 (12_Supplement): P3-11-03.

Debien V, Adam V, Coart E, Agostinetto E, Goulioti T, Molinelli C, Arahmani A, Zoppoli G, Piccart M. DECRESCENDO: de-escalating chemotherapy in HER2-positive, estrogen receptor-negative, node-negative early breast cancer. Future Oncol. 2023 Aug;19(24):1655-1667.

| **Study period:** | **Phase of development:** |
|---|---|
| The enrolment date and date of first treatment for the first subject was 17 Jan 2022. The first visit for the last subject took place on 28 Jul 2023. The first treatment for the last subject took place on 31 Jul 2023. The last visit for the last subject took place on 26 Nov 2024. The cut-off date for analysis is 11 Mar 2025. | Phase II |

**Objectives:**

Primary objective:

To evaluate 3-year recurrence-free survival (RFS) in subjects with human epidermal growth factor receptor 2 (HER2)-enriched tumors who achieve a complete pathological response (pCR) after neoadjuvant treatment with weekly paclitaxel (or docetaxel every 3 weeks) and dual HER2 blockade with pertuzumab and trastuzumab fixed-dose combination (FDC) by subcutaneous (SC) administration.

Secondary objectives:

Key secondary objective: To evaluate 3-year RFS in all subjects with HER2-positive/estrogen receptor (ER)-negative/progesterone receptor (PR)-negative, clinically node-negative breast cancer who achieve a pCR after neoadjuvant treatment with weekly paclitaxel (or docetaxel every 3 weeks) and dual HER2 blockade with pertuzumab and trastuzumab FDC SC.

Other secondary objectives:

- To assess pCR rates in the overall population and by primary tumor dimension.
- To assess, by pCR achievement group (pCR and residual invasive disease), the following outcomes:

- 3-year RFS
- Recurrence-free interval (RFI)
- 3-year invasive disease-free survival (iDFS)
- 3-year distant disease-free survival (dDFS)
- 3-year overall survival (OS)

All these outcomes were to be analyzed in all subjects and stratified by tumour size (T1 vs T2).

- To evaluate the short-and long-term safety of paclitaxel, docetaxel, pertuzumab and trastuzumab FDC SC, and trastuzumab emtansine (T-DM1).

All objectives (primary and secondary) evaluated at 3 years were planned to be evaluated at 5 years.

Exploratory objectives:

- To assess pCR rates by PAM50 subtypes
- To assess, by pCR achievement group (pCR and residual invasive disease), the following outcomes stratified by PAM50 results (HER2-enriched vs. non HER2-enriched):
  - 3-year RFS
  - RFI
  - 3-year iDFS
  - 3-year dDFS
  - 3-year OS
- To identify potential prognostic and/or predictive biomarkers in tissue and blood samples collected at baseline, surgery and disease recurrence. This might include but not be limited to the following:
  - To assess the prognostic value of circulating tumor DNA (ctDNA) levels at baseline, before surgery and at disease recurrence.
  - To characterize molecularly the ctDNA landscape at the time of recurrence.
  - To analyze survival endpoints in subgroups of subjects based on stromal tumor-infiltrating lymphocytes status in the pre-treatment biopsy.
  - To characterize molecularly the collected tumor samples in subjects with residual invasive disease, in order to explore mechanisms of resistance to neoadjuvant treatment and biomarkers of response to T-DM1.
  - To explore the impact of the post-surgery treatments (pertuzumab and trastuzumab FDC SC and T-DM1) on ovarian function and fertility in women who are premenopausal at the time of study enrolment.

**Methodology:**

This was a multicentre, open-label, dual-phase, single-arm phase II de-escalation trial evaluating an anthracycline-free strategy in subjects with HER2-positive/ER-negative/PR-negative, node-negative early breast cancer considered to be highly sensitive to dual HER2 blockade with the monoclonal antibodies pertuzumab and trastuzumab. The Investigational Medicinal Products (IMPs), all currently approved in breast cancer, were pertuzumab and trastuzumab FDC SC, T-DM1, paclitaxel, and docetaxel.

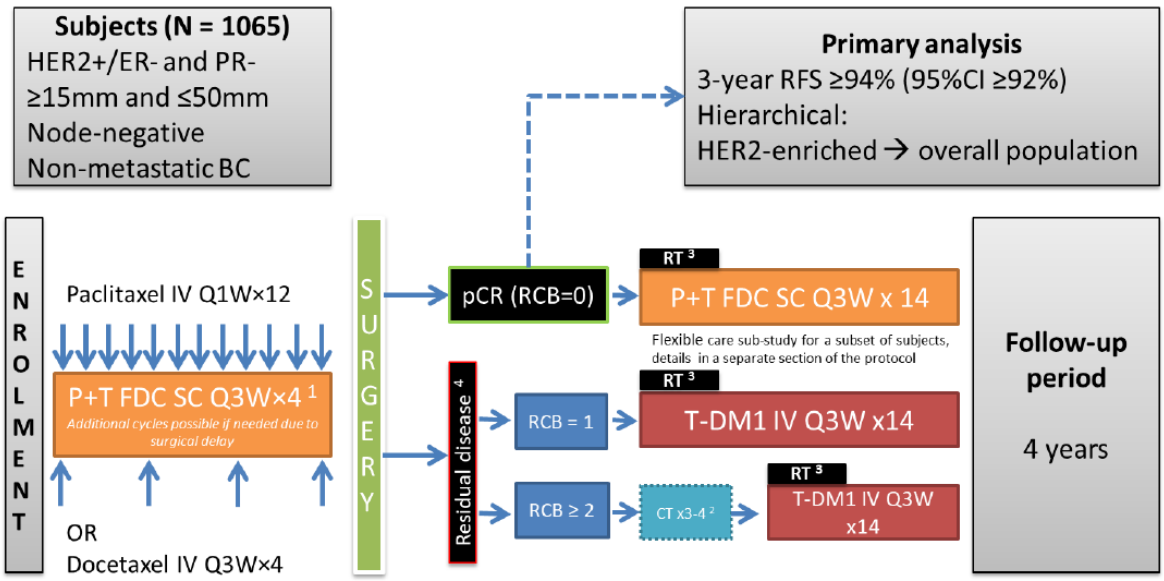
Eligible subjects were to receive preoperative (neoadjuvant) treatment consisting of 12 applications of weekly intravenous (IV) paclitaxel (or IV docetaxel, every 3 weeks for 4 cycles) and pertuzumab and trastuzumab FDC SC every 3 weeks for 4 cycles. Surgery was to be performed in all subjects after neoadjuvant treatment. If surgery was scheduled to take place 42 days or more since the previous administration of pertuzumab and trastuzumab FDC SC, one additional cycle of pertuzumab and trastuzumab FDC SC could be administered at investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. In this case, only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC would be administered in the adjuvant setting, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.

After surgery, subjects who achieved a pCR, corresponding to a residual cancer burden (RCB) score of 0, were to receive adjuvant pertuzumab and trastuzumab FDC SC for 14 cycles. Those with residual invasive disease (RCB score at surgery ≥ 1) were to receive salvage adjuvant T-DM1 for 14 cycles. In subjects with residual invasive disease classified as RCB score ≥2, three to four cycles of a standard anthracycline-based regimen should be administered before the administration of T-DM1. Adjuvant radiotherapy was mandatory after breast-conserving surgery, whereas it would be performed according to local guidelines after mastectomy. Radiotherapy would be administered concomitantly with pertuzumab and trastuzumab in subjects who achieved a pCR, and concomitantly with T-DM1 in

subjects with residual invasive disease (and after anthracycline-based chemotherapy in subjects who were to receive this treatment).

The trial was terminated early due to low recruitment, and the current Abbreviated Report focuses on safety, as recommended in the *Food and Drug Administration guidance for industry Submission of Abbreviated Reports and Synopses in Support of Marketing Applications*.

The figure below displays the design of the DECRESCENDO study.




Abbreviations: **CT**, chemotherapy; **ctDNA**, free circulating tumor DNA; **FDC**, fixed-dose combination; **FFPE**, formalin-fixed paraffin-embedded; **HER2**, human epidermal growth factor receptor 2; **P**, pertuzumab; **pCR**, pathologic complete response; **Q1W**, every week; **Q3W,** every 3 weeks; **RCB**, residual cancer burden (score); **RFS,** relapse-free survival; **RT**, radiotherapy; **SC**, subcutaneous; **T**, trastuzumab; **T-DM1**, trastuzumab emtansine.

*1 If surgery is scheduled with a significant delay (42 days or more since the previous administration of pertuzumab and trastuzumab FDC SC), one additional cycle of pertuzumab and trastuzumab FDC SC can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. In this case, only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC will be administered in the adjuvant setting, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.*
*Important note: If the time between two sequential injections of pertuzumab and trastuzumab FDC SC is less than 42 days (but more than 21+3 days), the maintenance dose of pertuzumab and trastuzumab FDC SC 600 mg/600 mg should be administered. The pertuzumab and trastuzumab FDC SC must not be interrupted for 42 consecutive days or more without a valid medical reason. If the treatment is interrupted for 42 days or more with the Sponsor's approval, a loading dose of pertuzumab and trastuzumab SC 1200 mg/600 mg must be administrated in order to restore adequate serum levels of pertuzumab and trastuzumab. The study treatment must not be interrupted for more than 60 consecutive days (except for the interval between the last neoadjuvant dose and the first adjuvant dose).*
*2 Anthracycline-based chemotherapy should be administered for 3 to 4 cycles for subjects who do not achieve a pCR and whose tumors have an RCB ≥2.*
*3 Adjuvant radiotherapy will be mandatory after breast-conserving surgery, whereas it will be performed according to local guidelines after mastectomy, and it will be administered concomitantly with pertuzumab and trastuzumab in subjects who achieve a pCR; and concomitantly with T-DM1 in subjects with residual invasive disease (after anthracycline-based chemotherapy in subjects who are assigned to receive this treatment).*
*4 Since this study will enrol only subjects with HER2-positive, ER-negative, and PR-negative disease at baseline, endocrine therapy is not a study IMP. If histopathological analysis finds that the surgical specimen from a subject with residual disease is ER-positive and/or PR-positive, adjuvant endocrine therapy may be administered concomitantly with study treatment, at the investigator's discretion and according to local guidelines.*

**Number of patients:**

In order to achieve the study objectives, the original sample size for the trial was 1065 subjects. This sample size was based on assumptions related to the proportion of subjects with HER2-enriched tumors and achieving pCR (75% of subjects with HER2-positive, ER/PR-negative disease were estimated to have HER2-enriched tumors per PAM50; PAM50 testing was estimated to have a rate of inconclusive results of 10%, independently of the HER2-enriched status; and the pCR rate after neoadjuvant treatment was estimated to be 70% for the HER2-enriched and 30% for the non-HER-enriched subsets) and on assumptions related to RFS (a true 3-year RFS rate of 94% for all subjects—with or without HER2-enriched tumors—achieving pCR, a target of 92% for the lower limit of the exact 95% confidence interval (CI), and a one-sided alpha level of 5%). According to these assumptions, a total of 500 subjects would be needed in the primary analysis population (HER2-enriched tumor

reaching pCR). In order to reach 500 subjects for the primary analysis, a total of 1065 subjects would need to be enrolled in the neoadjuvant part of the study, of which around 635 were expected to achieve pCR (i.e., the secondary analysis population). Since a 20% rate of screen failures was considered, at least 1330 subjects would need to be screened for this study. The trial was prematurely stopped due to excessively slow subject recruitment, which had a significant impact on the robustness of the scientific rationale and the financial feasibility of the study, affecting the scientific relevance and the financial support of the trial in the long-term. DECRESCENDO was terminated with a final sample size of 138 subjects.

**Diagnosis and main criteria for inclusion:**

Inclusion criteria:

Subjects had to meet all of the following criteria in order to be eligible for the study:

1. Male or female.
2. Age ≥18 years old.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
4. Subjects whose tumor measures ≥15 mm and ≤50 mm, according to clinical staging performed with imaging exams (either mammogram, ultrasound or breast magnetic resonance imaging [MRI]).
5. Must have histologically confirmed diagnosis of invasive HER2-positive and ER-negative/PR-negative breast cancer (analysis performed by the local laboratory).
   a. HER2-positive defined as a score of 3+ in immunohistochemistry (IHC) or a positive in-situ hybridization (ISH); ratio of HER2 copy number/chromosome 17 ≥2 or average HER2 copy number ≥6 signals per cell).
   b. ER-negative/PR-negative defined as ER and PR nuclear staining <1% by IHC.

   Note: subjects with micro-invasive carcinoma or ductal carcinoma in situ without invasive disease were not eligible.
6. Subjects with multifocal or multicentric invasive disease were eligible as long as all the biopsiable lesions could be characterised and are confirmed to be HER2-positive and ER and PR negative.

   Note: In the case of multifocal or multicentreic disease, only the biopsy from the largest lesion should be provided.
7. Node-negative disease (N0): no axillary lymph nodes identifiable at ultrasound, or in case of suspect axillary lymph nodes are identified, fine-needle aspiration or core biopsy had to be carried out to confirm that axillary status was negative. Axillary micrometastases (i.e., if the greatest diameter of the nodal metastasis in a sentinel node is 0.2 mm or less) were not allowed.
8. Serum pregnancy test (for women of childbearing potential) negative within 7 days prior to treatment start.
9. Women of childbearing potential had to agree to use one highly effective non-hormonal contraceptive method with a failure rate of less than 1% per year from the signing of the Informed Consent Form (ICF) until at least 7 months after last dose of study drugs; or they had to totally abstain from any form of sexual intercourse. Men with a partner of childbearing potential had to agree to use condom in combination with a spermicidal foam, gel, film, cream, or suppository, and agree to refrain from donating sperm, during the study treatment administration and for at least 7 months after the last administration of study treatment.
10. Adequate bone marrow and coagulation functions as defined below:
    a. Absolute neutrophil count ≥1500 /µL or $1.5x10^9$/L;
    b. Hemoglobin ≥9 g/dL (blood transfusions to reach these levels of hemoglobin were allowed);
    c. Platelets ≥100,000/µL or $100x10^9$/L;
    d. International normalized ratio and activated partial thromboplastin time ≤ 1.5 × the upper limit of normal (ULN).
11. Adequate liver function as defined below:
    a. Serum total bilirubin ≤1.5 x ULN. In case of known Gilbert's syndrome ≤3 x ULN was allowed;
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN;
    c. Alkaline phosphatase ≤2.5 x ULN.
12. Adequate renal function as defined below:
    a. Creatinine ≤1.5 x ULN or creatinine clearance >60 mL/min/1.73 $m^2$.

13. Completion of all necessary screening procedures within 28 days prior to enrolment.
14. Adequate cardiac function, defined as a left-ventricular ejection fraction (LVEF) ≥55% estimated by echocardiogram (ECHO) or multiple-gated acquisition scintigraphy (MUGA).
15. Availability of a pre-treatment tumor biopsy sample as specified below:
    a. At least one formalin-fixed, paraffin-embedded (FFPE) tumor block had to be available for central evaluation. Whenever possible, two FFPE tumor blocks should be available (preferred).
    b. If a block could not be provided, six unstained FFPE slides of 10 µm thickness and 20 unstained FFPE slides of 4 µm thickness from the pre-treatment tumor biopsy had to be provided as an alternative. These slides had to be freshly cut prior the shipment to the sponsor.
    c. In either case, the local pathologist had to evaluate an hematoxylin & eosin-stained slide to ensure that the tumor surface was at least 4 mm² and that tumor cellularity was ≥10%.

    Note 1: Tumor biopsy must be sent to the central research laboratory as soon as the subject is confirmed by the local investigator to be eligible for the study.

    Note 2: the inclusion of the subject is only based on local assessments. A central review of HER2, ER, and PR status will be performed a posteriori for quality control purposes.
16. Signed ICF obtained prior to any study-related procedure.
17. Subject was willing and able to comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations.

Inclusion criterion applicable to France only:

18. Affiliated to the French Social Security System.

Exclusion criteria:

Subjects meeting one of the following criteria were not eligible for this study:

1. Pregnant and/or lactating women.
2. Bilateral invasive breast cancer.
3. Evidence of metastatic breast cancer: all subjects must have had a computed tomography (CT)/MRI scan of the thorax/abdomen/pelvis to rule out metastatic breast cancer prior to enrolment. Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT could be used as an alternative to replace all the exams above. A screening bone scan had to have been done if the ALP and/or corrected calcium levels were above the institutional ULN at screening (if PET/CT was used as an alternative imaging exam, a bone scan and/or CT/MRI was not required).
4. Subject with a significant medical, neuro-psychiatric, or surgical condition, currently uncontrolled by treatment, which, in the investigator's opinion, might interfere with completion of the study.
5. Previous exposure to any anti-HER2 treatment.
6. Concomitant exposure to any investigational products as part of a clinical trial within 30 days prior to enrolment.
7. Subject with second primary malignancies diagnosed ≤ 5 years before enrolment in the study. Exceptions were: adequately treated non-melanoma skin cancer, in situ cancer of the cervix, ductal carcinoma in situ of the breast, and any other solid or hematological tumor diagnosed > 5 years before enrolment and for which no chemotherapy and no systemic treatment were necessary, with no evidence of disease recurrence.
8. Resting electrocardiogram (ECG) with corrected QT interval >470 msec detected on at 2 or more time points within a 24-hour period, or family history of long QT syndrome.
9. Serious cardiac illness or medical conditions including, but not confined to, the following:
    a. History of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade ≥3 symptomatic congestive heart failure or New York Heart Association Class ≥II;
    b. 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 2] or third-degree AV-block) – Serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality;
    c. Angina pectoris requiring anti-anginal medication;
    d. Clinically significant valvular heart disease;
    e. Evidence of transmural infarction on ECG;
    f. Evidence of myocardial infarction within 12 months prior to enrolment;

g. Poorly controlled hypertension (i.e., systolic >180 mm Hg or diastolic >100 mm Hg).

10. 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., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome.
11. Peripheral neuropathy (CTCAE version 5.0) grade ≥2.
12. Major surgery within 14 days prior to enrolment.
13. Subject with HIV, hepatitis B or hepatitis C infection documented by serology, except for those subjects with a previous exposure to hepatitis B who developed an effective immune response (HBSAg-negative and anti-HBS-positive).
14. Previous allogeneic bone marrow transplant.
15. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (CTCAE grade ≥3).
16. Subjects who received live attenuated vaccines within 14 days before enrolment.

Exclusion criterion applicable to France only:

17. Vulnerable persons according to the article L.1121-6 of the *Code de la Santé Publique* (CSP), adults who are the subject of a measure of legal protection or unable to express their consent according to article L.1121-8 of the CSP.

**Test product, dose and mode of administration, batch number:**

*Pertuzumab and trastuzumab FDC SC*

Pertuzumab and trastuzumab FDC SC is a fixed-dose (i.e., non-weight based) combination for SC injection. The loading dose and maintenance dose should be administered over 8 and 5 minutes, respectively, at a rate of ≤2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. A loading dose of pertuzumab and trastuzumab FDC SC (1200 mg pertuzumab and 600 mg trastuzumab) was to be administered in the first cycle and for subjects who have had 42 days or more since their last pertuzumab and trastuzumab FDC SC administration. A maintenance dose of pertuzumab and trastuzumab FDC SC consisting of 600 mg pertuzumab and 600 mg trastuzumab was to be given in the remaining cycles. Dose reductions were not allowed for pertuzumab and trastuzumab FDC SC. Since pertuzumab and trastuzumab were administered in the same formulation, it was not possible to interrupt each agent alone. The administered batches of the loading dose were the following: 1168940, 1170394, 1173059, 1176358, 1177493, 1178271, 1178278, 1179372, and 1181356. The administered batches of the maintenance dose were the following: 1168953, 1169801, 1170766, 1171938, 1173166, 1177232, 1179283, 1180245, 118165, and 1182690.

*Paclitaxel*

Neoadjuvant paclitaxel was to be administered IV at a dose of 80 mg/m². This drug was taken from the shelves of each hospital's pharmacy.

*Docetaxel*

Neoadjuvant docetaxel was to be administered IV at a dose of 75 mg/m². This drug was taken from the shelves of each hospital's pharmacy.

*Trastuzumab emtansine (T-DM1)*

Adjuvant T-DM1 was to be administered IV at a dose of 3.6 mg/kg for subjects with residual invasive disease. The administered batches were the following: 1168961, 1171435, 1174086, and 1176557.

**Duration of treatment:**

*Pertuzumab and trastuzumab FDC SC*

Neoadjuvant pertuzumab and trastuzumab FDC SC was to be given every 3 weeks for 4 cycles. Adjuvant pertuzumab and trastuzumab FDC SC was to be given every 3 weeks for 14 cycles. If an additional cycle of pertuzumab and trastuzumab FDC SC had been administered (e.g., for surgery delay) during the neoadjuvant phase only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC were to be administered in the adjuvant phase, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.

*Paclitaxel*

Neoadjuvant paclitaxel was to be administered weekly for 12 weeks.

*Docetaxel*

Neoadjuvant docetaxel was to be administered every 3 weeks for four cycles.

*Trastuzumab emtansine (T-DM1)*

Adjuvant T-DM1 was to be administered every 3 weeks for 14 cycles for subjects with residual invasive disease.

**Reference therapy, dose and mode of administration, batch number:**

Not applicable.

**Criteria for evaluation:**

**Efficacy**:

The primary efficacy measure of this trial was RFS, defined as the time from enrolment until the first occurrence of invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, or death from any cause. Secondary efficacy endpoints were pCR, defined as the absence of residual invasive tumor in the breast and axillary lymph nodes (pT0/Tis pN0) at surgery as per the local pathological report; RFI, defined as the time interval between enrolment and the first occurrence of invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, or death from breast cancer; dDFS, defined as the time from enrolment until the first occurrence of one distant recurrence, a second primary invasive (non-breast) cancer, or death from any cause; iDFS, defined as the time from enrolment until the first occurrence of invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, invasive contralateral breast cancer, second primary invasive (non-breast) cancer, or death from any cause; and OS, defined as the time from enrolment until death from any cause.

**Safety:**

Safety was assessed through recording of the incidence, severity and relationship to study treatment of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs), using CTCAE version 5 for their grading. These AEs were considered as treatment-emergent (i.e., TEAEs) if they started or worsened on or after the first day of study treatment.

**Statistical methods:**

A Statistical Analysis Plan (SAP) describing the statistical analysis in detail was provided as a separate document and signed before database lock. The intent-to-treat (ITT) Population was defined as all enrolled subjects, whether or not they received study treatment; the ITT Population was used to analyze baseline characteristics. A Sensitivity Population was defined as the subset of the ITT Population whose tumors were confirmed to be HER2-positive and ER-negative/PR-negative per central pathology review. The Safety Population comprised all subjects who received at least one dose of study treatment (starting in the neoadjuvant phase) and had at least one post-baseline safety assessment, analyzed according to the treatment that they actually received. The Safety Population was used for safety analyses.

**EFFICACY RESULTS:**

Between 17 Jan 2022 and 24 Jul 2023, 138 subjects were enrolled in the study. The ITT Population and the Safety Population comprised all 138 subjects. Of note, one subject (of a total of 139) was considered a screen failure, did not start any treatment, and is not accounted for in this report. Of 138 subjects starting neoadjuvant treatment, 131 (94.9%) underwent surgery, and 126 (91.3%) started adjuvant treatment. No subjects withdrew their consent, but four decided to withdraw from the study. Three subjects were lost to follow-up.

All enrolled subjects were women, and their mean age (± standard deviation) was 58.2 (± 11.86) years. The youngest subject was 29, and the oldest was 86 years old. Most (89.1%) subjects had an ECOG performance status of 0, and slightly above two-thirds were postmenopausal. Slightly over two-thirds of subjects had T2 tumors, and the lymph-node status was N0 in all but two subjects with missing information. The distribution of histological type and grade was typical of this population, with the predominance of invasive carcinoma of no special type (85.5%) and grade 2/3 tumors (39.9%/52.2%), respectively.

Due to low accrual, a decision was made to not carry out a complete efficacy evaluation, and only selected outcomes were analyzed: pCR rates and progression/recurrence events according to the RCB score. Among the 131 subjects who underwent surgery, a pCR (i.e., RCB=0, corresponding to ypT0N0

or subjects with missing information but receiving adjuvant pertuzumab and trastuzumab FDC SC) was reported in 113 subjects (86.3%); 10 subjects (7.6%) had an RCB score of 1, and eight subjects (6.1%) had an RCB score of 2 or greater. The rates of pCR were relatively similar between subjects with T1 (36/41, or 87.8%) and T2 (75/88, or 85.2%) tumors. On the other hand, the pCR rate was nominally higher among subjects with HER2-enriched (87/98, or 88.8%) than among those with non-HER2-enriched (26/33, or 78.8%) tumors. Corresponding figures for pCR rates among the 138 patients in the ITT Population were RCB=0 in 113 subjects (81.9%), RCB=1 in 10 subjects (7.2%), and RCB≥2 in eight subjects (5.8%). Regarding tumor progression or recurrence, this was reported in one subject with an RCB score of 0 and in two without an RCB score (since they did not undergo surgery).

**SAFETY RESULTS:**

Of 138 subjects starting neoadjuvant treatment, 129 were designated by investigators to receive paclitaxel as the chemotherapy partner to pertuzumab and trastuzumab FDC SC, and nine to receive docetaxel as such partner. Two subjects switched treatment from paclitaxel to docetaxel (Subject ID 0006 received eight administrations of paclitaxel and one of docetaxel, and Subject ID 0021 received one administration of paclitaxel and one of docetaxel). Moreover, one subject from the Safety Population (Subject ID 0152) was planned to receive paclitaxel in combination with pertuzumab and trastuzumab FDC SC, but did not receive paclitaxel, only pertuzumab and trastuzumab.

Subjects received a mean number of 4.2 cycles of pertuzumab and trastuzumab FDC SC. There were no dose interruptions of pertuzumab and trastuzumab FDC SC, and delayed administration of these antibodies was nominally less frequent, in relative terms, among subjects receiving paclitaxel than those receiving docetaxel. Among all subjects receiving paclitaxel, subjects received a mean of 11.3 administrations; delayed administrations were reported for 31.0% of subjects, dose adjustments for 27.9%, and dose interruptions for 9.4%. Among the nine subjects receiving docetaxel, subjects received a mean of 3.9 administrations; delayed administrations were reported for 33.0% of subjects, dose adjustments for 11.1%, and no dose interruptions were reported for docetaxel. Subjects received a mean number of 13.2 cycles of adjuvant treatment with pertuzumab and trastuzumab FDC SC; for T-DM1, subjects received a mean of 11.6 (with anthracyclines) to 12 (without anthracyclines) cycles. No delayed administrations, dose adjustments or dose interruptions were reported in the adjuvant phase.

Overall, all subjects had at least one TEAE, which were more frequently reported in the neoadjuvant (100% of subjects) and adjuvant (89.7%) parts of the study than during the surgery period (22.1%). In nearly two-thirds of subjects, the highest grade of the TEAE was 1 or 2, and for the remaining one-third it was grade 3 or 4. At least one serious TEAE was reported for 23 (16.7%) subjects, again more often in the neoadjuvant (9.4%) and adjuvant (7.1%) parts of the study than during the surgery period (1.5%). Most of these serious TEAEs were considered as treatment-related (17/23), particularly during the neoadjuvant (11/13) and surgery (2/2) parts of the study. At least one AESI of special interest (TEAESI) was reported for 31 (22.5%) subjects. Over the entire study period, relatedness to study drug was always more frequent for paclitaxel than for the other three study drugs for TEAEs, serious TEAEs, TEAEs leading to study-drug dose reduction, and TEAEs leading to permanent treatment discontinuation.

Overall in the study, the SOC categories with the largest number of subjects with reported TEAEs were "gastrointestinal disorders" (n=125; 90.6%), "skin and subcutaneous tissue disorders" (n=112; 81.2%), "general disorders and administration site conditions" (n=109; 79.0%), "nervous system disorders" (n=96; 69.6%), and "infections and infestations" (n=74; 53.6%). Of note, TEAEs under the SOC “cardiac disorders” were reported in only 10 (7.2%) subjects overall, five each in the neoadjuvant and adjuvant parts of the study. One TEAE was reported in the SOC category “neoplasms benign, malignant and unspecified (incl cysts and polyps)”: this was a case of tumor pain. The Preferred Terms reported in at least 10% of subjects in the study overall were "diarrhea" (n=108; 78.3%), "alopecia" (n=57; 41.3%), "asthenia" (n=51; 37.0%), "fatigue" (n=45; 32.6%), "neuropathy, peripheral" (n=44; 31.9%; with 14 additional reports of "peripheral sensory neuropathy", 10 of "paresthesia", two of "dysesthesia", two of "neurotoxicity", and two of "peripheral motor neuropathy"), "nausea"(n=41; 29.7%), "epistaxis" (n=33; 23.9%), "rash" (n=28; 20.3%; with 12 additional reports of different types of skin rash), "arthralgia" (n=26; 18.8%; with one additional case each of "arthritis" and "polyarthritis"); "radiation skin injury" (n=24; 17.4%), "anemia" (n=22; 15.9%), "headache" (n=20; 14.5%), "muscle spasms" (n=18; 13.0%), "cough" (n=17; 12.3%), "dry skin" (n=17; 12.3%), "dysgeusia" (n=17; 12.3%; with one additional report of "hypogeusia"), "pruritus" (n=17; 12.3%), "stomatitis" (n=17; 12.3%; with 25 additional reports of "mucosal inflammation" and one of "mucosal pain"), "COVID-19" (n=16; 11.6%); with one additional report of "COVID pneumonia"), "neutropenia" (n=16; 11.6%), "abdominal

pain" (n=14; 10.1%; with 9 additional reports of "abdominal pain, upper"), "gastroesophageal reflux disease" (n=14; 10.1%), "myalgia" (n=14; 10.1%), and "hot flush" (n=14; 10.1%).

Considering only the neoadjuvant part of the study, the SOC categories with the largest number of subjects with reported TEAEs were "gastrointestinal disorders" (n=119; 86.2%), "general disorders and administration site conditions" (n=99; 71.7%), "skin and subcutaneous tissue disorders" (n=97; 70.3%), "nervous system disorders" (n=85; 61.6%), “respiratory, thoracic and mediastinal disorders” (n=49; 35.5%), and "infections and infestations" (n=43; 31.2%). The Preferred Terms reported for the largest number of subjects were "diarrhea" (n=100; 72.5%), "alopecia" (n=55; 39.9%), "asthenia" (n=44; 31.9%), "neuropathy, peripheral" (n=40; 29.0%; with 12 additional reports of "peripheral sensory neuropathy", 10 of "paresthesia", two of "neurotoxicity", and one of "peripheral motor neuropathy"), "fatigue" (n=37; 26.8%), "nausea" (n=34; 24.6%), "epistaxis" (n=30; 21.7%), "rash" (n=25; 18.1%; with 10 additional reports of different types of skin rash), “mucosal inflammation” (n=23; 16.7%), and "anemia" (n=21; 15.2%).

Twenty-nine (22.1%) of 131 subjects undergoing surgery had at least one TEAE reported, more frequently under the SOC categories "infections and infestations" (n=8; 6,1%), "skin and subcutaneous tissue disorders" (n=7; 5,3%), and "general disorders and administration site conditions" (n=6; 4,6%).

Considering only the adjuvant part of the study, the SOC categories with the largest number of subjects with reported TEAEs were "gastrointestinal disorders" (n=52; 41.3%),"infections and infestations" (n=47; 37.3%), “general disorders and administration site conditions" (n=43; 34.1%), and "skin and subcutaneous tissue disorders" (n=41; 32.5%). The Preferred Terms reported for at least 10% of the 126 subjects were "diarrhea" (n=34; 27.0%), "radiation skin injury" (n=24; 19.0%), "asthenia" (n=20; 15.9%), "fatigue" (n=14; 11.1%), and "arthralgia" (n=13; 10.3%; with one additional case of "polyarthritis").

Overall, of the 35 (26.8%) subjects who had at least one TEAESI reported, the most frequent types were grade ≥2 neuropathy (n=22; 15,9%) and grade ≥3 diarrhea (n=8; 5,8%); grade ≥2 neuropathy was more often reported in the neoadjuvant part of the study, and grade ≥3 diarrhea exclusively in that part. There were two cases (1,4%) of LVEF decrease (absolute decrease >10% from baseline and/or LVEF value below 50%, excluding the baseline value). Of note, there were five cases (3.6%) of liver abnormalities that did not fulfil Hy’s law for drug-induced liver injury (DILI): two cases of “hepatic cytolysis” (one in the neoadjuvant phase and one in the adjuvant phase); two cases of “alanine aminotransferase increased” (in the neoadjuvant phase); and one case of “aspartate aminotransferase increased” (in the neoadjuvant phase).

Overall, across all SOC categories and study periods, the grade of the events for the 138 subjects with at least one TEAE reported was grade 1 in 13 subjects (9.4%), grade 2 in 75 subjects (54.3%), grade 3 in 42 subjects (30.4%), and grade 4 in eight subjects (5.8%).

No fatal (i.e., grade 5) TEAEs were reported. One death was reported during the follow-up period. This death was not considered to be treatment-related.

A total of 23 (16.7%) subjects had at least one serious TEAE. This was more frequent in the neoadjuvant (13 subjects, 9.4%) and adjuvant (nine subjects, 7.1%) than in the surgery part of the study (two subjects, 1.5%). Most subjects (14/23) with serious TEAEs had grade 3 events, five subjects (5/23) had grade 4 events, and no grade 5 events were reported. The most frequent SOC category with at least one subject with a reported serious TEAE was “infections and infestations” (nine subjects), in which the only Preferred Term reported for more than one subject was “pneumonia” (two subjects, both with grade 3 events); moreover, one subject had a grade 3 pneumonia reportedly related to coronavirus 2019 disease. The only other individual Preferred Term reported as a serious TEAE in more than one subject was “anaphylactic reaction”, reported in two subjects, (one grade 3 and one grade 4). All other individual Preferred Terms were reported in one subject each. The only subject with a report in the SOC “cardiac disorders” had a grade 2 left-atrial dilatation. Four subjects reportedly had an event in the SOC category “hepatobiliary disorders”: one each grade 2 “cholelithiasis”, grade 3 “cholestasis”, grade 3 “hepatic cirrhosis”, and grade 2 “porto-sinusoidal vascular disorder”.

**CONCLUSION:**

EFFICACY: Neoadjuvant treatment with an anthracycline-free regimen in patients with HER2-positive, hormone receptor-negative, node-negative early breast cancer resulted in a high rate of pCR. The majority of patients achieving pCR had the HER2-enriched PAM50 subtype.
SAFETY: The safety profile observed in DECRESCENDO confirms the tolerability of the investigational regimen combining trastuzumab and pertuzumab with a de-escalated chemotherapy regimen. Grade 3–4 adverse events occurred in approximately one-third of patients (36%), with a low

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| incidence of serious adverse events (16.7%) and no treatment-related deaths. Overall, no new safety concerns were observed. |
| **Date of the report:** 01 December 2025. |

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## 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Term |
|---|---|
| ACS | American Cancer Society |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| AV | Atrioventricular |
| CRF | Case Report Form |
| CSP | *Code de la Santé Publique* |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor DNA |
| dDFS | Distant disease-free survival |
| DILI | Drug-induced liver injury |
| ECD | Extracellular domain |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ER | Estrogen receptor |
| FDC | Fixed-dose combination |
| FFPE | Formalin-fixed, paraffin-embedded |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| HER2 | Human epidermal growth factor receptor 2 |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| iDFS | Invasive disease-free survival |
| IDMC | Independent Data Monitoring Committee |
| Ig | Immunoglobulin |
| IHC | Immunohistochemistry |
| IMP | Investigational Medicinal Product |
| ISH | In-situ hybridization |
| ITT | Intent-to-treat |
| LVEF | Left-ventricular ejection fraction |
| IV | Intravenous(ly) |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| MRI | Magnetic resonance imaging |
| MUGA | Multiple-gated acquisition scintigraphy |
| OS | Overall survival |
| pCR | Complete pathological response |
| PET | Positron emission tomography |
| PR | Progesterone receptor |
| RCB | Residual cancer burden |
| RFS | Recurrence-free survival |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous(ly) |
| SOC | System Organ Class |
| T-DM1 | Trastuzumab emtansine |
| TEAE | Treatment-emergent adverse event |
| TEAESI | Treatment-emergent adverse event of special interest |
| ULN | Upper limit of normal |

# 9. INVESTIGATIONAL PLAN

## 9.1 OVERALL STUDY DESIGN AND PLAN

DECRESCENDO was a multicentre, open-label, dual-phase, single-arm phase II de-escalation trial evaluating an anthracycline-free strategy in subjects with human epidermal growth factor receptor 2 (HER2)-positive/estrogen receptor (ER)-negative/progesterone receptor (PR)-negative, node-negative early breast cancer considered to be highly sensitive to dual HER2 blockade with the monoclonal antibodies pertuzumab and trastuzumab.

Eligible subjects were to receive preoperative (neoadjuvant) treatment consisting of 12 applications of weekly intravenous (IV) paclitaxel (or IV docetaxel, every 3 weeks for 4 cycles) and pertuzumab and trastuzumab as a subcutaneous (SC) fixed-dose combination (FDC) every 3 weeks for 4 cycles (see all doses in Section **9.4**). Surgery was to be performed in all subjects after neoadjuvant treatment. If surgery was scheduled to take place 42 days or more since the previous administration of pertuzumab and trastuzumab FDC SC, one additional cycle of pertuzumab and trastuzumab FDC SC could be administered at investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. In this case, only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC would be administered in the postoperative (adjuvant) setting, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall. Moreover, additional provisions were made regarding the time between doses and regarding interruptions of pertuzumab and trastuzumab FDC SC (see Section **9.4**).

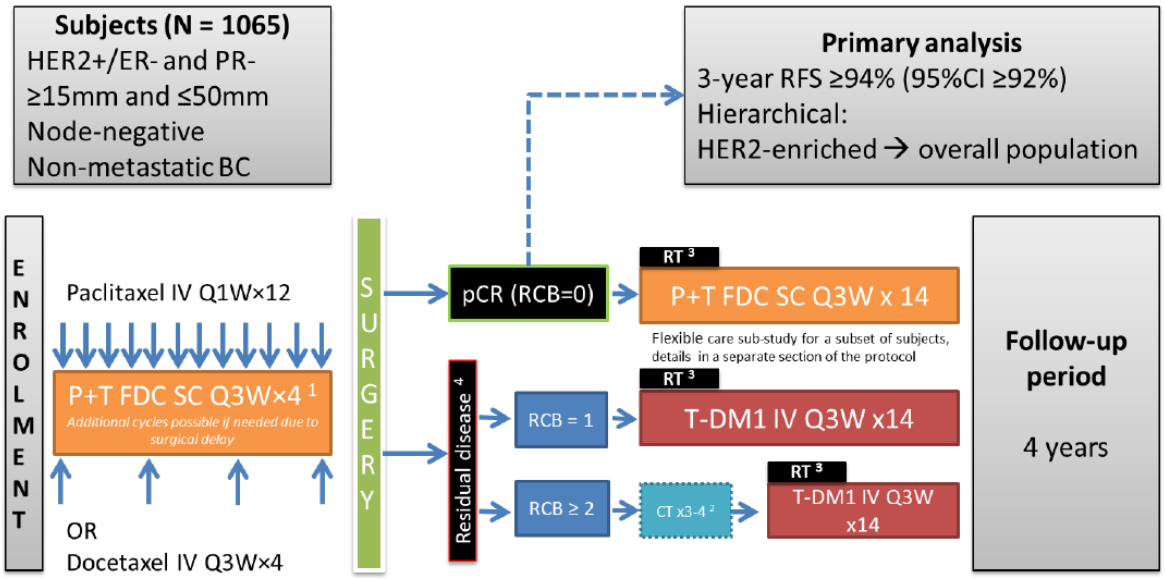
After surgery, subjects who achieved a complete pathological response (pCR), corresponding to a residual cancer burden (RCB) score of 0, were to receive adjuvant pertuzumab and trastuzumab FDC SC for 14 cycles. Those with residual invasive disease (RCB score at surgery ≥1) were to receive salvage adjuvant trastuzumab emtansine (T-DM1) for 14 cycles. In subjects with residual invasive disease classified as RCB score ≥2, three to four cycles of a standard anthracycline-based regimen should be administered before the administration of T-DM1 (Section **9.4.1**). Adjuvant radiotherapy was mandatory after breast-conserving surgery, whereas it would be performed according to local guidelines after mastectomy. Radiotherapy would be administered concomitantly with pertuzumab and trastuzumab in subjects who achieved a pCR, and concomitantly with T-DM1 in subjects with residual invasive disease (and after anthracycline-based chemotherapy in subjects who were to receive this treatment).

The primary objective of the trial was to evaluate 3-year relapse-free survival (RFS) in subjects with HER2-enriched tumors (as centrally determined by the PAM50 assay) who achieved a pCR after neoadjuvant treatment, and several secondary and exploratory endpoints were defined (see Section **9.5**). In order to achieve those objectives, the original total sample size for the trial was 1065 subjects. However, the trial was terminated early due to low recruitment, and the current Abbreviated Report focuses on safety, as recommended in the *Food and Drug Administration guidance for industry Submission of Abbreviated Reports and Synopses in Support of Marketing Applications*. The numbering system used in this document follows the *International Conference on Harmonisation (ICH) guidance, E3: Structure and Content of Clinical Study Reports*. **Figure 1** displays the design of the DECRESCENDO study.

Of note, the trial originally had a substudy on flexible care (not shown in **Figure 1**). After completion of neoadjuvant treatment and surgery in the main study, 121 of the subjects who achieved a pCR and thus were assigned to continue treatment with pertuzumab and trastuzumab FDC SC would be randomized at a 1:1 ratio to receive three cycles of pertuzumab and trastuzumab FDC SC every 3 weeks in the hospital, followed by three cycles in another setting outside the hospital, or to the same treatment starting with three cycles outside the hospital followed by three cycles in the hospital (treatment cross-over period). After the first 6

cycles of adjuvant treatment, subjects would be asked to choose between continuing treatment (for the remaining eight cycles, for a total of 14 cycles) within or outside the hospital, according to their preference (treatment continuation period). Subjects could request to change from outside the hospital to in the hospital administration (and vice-versa) at any moment during the treatment continuation period, but not in the treatment cross-over period. However, this substudy included only five patients, and therefore a statistical analysis was not carried out and will no longer be mentioned in the current report.

***Figure 1. Design of the DECRESCENDO study.***




Abbreviations: **CT**, chemotherapy; **ctDNA**, free circulating tumor DNA; **FDC**, fixed-dose combination; **FFPE**, formalin-fixed paraffin-embedded; **HER2**, human epidermal growth factor receptor 2; **P**, pertuzumab; **pCR**, pathologic complete response; **Q1W**, every week; **Q3W,** every 3 weeks; **RCB**, residual cancer burden (score); **RFS,** relapse-free survival; **RT**, radiotherapy; **SC**, subcutaneous; **T**, trastuzumab; **T-DM1**, trastuzumab emtansine.

*1 If surgery is scheduled with a significant delay (42 days or more since the previous administration of pertuzumab and trastuzumab FDC SC), one additional cycle of pertuzumab and trastuzumab FDC SC can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. In this case, only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC will be administered in the adjuvant setting, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.*

*Important note: If the time between two sequential injections of pertuzumab and trastuzumab FDC SC is less than 42 days (but more than 21+3 days), the maintenance dose of pertuzumab and trastuzumab FDC SC 600 mg/600 mg should be administered. The pertuzumab and trastuzumab FDC SC must not be interrupted for 42 consecutive days or more without a valid medical reason. If the treatment is interrupted for 42 days or more with the Sponsor's approval, a loading dose of pertuzumab and trastuzumab SC 1200 mg/600 mg must be administrated in order to restore adequate serum levels of pertuzumab and trastuzumab. The study treatment must not be interrupted for more than 60 consecutive days (except for the interval between the last neoadjuvant dose and the first adjuvant dose).*

*2 Anthracycline-based chemotherapy should be administered for 3 to 4 cycles for subjects who do not achieve a pCR and whose tumors have an RCB ≥2.*

*3 Adjuvant radiotherapy will be mandatory after breast-conserving surgery, whereas it will be performed according to local guidelines after mastectomy, and it will be administered concomitantly with pertuzumab and trastuzumab in subjects who achieve a pCR; and concomitantly with T-DM1 in subjects with residual invasive disease (after anthracycline-based chemotherapy in subjects who are assigned to receive this treatment).*

*4 Since this study will enrol only subjects with HER2-positive, ER-negative, and PR-negative disease at baseline, endocrine therapy is not a study IMP. If histopathological analysis finds that the surgical specimen from a subject with residual disease is ER-positive and/or PR-positive, adjuvant endocrine therapy may be administered concomitantly with study treatment, at the investigator's discretion and according to local guidelines.*

## 9.2 DISCUSSION OF STUDY DESIGN

With the development of anti-HER2 therapies, excellent outcomes have been achieved in subjects with node-negative, HER2-positive early breast cancer, as shown in the APT trial (Tolaney et al., 2015). However, minimizing chemotherapy-related side effects, particularly the long-term irreversible ones, remains a major priority. The main objective of the DECRESCENDO study was to offer chemotherapy "de-escalation" to subjects with ER-negative/PR-negative, node-negative disease with tumors ranging from 15 to 50 mm in diameter. This was done using a single-arm, phase-II trial design, which was considered appropriate in this setting, following other similar trials in lower-risk populations, such as the APT trial (Tolaney et al., 2015).

Although the APT trial only allowed subjects with tumors measuring up to 3 cm, DECRESCENDO allowed subjects with tumors measuring up to 5 cm, who may have a higher risk of recurrence. Moreover, only subjects with ER/PR-negative tumors were allowed in DECRESCENDO; since early recurrences are more frequent in this subgroup than in ER-positive subjects, the population of DECRESCENDO was also at higher risk from this point of view. On the other hand, the ADAPT trial showed high sensitivity to chemotherapy and dual HER2 blockade in HER2-positive/ER-negative/PR-negative tumors (Nitz et al., 2017). Tumor sensitivity to treatment with dual HER2 blockade is expected to be particularly high in subjects with HER2-enriched tumors, who constituted the population for the main analysis of DECRESCENDO. Finally, only node-negative subjects were allowed in DECRESCENDO, in order to select a population with a lower risk of recurrence—than those with positive nodes—and which may derive most benefit from a de-escalation strategy.

After neoadjuvant treatment and breast surgery, pCR—which is a prognostic factor in this population—was used to stratify subjects to receive risk-tailored adjuvant treatment. For subjects at lower risk (those with pCR), adjuvant treatment was chemotherapy-free and consisted only of the pertuzumab and trastuzumab FDC SC combination. Those without a pCR received more intense adjuvant treatment with T-DM1, based on the KATHERINE trial (von Minckwitz et al., 2019), and chemotherapy if the RCB was 2 or higher. The DECRESCENDO study had the potential to show that the de-escalation strategies used here would enable subjects to be spared the side-effects associated with the use of anthracyclines, alkylating agents, and platinum salts, all of which are often administered as part of the adjuvant or neoadjuvant chemotherapy schedules currently indicated for this population. These agents can induce severe long-term side effects, including congestive heart failure, ovarian failure, leukemia, and myelodysplastic syndromes.

## 9.3 SELECTION OF STUDY POPULATION

### 9.3.1 Inclusion criteria

Subjects had to meet all of the following criteria in order to be eligible for the study:

1. Male or female.
2. Age ≥18 years old.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
4. Subjects whose tumor measures ≥15 mm and ≤50 mm, according to clinical staging performed with imaging exams (either mammogram, ultrasound or breast magnetic resonance imaging [MRI]).
5. Must have histologically confirmed diagnosis of invasive HER2-positive and ER-negative/PR-negative breast cancer (analysis performed by the local laboratory).

a. HER2-positive defined as a score of 3+ in immunohistochemistry (IHC) or a positive in-situ hybridization (ISH); ratio of HER2 copy number/chromosome 17 ≥2 or average HER2 copy number ≥6 signals per cell).
b. ER-negative/PR-negative defined as ER and PR nuclear staining <1% by IHC.

Note: subjects with micro-invasive carcinoma or ductal carcinoma in situ without invasive disease were not eligible.

6. Subjects with multifocal or multicentric invasive disease were eligible as long as all the biopsiable lesions could be characterized and are confirmed to be HER2-positive and ER and PR negative.
   Note: In the case of multifocal or multicentric disease, only the biopsy from the largest lesion should be provided.
7. Node-negative disease (N0): no axillary lymph nodes identifiable at ultrasound, or in case of suspect axillary lymph nodes are identified, fine-needle aspiration or core biopsy had to be carried out to confirm that axillary status was negative. Axillary micrometastases (i.e., if the greatest diameter of the nodal metastasis in a sentinel node is 0.2 mm or less) were not allowed.
   ***Correction to nodal definition:***
   *The protocol stated that "axillary micrometastases (i.e., if the greatest diameter of the nodal metastasis in a sentinel node is 0.2 mm or less) were not allowed."*
   *This wording was inconsistent with standard AJCC definitions, in which deposits ≤0.2 mm are classified as isolated tumor cells (ITCs; pN0[i]), whereas micrometastases are defined as deposits >0.2 mm to ≤2.0 mm (pN1mi).*
   *The study population was intended to include patients with pathologically node-negative (pN0) disease. Subjects with initial tumors (T1 and T2) and presenting node-negative disease are probably the best candidates for de-escalation strategies, given the low risk of recurrence expected in this population. Therefore, only node-negative subjects were enrolled in DECRESCENDO, in order to select a population with a low risk of recurrence and who may derive the most benefit from a de-escalation strategy.*
   *All enrolled patients were confirmed as pN0 according to local pathology, and no patient with any isolated tumor cells or nodal disease was enrolled.*
   *This clarification of the nodal definition does not alter the study conduct or the interpretation of the results.*
8. Serum pregnancy test (for women of childbearing potential) negative within 7 days prior to treatment start.
9. Women of childbearing potential had to agree to use one highly effective non-hormonal contraceptive method with a failure rate of less than 1% per year from the signing of the Informed Consent Form (ICF) until at least 7 months after last dose of study drugs; or they had to totally abstain from any form of sexual intercourse. Men with a partner of childbearing potential had to agree to use condom in combination with a spermicidal foam, gel, film, cream, or suppository, and agree to refrain from donating sperm, during the study treatment administration and for at least 7 months after the last administration of study treatment.
10. Adequate bone marrow and coagulation functions as defined below:
    a. Absolute neutrophil count ≥1500 /µL or $1.5x10^9$/L;
    b. Hemoglobin ≥9 g/dL (blood transfusions to reach these levels of hemoglobin were allowed);
    c. Platelets ≥100,000/µL or $100x10^9$/L;
    d. International normalized ratio and activated partial thromboplastin (aPTT) time ≤ 1.5 × the upper limit of normal (ULN).
11. Adequate liver function as defined below:
    a. Serum total bilirubin ≤1.5 x ULN. In case of known Gilbert's syndrome ≤3 x ULN was allowed;

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN;
c. Alkaline phosphatase (ALP) ≤2.5 x ULN.

12. Adequate renal function as defined below:
    b. Creatinine ≤1.5 x ULN or creatinine clearance >60 mL/min/1.73 $m^2$.
13. Completion of all necessary screening procedures within 28 days prior to enrolment.
14. Adequate cardiac function, defined as a left-ventricular ejection fraction (LVEF) ≥55% estimated by echocardiogram (ECHO) or multiple-gated acquisition scintigraphy (MUGA).
15. Availability of a pre-treatment tumor biopsy sample as specified below:
    a. At least one freshly frozen, paraffin-embedded (FFPE) tumor block had to be available for central evaluation. Whenever possible, two FFPE tumor blocks should be available (preferred).
    b. If a block could not be provided, six unstained FFPE slides of 10 µm thickness and 20 unstained FFPE slides of 4 µm thickness from the pre-treatment tumor biopsy had to be provided as an alternative. These slides had to be freshly cut prior the shipment to the sponsor.
    c. In either case, the local pathologist had to evaluate an hematoxylin & eosin (H&E)-stained slide to ensure that the tumor surface was at least 4 $mm^2$ and that tumor cellularity was ≥10%.

    Note 1: Tumor biopsy must be sent to the central research laboratory as soon as the subject is confirmed by the local investigator to be eligible for the study.
    Note 2: the inclusion of the subject is only based on local assessments. A central review of HER2, ER, and PR status will be performed a posteriori for quality control purposes.
16. Signed ICF obtained prior to any study-related procedure.
17. Subject was willing and able to comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations.

Inclusion criterion applicable to France only:

18. Affiliated to the French Social Security System.

### 9.3.2 Exclusion criteria

Subjects meeting one of the following criteria were not eligible for this study:

1. Pregnant and/or lactating women.
2. Bilateral invasive breast cancer.
3. Evidence of metastatic breast cancer: all subjects must have had a computed tomography (CT)/MRI scan of the thorax/abdomen/pelvis to rule out metastatic breast cancer prior to enrolment. Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT could be used as an alternative to replace all the exams above. A screening bone scan had to have been done if the ALP and/or corrected calcium levels were above the institutional ULN at screening (if PET/CT was used as an alternative imaging exam, a bone scan and/or CT/MRI was not required).
4. Subject with a significant medical, neuro-psychiatric, or surgical condition, currently uncontrolled by treatment, which, in the investigator's opinion, might interfere with completion of the study.
5. Previous exposure to any anti-HER2 treatment.
6. Concomitant exposure to any investigational products as part of a clinical trial within 30 days prior to enrolment.
7. Subject with second primary malignancies diagnosed ≤ 5 years before enrolment in the study. Exceptions were: adequately treated non-melanoma skin cancer, in situ cancer of the cervix, ductal carcinoma in situ of the breast, and any other solid or hematological

tumor diagnosed > 5 years before enrolment and for which no chemotherapy and no systemic treatment were necessary, with no evidence of disease recurrence.

8. Resting electrocardiogram (ECG) with corrected QT interval >470 msec detected on at 2 or more time points within a 24-hour period, or family history of long QT syndrome.
9. Serious cardiac illness or medical conditions including, but not confined to, the following:
    a. History of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade ≥3 symptomatic congestive heart failure or New York Heart Association Class ≥II;
    b. 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 2] or third-degree AV-block) – Serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality;
    c. Angina pectoris requiring anti-anginal medication;
    d. Clinically significant valvular heart disease;
    e. Evidence of transmural infarction on ECG;
    f. Evidence of myocardial infarction within 12 months prior to enrolment;
    g. Poorly controlled hypertension (i.e., systolic >180 mm Hg or diastolic >100 mm Hg).
10. 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., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome.
11. Peripheral neuropathy (CTCAE version 5.0) grade ≥2.
12. Major surgery within 14 days prior to enrolment.
13. Subject with HIV, hepatitis B or hepatitis C infection documented by serology, except for those subjects with a previous exposure to hepatitis B who developed an effective immune response (HBSAg-negative and anti-HBS-positive).
14. Previous allogeneic bone marrow transplant.
15. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (CTCAE grade ≥3).
16. Subjects who received live attenuated vaccines within 14 days before enrolment.

Exclusion criterion applicable to France only:

17. Vulnerable persons according to the article L.1121-6 of the *Code de la Santé Publique* (CSP), adults who are the subject of a measure of legal protection or unable to express their consent according to article L.1121-8 of the CSP.

### 9.3.3 Removal of subjects from therapy or assessment

The study treatment was to be administered until completion of the adjuvant treatment or until any of the following:

- Evidence of disease progression or recurrence;
- Unacceptable adverse event (AE);
- Withdrawal of consent by the subject;
- Changes in the subject's condition that contraindicate further treatment in the judgment of the investigator;
- Any medical condition that the investigator or Sponsor determines may jeopardize

the subject's safety if he or she continues to receive study treatment;
- Investigator or Sponsor decision that treatment discontinuation is in the best interest of the subject;
- Pregnancy.

Subjects had the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator had the right to withdraw a subject from the study at any time. Reasons for withdrawal from the study might include, but were not limited, to withdrawal of consent, study termination or site closure, and subject failure to comply with protocol requirements as determined by the investigator or Sponsor. Subjects who withdrew from the study were not to be replaced. Further provisions regarding the documentation of withdrawals and further evaluation of safety and vital status, as well as further anticancer treatment and attempts to mitigate loss to follow-up for these subjects are provided in Section 4.4 of the Protocol.

Pertuzumab and trastuzumab FDC SC could not be interrupted for 42 consecutive days or more without a valid medical reason. The study treatment could not have been interrupted for more than 60 consecutive days (except for the interval between the last neoadjuvant dose and the first adjuvant dose). A subject could have a maximum of 60 consecutive days without receiving chemotherapy or T-DM1. If a delay of more than 60 days occured, treatment could have not been reintroduced, unless this was authorized by the Sponsor's medical team. Definitions related to disease progression and recurrence are provided in Section **9.5.1**.

The Sponsor had the right to close a study site at any time for reasons that included, but were not limited to, excessively slow recruitment, poor protocol adherence, inaccurate or incomplete data recording, non-compliance with ICH guidelines for Good Clinical Practice (GCP), and the absence of study activity (i.e., all subjects had completed the study and all obligations had been fulfilled).

## 9.4 TREATMENTS

### 9.4.1 Treatments administered

**Investigational medicinal products**

*Pertuzumab and trastuzumab FDC SC*

Pertuzumab and trastuzumab FDC SC (Phesgo®) is a fixed-dose (i.e., non-weight based) combination that has marketing authorization in Europe for the neoadjuvant treatment of adult subjects with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence and for the adjuvant treatment of adult subjects with HER2-positive early breast cancer at high risk of recurrence (see Summary of Product Characteristics, SmPC). It was provided free of charge by F. Hoffmann-La Roche Ltd. to all participating sites and labelled for investigational use only. Accurate records of the IMP reception, dispensing and destruction or return to the Sponsor (if applicable) were to be recorded on the Drug Accountability Form. More details about dispensing and handling are provided in the Protocol, and instructions for preparation were found in the IMP Management Manual.

All pertuzumab and trastuzumab FDC SC doses were administered by SC injection. The loading dose and maintenance dose should be administered over 8 and 5 minutes, respectively, at a rate of ≤2 mL/min with hand-held syringe to the thigh on Day 1 of each 3-week treatment cycle. Subjects should be monitored for at least 30 minutes after their first pertuzumab and trastuzumab FDC SC dose administration, and for at least 15 minutes following each subsequent administration.

Neoadjuvant pertuzumab and trastuzumab FDC SC was to be given every 3 weeks for 4 cycles. A loading dose of pertuzumab and trastuzumab FDC SC (1200 mg pertuzumab and 600 mg trastuzumab) was to be administered in the first cycle and for subjects who have had 42 days or more since their last pertuzumab and trastuzumab FDC SC administration. A maintenance dose of pertuzumab and trastuzumab FDC SC consisting of 600 mg pertuzumab and 600 mg trastuzumab was to be given in the remaining cycles.

Adjuvant pertuzumab and trastuzumab FDC SC was to be given every 3 weeks for 14 cycles. A loading dose (1200 mg pertuzumab and 600 mg trastuzumab) was to be administered for subjects who had 42 days or more since their last pertuzumab and trastuzumab FDC SC administration. A maintenance dose (600 mg pertuzumab and 600 mg trastuzumab) was to be given in the remaining cycles. If an additional cycle of pertuzumab and trastuzumab FDC SC had been administered (e.g., for surgery delay) during the neoadjuvant phase only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC were to be administered in the adjuvant phase, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.

Previous experience with pertuzumab and trastuzumab FDC SC has not revealed any new risks beyond those identified already as associated with the use of pertuzumab IV and trastuzumab IV/SC administered as single agents. Additional information can be found in the SmPC.

*Paclitaxel*

Paclitaxel is manufactured by different pharmaceutical companies and has marketing authorization in Europe for several indications related to breast cancer. The formulation of paclitaxel to be used in the study was the one commonly available at the site pharmacy. Paclitaxel was to be taken from the commercial stocks of the hospital pharmacies and to be re-labelled by the pharmacists before providing them to the subjects. Accurate records of the IMP dispensing and destruction were to be recorded on the Drug Accountability Form. Dispensing and handling were to be done according to each site's pharmacy practice. More details are provided in the Protocol. Neoadjuvant paclitaxel was to be administered IV at a dose of 80 mg/m² weekly for 12 weeks. The adverse reactions observed for paclitaxel can be found in the SmPC.

*Docetaxel*

Docetaxel is manufactured by different pharmaceutical companies and has marketing authorization in Europe for several indications related to breast cancer. The formulation of docetaxel to be used in the study was the one commonly available at the site pharmacy. Docetaxel was to be taken from the commercial stocks of the hospital pharmacies and to be re-labelled by the pharmacists before providing them to the subjects. Accurate records of the IMP dispensing and destruction were to be recorded on the Drug Accountability Form. Dispensing and handling were to be done according to each site's pharmacy practice. More details are provided in the Protocol. Neoadjuvant docetaxel was to be administered IV at a dose of 75 mg/m² IV every 3 weeks for 4 cycles. The adverse reactions observed for docetaxel can be found in the SmPC.

*Trastuzumab emtansine (T-DM1)*

T-DM1 (Kadcyla®) has marketing authorization in Europe for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy. It was provided free of charge by F. Hoffmann-La Roche Ltd. to all participating sites and labelled

for investigational use only. Accurate records of the IMP reception, dispensing and destruction or return to the Sponsor (if applicable) were to be recorded on the Drug Accountability Form. More details about dispensing and handling are provided in the Protocol, and instructions for preparation were found in the IMP Management Manual. Adjuvant T-DM1 was to be administered IV at a dose of 3.6 mg/kg every 3 weeks for 14 cycles for subject with residual invasive disease.

**Non-investigational medicinal products**

Information on formulation, preparation, stability, storage conditions, contraindications, special warnings/precautions for use and toxicity of non-IMPs could be found in the corresponding package inserts or SmPCs. Treatment management and compliance with these agents were left to the discretion of the site.

*Anthracycline-based chemotherapy*

After surgery, in subjects with residual invasive disease classified by an RCB score ≥2, three to four cycles of one of the standard anthracycline-based chemotherapy regimens should be administered before the start of T-DM1. The standard-of-care, anthracycline-based chemotherapy regimens accepted in the study are listed in **Table 1**.

***Table 1.*** ***Accepted anthracycline-based chemotherapy regimens***

| Regimen | Agents | Number of cycles | Interval between cycles |
|---|---|---|---|
| AC | Doxorubicin 60 mg/m$^2$ IV on D1<br>Cyclophosphamide 600 mg/m$^2$ IV on D1 | 4 | 14 to 21 days |
| EC | Epirubicin 90 mg/m$^2$ IV on D1<br>Cyclophosphamide 600 mg/m$^2$ IV on D1 | 4 | 14 to 21 days |
| FEC | Fluorouracil 500 mg/m$^2$ IV on D1<br>Epirubicin 90 mg/m$^2$ IV on D1<br>Cyclophosphamide 500 mg/m$^2$ IV on D1 | 3 | 14 to 21 days |
| FAC | Fluorouracil 500 mg/m$^2$ IV on D1<br>Doxorubicin 50 mg/m$^2$ IV on D1<br>Cyclophosphamide 500 mg/m$^2$ IV on D1 | 3 | 14 to 21 days |

D, day; IV, intravenously.

*Endocrine Therapy*

This study was designed to enroll only subjects with HER2-positive, ER-negative, and PR-negative disease at baseline. However, adjuvant endocrine therapy (concomitantly with study treatment, at the investigator's discretion and according to local guidelines) was allowed if residual disease containing ER-positive and/or PR-positive breast cancer was found upon histopathological analysis of the surgical specimen.

*Hematopoietic growth factors*

Hematopoietic growth factors (erythropoietin and granulocyte-colony-stimulating factors) could be administered to any subject at any time according to local site guidelines, at the investigator's discretion.

*Paclitaxel and docetaxel pre-medication*

All subjects were to be given premedication according to local guidelines consisting of corticosteroids and antihistamines before paclitaxel and docetaxel administration, in order to prevent severe hypersensitivity reactions.

### 9.4.2 Identity of investigational products

*Pertuzumab and trastuzumab FDC SC*

Pertuzumab and trastuzumab FDC SC is a ready-to-use formulation containing the active substances (pertuzumab and trastuzumab), as well as recombinant human hyaluronidase (rHuPH20) for SC administration. Pertuzumab and trastuzumab are recombinant humanized immunoglobulin (Ig) G1κ monoclonal antibodies which target HER2, also known as c-erbB-2, a transmembrane glycoprotein with intrinsic tyrosine-kinase activity. Pertuzumab and trastuzumab bind to distinct HER2 epitopes without competing and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are given in combination.

A loading and maintenance dose of pertuzumab and trastuzumab FDC SC are provided 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. The administered batches of the loading dose were the following: 1168940, 1170394, 1173059, 1176358, 1177493, 1178271, 1178278, 1179372, and 1181356.
- 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. The administered batches of the maintenance dose were the following: 1168953, 1169801, 1170766, 1171938, 1173166, 1177232, 1179283, 1180245, 118165, and 1182690.

*Paclitaxel*

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability inhibits the normal dynamic reorganization of the microtubule network, which is essential for interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

The metabolism of paclitaxel is catalyzed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administration of paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because it can result in lower paclitaxel exposures and its efficacy may be compromised.

*Docetaxel*

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown *in vitro* to disrupt the micro tubular network in cells which is essential for vital mitotic and interphase cellular functions.

*Trastuzumab emtansine (T-DM1*)

T-DM1 is a HER2-targeted antibody-drug conjugate which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. T-DM1 has the mechanisms of action of both trastuzumab and DM1. Llike trastuzumab, it binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fcγ receptors and complement C1q. In addition, T-DM1, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signalling through the phosphatidylinositol 3-kinase pathway, and mediates antibody-dependent cell-mediated cytotoxicity in human breast cancer cells that overexpress HER2. DM1, the cytotoxic component of T-DM-1, binds to tubulin. By inhibiting tubulin polymerization, both DM1 and T-DM1 cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from *in vitro* cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids. The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

The administered batches were the following: 1168961, 1171435, 1174086, and 1176557.

### 9.4.3 Method of assigning subjects to treatment groups

This was a single-arm trial. All eligible subjects were to start neoadjuvant treatment according to the same schedule (see **Figure 1**). On the other hand, adjuvant therapy could differ among subjects depending on pathological response to neoadjuvant therapy.

### 9.4.4 Selection of doses in the study

All starting doses used in the study, both for IMPs and for non-IMPs, were the conventional doses described in the SmPC for the corresponding agents.

Dose reductions were not allowed for pertuzumab and trastuzumab throughout the study, since they were administered in the same formulation. If the time between two sequential injections of pertuzumab and trastuzumab FDC SC was less than 42 days (but more than 21 + 3 days), the maintenance dose of pertuzumab and trastuzumab FDC SC 600 mg/600 mg should be administered. Pertuzumab and trastuzumab FDC SC should not be interrupted for 42 consecutive days or more without a valid medical reason. If the treatment was interrupted for 42 days or more with the Sponsor's approval, a loading dose of pertuzumab and trastuzumab SC 1200 mg/600 mg should be administered in order to restore adequate serum levels of pertuzumab and trastuzumab.

In the neoadjuvant phase, if the investigator decided to permanently interrupt neoadjuvant chemotherapy (paclitaxel or docetaxel) due to AEs, re-introduction of chemotherapy with the alternative taxane (i.e., a switch from paclitaxel to docetaxel and vice-versa) was allowed at the treating physician's discretion. If neoadjuvant chemotherapy was delayed due to an AE and the investigator judged that the AE was not related to anti-HER2 treatment, pertuzumab and trastuzumab FDC SC could be administered without delay.

If one of the doses of neoadjuvant chemotherapy or adjuvant T-DM1 was missed/skipped for reasons other than AEs, the missed dose could be administered after the last dose, to complete the planned chemotherapy cycles (12 weeks for paclitaxel and four cycles for docetaxel, 14 cycles for T-DM1). A subject could have a maximum of 60 consecutive days without receiving chemotherapy or T-DM1. If a longer delay occurred, treatment should not be reintroduced, unless authorized by the Sponsor's medical team.

The study protocol made provisions for dose modifications in case of non-hematological toxicity related to paclitaxel or docetaxel (**Table 2**), general toxicity—except LVEF decreases—related to pertuzumab and trastuzumab FDC SC (**Table 3**), LVEF decreases related to pertuzumab and trastuzumab FDC SC (**Table 4**), and LVEF decreases related to T-DM1 (**Table 5**)

***Table 2.*** ***Dose modification for non-hematological toxicity related to paclitaxel and docetaxel***

| Highest grade* | Dose modification |
|---|---|
| Grade 1 | No dose change, symptom management according to local guidelines. |
| Grade 2 | No dose change, symptom management according to local guidelines. In case of diarrhea or neuropathy, dose reduction (20% per dose reduction) or dose delay until recovery to grade ≤1 may be considered. |
| Grade 3 | Treatment interruption until recovery to grade ≤1. Symptom management according to local guidelines. Reintroduction with dose-reduction (20% per dose reduction). |
| Grade 4 | As a general rule, consider permanent treatment interruption. Symptom management according to local guidelines. Dose reduction (20% per dose reduction) and dose delay until recovery to grade ≤1 might be considered in selected cases after discussion with the Sponsor's medical team. |

*According to Common Terminology Criteria for Adverse Events, v5.0.

***Table 3.*** ***Dose modification for pertuzumab and trastuzumab FDC SC toxicity, except LVEF***

| Highest grade* | Dose modification |
|---|---|
| Grade 1 | No dose change, symptom management according to local guidelines |
| Grade 2 | No dose change, symptom management according to local guidelines. In case of diarrhea, dose delay until recovery to grade ≤1 may be considered. |
| Grade 3 | Treatment interruption until recovery to grade ≤1. Symptom management according to local guidelines. Reintroduction per investigator's discretion. |
| Grade 4 | As a general rule, consider permanent treatment interruption. Symptom management according to local guidelines. Dose delay until recovery to grade ≤1 might be considered in selected cases after discussion with the sponsor's medical team. |

*According to Common Terminology Criteria for Adverse Events, v5.0.

LVEF, left-ventricular ejection fraction.

***Table 4.*** ***Dose modification for LVEF decrease with pertuzumab and trastuzumab FDC SC***

| Severity | Dose modification |
|---|---|
| Absolute decrease <10% in LVEF in comparison with baseline LVEF value; LVEF ≥50% and no symptoms | No treatment modification. According to local guidelines, referral to a cardiologist is recommended. |

| Severity | Dose modification |
|---|---|
| Absolute decrease ≥10% in comparison with baseline LVEF and/or LVEF value <50% asymptomatic or in case of symptoms (cough, dyspnea, chest pain, shortness of breath) | Pertuzumab and trastuzumab FDC SC should be withheld for at least 3 weeks. LVEF should be re-assessed within 3 weeks. The management of symptoms must be started according to local guidelines (beta-blockers, angiotensin converting enzymeinhibitors). Referral to a cardiologist is advised. Pertuzumab and trastuzumab FDC may be resumed only if LVEF has recovered to ≥50% or to a difference of <10% points below pre-treatment values, and subject is asymptomatic, after discussion with the sponsor's medical team. If after LVEF recovery and treatment reintroduction, another LVEF drop occurs (absolute value <50% or LVEF decrease ≥10%), treatment must be permanently discontinued. |

LVEF, left-ventricular ejection fraction.

***Table 5.*** ***Dose modification for LVEF decrease with T-DM1***

| Severity or highest grade* | Dose modification |
|---|---|
| LVEF ≥50% | Continue treatment with T-DM1. |
| LVEF 45% to <50% and decrease is <10% points from LVEF value prior to starting T-DM1 treatment | Continue treatment with T-DM1. Repeat LVEF assessment within 3 weeks. |
| LVEF 45% to <50% and decrease is ≥10% points from LVEF value prior to starting T-DM1 treatment | Do not administer T-DM1. Repeat LVEF assessment within 3 weeks. If LVEF remains <50% and has not recovered to <10% points, discontinue T-DM1. Symptom management must be started according to local guidelines (beta-blockers, angiotensin converting enzyme inhibitors). Referral to a cardiologist is advised. |
| LVEF <45% | Do not administer T-DM1. Repeat LVEF assessment within 3 weeks. If LVEF <45% is confirmed, discontinue T-DM1. Symptom management must be started according to local guidelines (beta-blockers, angiotensin converting enzyme inhibitors). Referral to a cardiologist is advised. |
| Symptomatic heart failure, grade 3-4 left ventricular systolic dysfunction or grade 3-4 heart failure, or grade 2 heart failure accompanied by LVEF <45% | Discontinue T-DM1. Symptom management must be started according to local guidelines (beta-blockers, angiotensin converting enzyme inhibitors). Referral to a cardiologist is advised. |

*According to Common Terminology Criteria for Adverse Events, v5.0.

LVEF, left-ventricular ejection fraction.

### 9.4.5 Selection and timing of dose for each subject

For each subject, doses of pertuzumab and trastuzumab FDC SC were fixed (not based on weight or body surface area [BSA]). For paclitaxel and docetaxel, doses were based on BSA. For T-DM1, doses were based on body weight.

The doses of neoadjuvant chemotherapy and adjuvant T-DM1 did not need to be recalculated according to subject's BSA or weight before each administration, unless there was ≥10% change in weight from baseline. If the doses of neoadjuvant chemotherapy and/or T-DM1 were recalculated due to changes in weight, a new dose recalculation should only be performed if there was a new change of ≥10% in weight since the previous dose adjustment. If the investigator decided to reduce chemotherapy or T-DM1 dose due to toxicity, further dose escalation was not allowed.

### 9.4.6 Blinding

This was an open-label study.

### 9.4.7 Prior and concomitant therapy

The protocol specified that subjects could not receive any treatment with an anti-HER2 agent and any investigational products as part of a clinical trial within 30 days prior to enrolment.

**Allowed concomitant treatments**

Concomitant treatments were any medication used by the subject from 28 days prior to the first administration of study treatment through the end of study for the subject. All concomitant treatments, medications and therapies (including start/stop dates, dose, indication and any other relevant details) were to be recorded in the Case Report form (CRF) up to 30 days after the last administration of study treatments. The use of hematopoietic growth factors and transfusions of blood derivates were allowed per investigator's discretion during the whole period of study treatment. Vaccines without live micro-organisms (inactive components) were allowed during study treatment.

**Cautionary concomitant treatments**

Concomitant use of herbal therapies was not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer could be used during the study at the discretion of the investigator.

**Prohibited concomitant treatments**

Use of the following concomitant therapies was prohibited:

- Any investigational therapy or agent (other than protocol-mandated study treatment) was prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Any anti-cancer treatment other than adjuvant radiotherapy or bone-density-modifying treatment.
- Regular systemic treatment with steroids. Short-term corticosteroid to treat and prevent allergic or infusion reactions were allowed, but the dose should not exceed >20 mg/day of dexamethasone (or equivalent) for > 7 consecutive days.
- Hormone-replacement therapy was prohibited during the whole study duration for the subject.
- Topical estrogens (including any intra-vaginal preparations), megestrol acetate, and selective ER modulators used with prophylactic intent were prohibited during the whole study duration for the subject. Postmenopausal women with significant vaginal discomfort associated with antiestrogen therapy could be considered for intermittent use of low-dose topical estrogens if alternative methods were unsuccessful at ameliorating symptoms.
- Live attenuated vaccines were prohibited from 2 weeks before enrolment until 30 days after the last administration of the last dose of study treatment.
- Prohibited concomitant medications for (neo)adjuvant chemotherapy were the ones described in the SmPC of each drug.

### 9.4.8 Treatment compliance

Since treatment administration was to be done by trained staff in participating sites and under the supervision of experienced investigators, no specific measures of treatment compliance have been planned other than the analysis of exposure to treatment.

## 9.5 EFFICACY AND SAFETY VARIABLES

### 9.5.1 Efficacy and safety measures

The planned primary efficacy measure of this trial was RFS, defined as the time from enrolment until the first occurrence of invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, or death from any cause. Secondary efficacy endpoints were pCR, defined as the absence of residual invasive tumor in the breast and axillary lymph nodes (ypT0/Tis ypN0) at surgery as per the local pathological report; recurrence-free interval (RFI), defined as the time interval between enrolment and the first occurrence of invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, or death from breast cancer; distant disease-free survival (dDFS), defined as the time from enrolment until the first occurrence of distant recurrence, a second primary invasive (non-breast) cancer, or death from any cause; invasive disease-free survival (iDFS), defined as the time from enrolment until the first occurrence of invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, invasive contralateral breast cancer, second primary invasive (non-breast) cancer, or death from any cause; and overall survival, defined as the time from enrolment until death from any cause.

Safety was assessed through recording of the incidence, severity, and relationship to study treatment of AEs, SAEs and AEs of special interest (AESIs), using CTCAE version 5 for their grading and coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 28.0). The following events were considered AESIs:

- LVEF decrease, defined as a decrease in LVEF of >10% (in absolute value) in comparison with baseline, or an ejection fraction value <50% (in a subject who previously had an ejection fraction >50%) at any time point, detected either by echocardiogram or MUGA.
- Peripheral sensory neuropathy and/or peripheral motor neuropathy of ≥2.
- Diarrhea of grade ≥3.
- Thrombocytopenia of grade ≥3.
- Potential drug-induced liver injury (DILI): The finding of an elevated ALT or AST (>3 x ULN) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other reasons explaining the combination of increased aminotransferase and total bilirubin causes of hyperbilirubinemia (as defined by Hy's law). Regardless of causality, investigators must report as an AESI the occurrence of either of the following:
  - Treatment-emergent ALT or AST >3 x ULN in combination with total bilirubin >2 x ULN;
  - Treatment-emergent ALT or AST >3 x ULN in combination with clinical jaundice.
- Suspected transmission of an infectious organism, virus, or infectious particle by pertuzumab and trastuzumab FDC SC or T-DM1, pathogenic or non-pathogenic. This applies only when contamination of the study drug is suspected.

Exploratory measures included biomarkers of response and treatment resistance, and self-reported markers of ovarian function–menses and pregnancy.

**Assessments and flow charts**

The study was carried out as described below and according to the flowcharts shown in **Table 6**, **Table 7**, **Table 8**, and **Table 9**.

**Screening period**

During the screening period, following the signature of the ICF, the investigator confirmed subject eligibility by conducting the assessments described below. All screening evaluations were to be performed within 28 days before enrolment, except if described differently in the text below.

The evaluations and procedures to be conducted in the screening period include the following:

- ICF signature and signature date to be obtained prior any study specific procedures (subject to be registered in Subject Registration Tool = step 1).
- Eligibility check: review of inclusion and exclusion criteria.
- Past medical and surgical history
- Ovarian function assessment:
  - Menstrual and fertility history including number of previous pregnancies, number of previous live births, desire for future pregnancy and fertility preservation.
  - Contraceptive method for all female subjects of childbearing potential **within 1 month prior to study enrolment**.
  - Hormone replacement therapy intake **within 1 month prior to study enrolment**.
  - Gonadotropin-releasing hormone (GnRH) agonist or antagonist intake **within the last 6 months prior to study enrolment**.
- Demographic data: gender, year of birth.
- Concomitant medications, contraception, therapies and procedures from 28 days prior to the first administration of study treatment.
- Medical consultation including:
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms and height in centimeters) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems, breast examination and regional lymph node palpation.
  - Vital signs: temperature, blood pressure, heart rate, respiratory rate.
  - ECOG performance status
  - Smoking status and history.
- Electrocardiogram (ECG).
- ECHO or MUGA for the assessment of LVEF (same method should be used throughout the study).
- Laboratory tests (blood): hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, gamma-glutamyl transferase (GGT), ALP, total bilirubin, calcium, sodium, potassium, magnesium, albumin, glucose, free tyroxine (T4), and thyroid-stimulating hormone (TSH).
- Serum pregnancy test for all female subjects of childbearing potential **within 7 days prior to treatment start**.
- Previous results of breast mammogram or MRI (results within 60 days before enrolment are acceptable)
- CT or MRI of the thorax, abdomen and pelvis; bone scan (in case of elevated ALP and/or corrected calcium levels) – all these radiological assessments had to be negative for metastatic breast cancer. FDG-PET/CT could be used as an alternative to replace all the exams above.

- Tumor tissue was mandatory for all subjects at screening:
  - At least one FFPE tumor block had to be available for central assessment. Whenever possible, two FFPE tumor blocks should be available (preferred).
  - If a block could not be provided, six unstained FFPE slides of 10 µm thickness, and 20 unstained FFPE slides of 4 µm thickness from the pre-treatment tumor biopsy had to be available as an alternative. Slides were to be freshly cut for the study purposes.
  - The local pathologist was to evaluate an H&E-stained slide to ensure that the tumor surface was at least 4 $mm^2$ and that tumor cellularity was ≥10%.

  Note: Tumor biopsy was to be sent to the central research laboratory as soon as the subjects was confirmed by the local investigator to be eligible for the study.

- Plasma sample collection for biomarker analyses
- Whole blood sample
- SAEs related to protocol-mandated intervention

Results of all screening evaluations and procedures were to be reviewed by the investigator to ensure that all eligibility criteria had been satisfied prior to subject enrolment. A screening failure was defined as any subject who signed the ICF but was not enrolled in the study. Any screen failure had to be documented by the participating sites and recorded in the Subject Registration Tool.

**Study treatment period**

Study treatment period was to start within 7 days after subject enrolment and included neoadjuvant the treatment phase, surgery, and the adjuvant treatment phase.

*Neoadjuvant treatment*

- During the neoadjuvant part of the study, the following evaluations and procedures were to be performed every 3 weeks, within 3 days prior to treatment administration, unless stated otherwise in the text below:
- Pertuzumab and trastuzumab FDC SC administration every 3 weeks (±3 days) **for all subjects**
- Docetaxel administration every 3 weeks (±3 days) **for subjects treated with docetaxel**
- Paclitaxel administration every week (±2 days) **for subjects treated with paclitaxel**
- Evaluation of concomitant medications, therapies and procedures.
- Ovarian function assessment: contraceptive method for all female subjects of childbearing potential and GnRH agonist or antagonist intake.
- A medical consultation that had to include:
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms), evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems, breast examination and regional lymph node palpation. If the physical examination at screening was done within 3 days prior to the first day of treatment administration, there was no need to repeat this procedure before treatment administration at the first cycle.
  - Vital signs: temperature, blood pressure, heart rate, respiratory rate.
- ECOG performance status

- AEs, including serious AEs (SAEs) and AESIs, documented according to CTCAE v5, and pregnancies, exposures during lactation, overdoses, abuses, misuses, and medication errors (defined in Section 8.2.8 of the protocol).
- Recurrent/new cancer assessment, performed according to local guidelines and American Cancer Society (ACS)/American Socitey of Clinical Oncology (ASCO) Breast Cancer Survivorship Care Guideline.
  Note: At least a clinical assessment had to be performed. Imaging was to be performed in accordance with local guidelines.
- In case of disease progression during the neoadjuvant treatment, plasma samples were to be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.
- Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential.
- Laboratory tests including hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose had to be performed every week for subjects treated with paclitaxel (within 2 days prior to treatment administration) or every 3 weeks for subjects treated with docetaxel (within 3 days prior to treatment administration). If the laboratory tests at screening was done within 3 days prior to the first day of treatment administration, there was no need to repeat this procedure before treatment administration at the first cycle.

*Surgery*

Surgery was to be performed at 28 days (-7 days/+ 14 days) after the last dose of the neoadjuvant treatment. The surgical technique and the type of surgery performed should be defined according to local guidelines.

The following evaluations and procedures were to be performed:

*Within 7 days prior to surgery:*

- Laboratory tests: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose, prothrombin time, aPTT.
- Evaluation of concomitant medications, therapies and procedures.
- Ovarian function assessment: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential, and GnRH agonist or antagonist intake.
- Medical consultation
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.
  - Vital signs: temperature, blood pressure, heart rate, respiratory rate.
  - ECOG performance status.
  - Smoking status
- AEs, including SAEs and AESIs, documented according to CTCAE v5, and pregnancies, exposures during lactation, overdoses, abuses, misuses, and medication errors.
- MUGA or ECHO to evaluate cardiac function (same method as for screening should be used).

- Urine pregnancy test (if positive to be confirmed by serum test) should be performed before surgery for all female subjects of childbearing potential.
- Recurrent/new cancer assessment, performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline.
  Note: At least a clinical assessment should be performed. Imaging should be performed in accordance with local guidelines.
- Plasma samples for biomarker analyses.

*At surgery*

If evidence of residual invasive disease was found in the pathological specimen obtained after surgery, a FFPE tissue sample of residual invasive disease (the most representative block of the residual disease will be selected) had to be collected. If a pCR (pT0/Tis pN0) occured, no sample was required.

*Adjuvant treatment*

*For subjects who achieved a pCR (RCB = 0)*

Adjuvant pertuzumab and trastuzumab FDC SC should be started **within 28 days (±14 days) after surgery**.

The following evaluations and procedures were to be performed:

**At first cycle**

- Ovarian function assessment: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation, contraceptive method for all female subjects of childbearing potential, and GnRH agonist or antagonist intake.

**Every cycle (±3 days)**

- Treatment administration: pertuzumab and trastuzumab FDC SC

**Every 3 cycles (± 3 days)** unless stated otherwise in the text below**:**

- AEs, including SAEs and AESIs, documented according to CTCAE v5, and pregnancies, exposures during lactation, overdoses, abuses, misuses, and medication errors.
- Concomitant medications, therapies and procedures
- Medical consultation must be performed every 3 cycles (within 3 days prior to treatment administration) and must include:
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.
  - Vital signs: temperature, blood pressure, heart rate, respiratory rate.
  - ECOG performance status
  - Smoking status.
- Laboratory tests (within 3 days prior to treatment administration): hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose.

- Urine pregnancy test (within 3 days prior to treatment administration; if positive to be confirmed by serum test) had to be performed for all female subjects of childbearing potential.
  Note: Additional urine pregnancy testing could be performed if clinically indicated or if required per local guidelines, for the duration of study treatment and until 7 months after the last dose of study treatment. Any positive urine pregnancy test needed to be confirmed by serum pregnancy test.
- Recurrent/new cancer assessment, performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline.
  Note: At least a clinical assessment should be performed. Imaging should be performed in accordance with local guidelines.
- In case of disease recurrence, plasma samples had to be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.

**Every 4 cycles**

- MUGA or ECHO (within 7 days prior to treatment administration) to evaluate cardiac function during study treatment (same method as for screening should be used).

*For subjects with residual invasive disease (RCB≥1)*

For adjuvant T-DM1 or anthracycline-based chemotherapy, the adjuvant treatment was to start **within 28 days (+14 days)** after surgery. The following evaluations and procedures were to be performed:

- **Before anthracycline-based chemotherapy administration (only for subjects with RCB ≥2)**
  - MUGA or ECHO to evaluate cardiac function: within 7 days prior to the first cycle of anthracycline-based chemotherapy (same method as for screening should be used). **LVEF ≥55%** was necessary before administration of standard anthracycline-based chemotherapy.
- Anthracycline-based chemotherapy administration: three cycles of FAC or FEC, or three to four cycles of AC or EC, as described in **Table 1**.
- **At first cycle of T-DM1 (for all subjects with residual disease):**
  - MUGA or ECHO to evaluate cardiac function: within 15 days after the last cycle of anthracycline-based chemotherapy (same method as for screening should be used). **LVEF ≥50%** was necessary before administration of T-DM1.
  - Ovarian function assessment: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and GnRH agonist or antagonist intake.

**Every cycle**

- Treatment administration (±3 days): T-DM1.
- Concomitant medications, therapies and procedures.
- Medical consultation must be performed within 3 days prior to treatment administration and must include:
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.

  - Vital signs: temperature, blood pressure, heart rate, respiratory rate.
  - ECOG performance status.
- Laboratory tests (within 3 days prior to treatment administration): hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose.
- AEs, including SAEs and AESIs, documented according to CTCAE v5, and pregnancies, exposures during lactation, overdoses, abuses, misuses, and medication errors.
- Recurrent/new cancer assessment, performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline.
  Note: At least a clinical assessment should be performed. Imaging should be performed in accordance with local guidelines.
- In case of disease recurrence, plasma samples must be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.

**Every 3 cycles**

- Urine pregnancy test (within 3 days prior to treatment administration; if positive, to be confirmed by serum test) had to be performed for all female subjects of childbearing potential.
  Note: Additional urine pregnancy testing could be performed, if clinically indicated or if required per local guidelines, for the duration of study treatment and until 7 months after the last dose of study treatment. Any positive urine pregnancy test needed to be confirmed by serum pregnancy test.

**Every 4 cycles**

- MUGA or ECHO (within 7 days prior to treatment administration) to evaluate cardiac function during study treatment (same method as for screening should be used).

**End-of-treatment visit**

When a subject completed or discontinued study treatment, an end-of-treatment (EOT) visit should be carried out **30 days (± 3 days) after the last administration of study treatment**. The following evaluations and procedures had to be performed:

- Concomitant medications, therapies and procedures.
- Ovarian function assessment: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and GnRH agonist or antagonist intake.
- Medical consultation including:
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.
  - Vital signs: temperature, blood pressure, heart rate and respiratory rate.
  - ECOG performance status score
  - Smoking status
- Laboratory tests: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, GGT, ALP, total bilirubin, calcium, sodium, potassium, magnesium, glucose, free T4, and TSH.

- Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential.
- MUGA or ECHO to evaluate cardiac function (same method as for screening and study treatment period should be used).
- All AEs, including SAEs and AESIs, documented according to CTCAE v 5, and pregnancies.
- Recurrent/new cancer assessment, performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline.
  Note: At least a clinical assessment should be performed. Imaging should be performed in accordance with local guidelines.

**Follow-up period**

After the completion of study treatment or discontinuation of study treatment, subjects were to be followed for a total of 47 months (44 months for subjects who receive adjuvant anthracycline-based chemotherapy).

The first follow-up visit should be performed 2 months (± 7 days) after the EOT visit. Subsequent follow-up visits were be performed every 3 months (± 14 days) for the first 2 years and then every 6 months (± 28 days) for the last 2 years (Table 10).

The following evaluations and procedures should be conducted at each follow-up visits unless stated otherwise in the text below:

- Medical consultation including:
  - Physical examination: complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.
  - Vital signs: blood pressure and heart rate.
  - ECOG performance status score.
- Ovarian function assessment: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake **at the first follow-up visit and then once a year for the 3 following years**.
- Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential **during the 3 first follow-up visits**.
- Laboratory tests: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose.
- SAEs, AESIs documented according to CTCAE v5, and pregnancies.
- Recurrent/new cancer assessment, performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline.
  Note: At least a clinical assessment should be performed. Imaging should be performed in accordance with local guidelines.
- Subsequent cancer treatments (name of the drug, dosage, date when treatment started, date when any treatment was interrupted).
- MUGA or ECHO had to be performed to evaluate cardiac function every 6 months during the first year of follow-up (same method as for screening and treatment period should be used). After the first year, no additional MUGA or ECHO was performed.
- Mammogram or breast MRI had to be performed **annually**. For subjects submitted to conservative surgery, bilateral mammograms/MRI were required, whereas for subjects

submitted to mastectomy, unilateral mammogram/MRI in the non-operated breast was accepted.

- In case of disease recurrence, plasma samples had to be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.

**End-of-study visit**

When a subject completed the 4-year planned follow-up period or was discontinued from the study, the last follow-up visit was considered as the end-of-study visit.

***Table 6.*** ***Study procedures during screening, neoadjuvant treatment and before/at surgery (all subjects).***

| Assessment | Screening 28 days before enrolment | Neoadjuvant treatment (weeks) must start within 7 days after enrolment date. | | | | | | | | | | | Before surgery [r] | Surgery [t] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 [q] | | |
| ICF signature | X | | | | | | | | | | | | | | |
| Eligibility criteria | X | | | | | | | | | | | | | | |
| Past medical, cancer and surgical history | X | | | | | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | | | | | |
| Concomitant medications, therapies & procedures | X | X | | | X | | | X | | | X | | | X | |
| Ovarian function assessment | X [a] | X[b] | | | X[b] | | | X[b] | | | X[b] | | | X [c] | |
| Physical examination [d] | X | X | | | X | | | X | | | X | | | X | |
| Vital signs | X | X | | | X | | | X | | | X | | | X | |
| ECOG PS | X | X | | | X | | | X | | | X | | | X | |
| ECG | X | | | | | | | | | | | | | | |
| ECHO or MUGA | X | | | | | | | | | | | | | X | |
| Laboratory tests (screening & before surgery) | X [e] | | | | | | | | | | | | | X [s] | |
| Laboratory tests for subjects treated with **paclitaxel** [f] | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Laboratory tests for subjects treated with **docetaxel** [f] | | X | | | X | | | X | | | X | | | | |
| Pregnancy test [g] | X [h] | X | | | X | | | X | | | X | | | X | |
| Previous results of breast mammography or MRI [i] | X | | | | | | | | | | | | | | |
| Radiological assessment to exclude metastatic breast cancer [j] | X | | | | | | | | | | | | | | |
| Archival tumour sample (FFPE) [k] | X | | | | | | | | | | | | | | |
| Plasma sample | X | | | | | | | | | | | | | X | |
| Whole blood sample | X | | | | | | | | | | | | | | |
| SAEs / Aes [l] | X | X | | | | | | | | | | | | X | X |
| Recurrent/new cancers assessment [m] | | X | | | X | | | X | | | X | | | X | |
| FFPE tumour sample collection [n] | | | | | | | | | | | | | | | X |
| **Treatment administration** | | | | | | | | | | | | | | | |
| Pertuzumab and trastuzumab FDC SC [o] | | X | | | X | | | X | | | X | | | | |
| Paclitaxel [p] | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Docetaxel [p] | | X | | | X | | | X | | | X | | | | |

*a. Ovarian function assessment* ***at screening:*** *menstrual and fertility history including number of previous pregnancies, number of previous live births, desire for future pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential* ***within one month prior to study enrolment;*** *Hormone replacement therapy intake* ***within one month prior to study enrolment;*** *and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake* ***within the last 6 months prior to study enrolment.***
*b. Ovarian function assessment* ***during neoadjuvant treatment period****: contraceptive method for all female subjects of childbearing potential and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake.*

*c. Ovarian function assessment **before surgery**: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake.*
*d. Complete physical examination should include physical measurements (body weight in kilograms and height in centimeters [at screening]) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation. If the physical examination at screening is done within 3 days prior to the first day of treatment administration, there is no need to repeat this procedure before treatment administration at the first cycle.*
*e. Laboratory tests at screening include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, GGT, ALP, total bilirubin, calcium, sodium, potassium, magnesium, albumin, glucose, free T4, TSH. If the laboratory tests at screening are done within 3 days prior to the first day of treatment administration, there is no need to repeat this procedure before treatment administration at the first cycle.*
*f. Laboratory tests during neoadjuvant phase: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose. Laboratory tests must be performed **every week** (within 1 day prior to treatment administration) **for subjects treated with paclitaxel** and **every 3 weeks** (within 3 days prior treatment administration) **for subjects treated with docetaxel.***
*g. Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential within 3 days prior to treatment administration.*
*h. Serum pregnancy test for all female subjects of childbearing potential within 7 days prior to treatment start.*
*i. Results within 60 days before enrolment are acceptable*
*j. CT or MRI of the thorax, abdomen and pelvis; bone scan (in case of elevated ALP and/or corrected calcium levels) – all these exams must be negative for metastatic breast cancer. FDG/PET-CT can be used as an alternative to replace all the exams above.*
*k. At least one FFPE tumor block must be provided. Whenever possible, two FFPE tumor blocks should be provided (preferred).If a block cannot be provided, 6 unstained FFPE slides of 10 µm thickness and 20 unstained FFPE slides of 4 µm thickness from the pre-treatment tumor biopsy must be provided as an alternative.*
*Note: Tumor biopsy must be sent to the central research laboratory as soon as the subject is confirmed by the local investigator to be eligible for the study.*
*l. **At screening,** SAEs related to protocol-mandated intervention; **During neoadjuvant treatment period and before surgery**: AEs including SAEs documented according to CTCAE v5, and AESIs, pregnancies, exposures during lactation, overdoses, abuses, misuses and medication errors, as described in the section 8.2.*
*m. The assessment of recurrent disease/new cancers shall be performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline. In case of disease recurrence, plasma samples must be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.*
*Note : At least a clinical assessment should be performed. The imaging should be performed in accordance with local guidelines.*
*n. FFPE tissue sample of residual invasive disease (the most representative block of the residual disease will be selected) must be collected in case there is still residual invasive disease is found in the surgical specimen after neoadjuvant treatment.*
*o. Pertuzumab and trastuzumab FDC SC for 4 cycles, every 21 days: loading dose of pertuzumab and trastuzumab FDC SC (1200 mg of pertuzumab and 600 mg of trastuzumab) for the first administration, followed by a maintenance dose of pertuzumab and trastuzumab FDC SC (600 mg pertuzumab and 600 mg of trastuzumab).*
*p. Paclitaxel 80 mg/m2 IV weekly for 12 weeks, **OR** docetaxel 75 mg/m2 IV every 3 weeks for 4 cycles.*
*q. If surgery is scheduled with a significant delay (42 days or more since the previous administration of pertuzumab and trastuzumab FDC SC), one additional cycle of pertuzumab and trastuzumab FDC SC can be administered at the investigator's discretion before surgery, in order to maintain adequate serum levels of pertuzumab and trastuzumab. In this case, only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC will be administered in the adjuvant setting, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.*
*Important note: If the time between two sequential injections of pertuzumab and trastuzumab FDC SC is less than 42 days (but more than 21+3 days), the maintenance dose of pertuzumab and trastuzumab FDC SC 600 mg/600 mg should be administered. The pertuzumab and trastuzumab FDC SC must not be interrupted for 42 consecutive days or more without a valid medical reason. If the treatment is interrupted for 42 days or more with the Sponsor's approval, a loading dose of pertuzumab and trastuzumab SC 1200mg/600mg must be administrated in order to restore adequate serum levels of pertuzumab and trastuzumab. The study treatment must not be interrupted for more than 60 consecutive days (except for the interval between the last neoadjuvant dose and the first adjuvant dose).*
*r. All exams must be performed within 7 days (±3 days) before surgery.*
*s. Laboratory tests before surgery include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose, PT, aPTT*

*t. Surgery must be performed **at 28 days (-7 days/+ 14 days)** after the last dose of neoadjuvant treatment.*

***Table 7.** Study procedures during adjuvant treatment and EOT visit (subjects who achieve a pCR [RCB=0]).*

| Assessment | Adjuvant treatment (cycles); 1 cycle = 3 weeks must start within 28 days (±14 days) after surgery | | | | | | | | | | | | | | EOT visit 30 days (± 3 days) after the last administration of study treatment. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| **Treatment administration** | | | | | | | | | | | | | | | |
| Pertuzumab and trastuzumab FDC SC [a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Procedures** | | | | | | | | | | | | | | | |
| Concomitant medications, therapies & procedures | X | | | X | | | X | | | X | | | X | | X |
| Ovarian function assessment [b] | X | | | | | | | | | | | | | | X |
| Physical examination [c] | X | | | X | | | X | | | X | | | X | | X |
| Vital signs | X | | | X | | | X | | | X | | | X | | X |
| ECOG PS | X | | | X | | | X | | | X | | | X | | X |
| Laboratory tests [d] | X | | | X | | | X | | | X | | | X | | X [h] |
| Pregnancy test [e] | X | | | X | | | X | | | X | | | X | | X |
| SAEs/ AEs [f] | X | | | | | | | | | | | | | | X |
| Recurrent/new cancers assessment [g] | X | | | X | | | X | | | X | | | X | | X |
| ECHO or MUGA | | | | X | | | | X | | | | X | | | X |

*a. Pertuzumab and trastuzumab FDC SC for 14 cycles: loading dose of pertuzumab and trastuzumab FDC SC (1200 mg of pertuzumab and 600 mg of trastuzumab in case the interval from the last administration is 42 days or more); followed by maintenance dose of pertuzumab and trastuzumab FDC SC (600 mg of pertuzumab and 600 mg of trastuzumab) every 21 days. Study treatment must not be interrupted for more than 60 consecutive days (except for the interval between the last neoadjuvant dose and the first adjuvant dose). If during the neoadjuvant phase an additional cycle of pertuzumab and trastuzumab FDC SC has been administered (e.g., for surgery delay, see third bullet point in the above paragraph 5.1 Neoadjuvant phase), only 13 (instead of 14) cycles of pertuzumab and trastuzumab FDC SC will be administered in the adjuvant phase, in order to reach a total number of 18 cycles of pertuzumab and trastuzumab FDC SC overall.*
*b. Ovarian function assessment includes menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake*
*c. Complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.*
*d. Laboratory tests during adjuvant treatment include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose.*
*e. Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential within 3 days prior to treatment administration. Additional urine pregnancy testing may be performed, if clinically indicated or if required per local guidelines, for the duration of study treatment and until 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.*

*f. **During adjuvant treatment:** AEs including SAEs documented according to CTCAE v5, and AESIs, pregnancies, exposures during lactation, overdoses, abuses, misuses and medication errors, as described in the section 8.2; **At the end of treatment visit**: All AEs including SAEs documented according to CTCAE v 5, AESIs, and pregnancies as described in the section 8.2.*
*g. The assessment of recurrent disease/new cancers shall be performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline. In case of disease recurrence, plasma samples must be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.*
*Note: At least a clinical assessment should be performed. The imaging should be performed in accordance with local guidelines.*
*h. Laboratory tests at the EOT visit include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, calcium, magnesium, potassium, glucose, TSH, free T4.*

***Table 8.** **Study procedures during adjuvant treatment and EOT visit (subjects with residual invasive disease).***

| Assessment | Adjuvant treatment must start **within 28 days (+14 days)** after surgery | | | | | | | | | | | | | | **EOT visit** 30 days (± 3 days) after the last administration of study treatment. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Anthracycline-based chemotherapy[a] | **T-DM1 (cycles) ; 1 cycle = 3 weeks** must start within **28 days (+14 days)** after surgery | | | | | | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| **Treatment administration** | | | | | | | | | | | | | | | | |
| Anthracycline-based chemotherapy[a] | X[a] | | | | | | | | | | | | | | | |
| T-DM1 [b] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Procedures** | | | | | | | | | | | | | | | | |
| Concomitant medications, therapies & procedures | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Ovarian function assessment [c] | | X | | | | | | | | | | | | | | X |
| Physical examination [d] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECOG PS | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Laboratory tests [e] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X [i] |
| SAEs/AEs [f] | | | | | | | | X | | | | | | | | X |
| Pregnancy test [g] | X | X | | | X | | | X | | | X | | | X | | X |
| Recurrent/new cancers assessment [h] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECHO or MUGA | X[j] | | | | X | | | | X | | | | X | | | X |

*a. For subjects who do not achieve a pCR and with residual invasive disease classified as RCB ≥2 only, additional cycles of standard regimen anthracycline-based chemotherapy (see Table 1) should be administered, before T-DM1. Subjects receiving anthracycline-based adjuvant chemotherapy should have LVEF assessment by ECHO or MUGA (same method as for screening) 7 days before anthracyclines and 15 days after its administration. LVEF≥55% is necessary before anthracycline-based chemotherapy. The rest of assessments (physical examination, vital signs, ECOG PS, Laboratory tests) should be done according to local guidelines.*

*b. T-DM1 IV 3.6 mg/kg every 3 weeks for 14 cycles. Study treatment must not be interrupted for more than 60 consecutive days.*
*c. Ovarian function assessment includes menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake*
*d. Complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.*
*e. Laboratory tests (within 3 days prior to treatment administration) during adjuvant treatment include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose.*
*f.* ***During adjuvant treatment;*** *AEs including SAEs documented according to CTCAE v5, and AESIs, pregnancies, exposures during lactation, overdoses, abuses, misuses and medication errors, as described in the section 8.2;* ***At the end of treatment visit****: All AEs including SAEs documented according to CTCAE v 5, AESIs, and pregnancies as described in the section 8.2.*
*g. Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential (within 3 days prior to treatment administration). Additional urine pregnancy testing may be performed, if clinically indicated or if required per local guidelines, for the duration of study treatment and until 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.*
*h. The assessment of recurrent disease/new cancers shall be performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline. Note: At least a clinical assessment should be performed. The imaging should be performed in accordance with local guidelines.*
*In case of disease recurrence, plasma samples must be collected for plasma biomarker analysis, and all efforts should also be made to provide also FFPE tissue specimens of the recurrence.*
*i. Laboratory tests at the EOT visit include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, , total bilirubin, sodium, calcium, magnesium, potassium, glucose, TSH, free T4.*
*j. MUGA or ECHO should be performed to evaluate cardiac function within 7 days prior to the first cycle of anthracycline-based chemotherapy and within 15 days after the last cycle of anthracycline-based chemotherapy. Same method as for screening should be used. LVEF ≥55% is necessary before administration of standard anthracycline-based chemotherapy. LVEF ≥50% is necessary before administration of T-DM1.*

***Table 9.*** ***Study procedures during the follow-up period.***

| Assessment | Follow-up period (years) [a] | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Physical examination [b] | Every 3 months | Every 3 months | Every 6 months | Every 6 months |
| Vital signs | Every 3 months | Every 3 months | Every 6 months | Every 6 months |
| ECOG PS | Every 3 months | Every 3 months | Every 6 months | Every 6 months |
| Ovarian function assessment [c] | At 1st visit | Once a year | Once a year | Once a year |
| Pregnancy test [d] | At month 2,5 & 8 | | | |
| Laboratory tests [e] | Every 3 months | Every 3 months | Every 6 months | Every 6 months |
| Recurrent/new cancers assessment [f] | Every 3 months | Every 3 months | Every 6 months | Every 6 months |
| Subsequent cancer treatments | Every 3 months | Every 3 months | Every 6 months | Every 6 months |
| Echocardiogram or MUGA | Every 6 months | | | |
| Mammogram and/or breast MRI [g] | X | X | X | X |
| SAEs/AESIs & pregnancies [h] | X | | | |
| Plasma sample (to be collected in case of disease recurrence) | X | | | |
| Tissue FFPE sample (to be collected, whenever a biopsy is feasible, in case of disease recurrence). | X | | | |

*a. The first follow-up visit will be performed 2 months (± 7 days) after the EOT visit. Subsequent follow-up visits must be performed every 3 months (± 14 days) for the first 2 years and then every 6 months (± 28 days) for the last 2 years*
*b. Complete physical examination should include physical measurements (body weight in kilograms) and evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, neurologic systems, breast examination and regional lymph node palpation.*
*c. Ovarian function assessment: menstrual and fertility history including desire for future pregnancy, attempts at pregnancy and fertility preservation; contraceptive method for all female subjects of childbearing potential and gonadotropin-releasing hormone (GnRH) agonist or antagonist intake* ***at the first follow-up visit and then once a year for the 3 following years****.*
*d. Urine pregnancy test (if positive to be confirmed by serum test) for all female subjects of childbearing potential.*
*e. Laboratory tests include: hemoglobin, total platelet count, white blood cell count, absolute neutrophil count, ALT, AST, creatinine, total bilirubin, sodium, potassium, glucose.*
*f. The assessment of recurrent disease/new cancers shall be performed according to local guidelines and ACS/ASCO Breast Cancer Survivorship Care Guideline. Note: At least a clinical assessment should be performed. The imaging should be performed in accordance with local guidelines.*
*If a subject is diagnosed with disease recurrence, a tumor sample (FFPE) from recurrent invasive disease and a plasma sample have to be collected*
*g. Mammogram or breast MRI must be performed annually. For subjects submitted to conservative surgery, bilateral mammograms/MRI are required, whereas for subjects submitted to mastectomy, unilateral mammogram/MRI in the non-operated breast is accepted.*
*h. During the follow-up period, only SAE related to IMPs will be collected. LVEF events will be collected until 1 year after last administration of IMPs. Data regarding pregnancies (occurrence of pregnancy, outcomes, fetal status) will be collected until 7 months after the last administration of IMPs.*

### 9.5.2 Appropriateness of measurements

All efficacy and safety measures planned for the study are standard methods for clinical trials in early breast cancer, including the definition of time-to-event endpoints (according to the Standardized Definitions for Efficacy End Points system [Hudis et al, 2007]), and AEs (using CTCAE). No new methods have been used in the study.

### 9.5.3 Drug concentration measurements

Not applicable for the present study.

## 9.6 DATA QUALITY ASSURANCE

Throughout the study, dedicated Sponsor study team members such as data managers and medical fellows were to verify the collected data to ensure that the rights and well-being of subjects were protected; the reported study data were accurate, complete and verifiable based on source documents; and the conduct of the study was compliant with ICH GCP, the applicable regulatory requirements, the study protocol, and the study guidelines. Furthermore, to ensure that all the above-mentioned requirements were properly implemented in each country, academic research organizations and cooperative groups were involved in the study. These entities were responsible for overseeing the conduct of the study at site level and held regular meetings if needed with the sponsor to address any concerns or issues raised during the trial set-up, conduct and closure phase. To ensure compliance with the protocol, CRF completion guidelines, study documentation, standard operating procedures, ICH GCP, and all applicable regulatory requirements, the Sponsor could conduct quality assurance audits on participating sites. Regulatory agencies could also conduct regulatory inspection of the study. The investigator had to inform the Sponsor if an inspection by a regulatory agency had been scheduled at his/her site. Such audits/inspections could occur at any time during or after completion of the study. If an audit or inspection occurred, the investigator and institution were to agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues in the presence of the Sponsor, as needed or required.

### 9.6.1 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

A pathology manual was used to help standardize the work across laboratories. This manual explained how to assess baseline samples for HER2 and hormone-receptor status. It also describes the steps to handle surgical tumor samples to measure the response to treatment using the RCB score. Using this manual helped make sure all laboratories followed the same procedures, reducing differences and improving the quality of the results.

## 9.7 STATISTICAL METHODS PLANNED AND DETERMINATION OF SAMPLE SIZE

### 9.7.1 Statistical and analytical plans

A Statistical Analysis Plan (SAP) was finalized and signed before database lock (see Appendix **16.1.9** for further details on the SAP). The SAP described the following populations for analysis:

- Intent-to-treat (ITT) Population: all enrolled subjects, whether or not they received study treatment. The ITT Population was to be used for all baseline characteristics.

- Sensitivity Population: a subset of the ITT Population consisting of enrolled subjects whose tumors were confirmed to be HER2-positive and ER-negative/PR-negative per central pathology review.
- Safety Population: all subjects who received at least one dose of study treatment (starting in neoadjuvant phase) and had at least one post-baseline safety assessment, analyzed according to the treatment that they actually received. The Safety Population was to be used for safety analyses.

Descriptive statistics were to be presented in contingency tables with frequencies and percentages for categorical data, and summarized using number of non-missing values, mean, standard deviation, median, minimum and maximum values for continuous data. No inferential analyses were planned in the SAP. Tables were to be created by treatment arm or period, as appropriate. Listings with individual values were to be provided for all data presented in the tables.

If a subject discontinued or was lost to follow-up before establishing the pCR status, the subject was considered as not having attained pCR. This is considered a conservative approach to dealing with missing data. If pCR was not recorded within the secondary analysis population and, by extension, in the ITT population, all subjects receiving pertuzumab and trastuzumab FDC SC in the adjuvant setting were considered as having achieved pCR. This operational rule may overestimate pCR in the absence of surgical confirmation. Subjects receiving T-DM1 were considered as not achieving pCR.

Related AEs were defined as events with a relationship to study treatment equal to 'Related (Reasonable possibility)' or with missing relationship. AEs were considered to be treatment-emergent (TEAEs) if they started or worsened on or after the first dose of study treatment. Missing or partial AE start date was imputed in order to include events in summary tables in case of doubt (see section 4.5 of the SAP for more details).

The number of subjects who experienced TEAEs of all types (TEAEs, serious TEAEs, and TEAESIs) were summarized by System Organ Class (SOC) and Preferred Term, and additional listings were added by grade as well. Subjects were counted only once for each Preferred Term. In case a subject experienced the same event more than once, the event with the worst severity was considered.

This study had an Independent Data Monitoring Committee (IDMC) whose members included experts in the field of breast cancer and statisticians not related to the trial or the Sponsor. All study objectives, endpoints and safety data were to be periodically reviewed by the IDMC, which had the ability to recommend suspension of enrolment in case of safety concerns at any of the assessments, as well as modifications to the study, including its interruption. A separate charter was developed defining the responsibilities and procedures of the IDMC.

### 9.7.2 Determination of sample size

The required sample size for the study was justified based on the following assumptions:

- Proportion of subjects with HER2-enriched tumors and attained pCR rate
  - Among subjects with HER2-positive per IHC or ISH, ER-negative/PR-negative tumors, it was estimated that 75% would have HER2-enriched tumors per PAM50;
  - PAM50 testing was estimated to have a rate of inconclusive results of 10%, regardless of the HER2-enriched status;

  - Among subjects with HER2-enriched tumors, it was estimated that the pCR rate after neoadjuvant treatment with paclitaxel (or docetaxel), pertuzumab and trastuzumab FDC SC would be 70%;
  - Among subjects with non-HER2-enriched tumors, it was estimated that the pCR rate after neoadjuvant treatment with paclitaxel (or docetaxel), pertuzumab and trastuzumab FDC SC would be 30%;
- Anticipated RFS and design characteristics
  - A true RFS of 94% at 3 years for subjects with HER2-enriched tumors and achieving pCR, and the same rate of RFS for all subjects reaching pCR;
  - A target of 92% for the lower limit of the exact 95% confidence interval (CI);
  - A one-sided alpha-error level of 5%.

According to these assumptions and requirements, a total of 500 subjects would be needed in the primary analysis population (HER2-enriched tumor subtype and reaching pCR). In order to obtain 500 subjects for the primary analysis, a total of 1065 subjects would need to be enrolled in the neoadjuvant part of the study, of which around 635 were expected to achieve pCR (i.e., the secondary analysis population). Around 430 subjects were expected not to achieve pCR and would therefore be in the adjuvant T-DM1 group. Assuming a 20% rate of screening failure, at least 1330 subjects would need to be screened for this study. The rates of screening failures and pCR events were to be monitored during the study, and if these rates were different than expected, the sample size might be increased accordingly, in order to obtain at least a final 500 evaluable subjects for the primary analysis.

## 9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The initial study protocol (version 1.1, see Appendix **16.1.1**), dated 22 January 2021, was subject to three amendments.

The first amendment, dated 28 May 2021 (Protocol version 1.1), was done in response to the request for information from the French *Agence nationale de sécurité du médicament et des produits de santé* (France – INI-0034). The more substantial changes were to make mandatory anthracycline-based chemotherapy for subjects with residual disease (RCB score ≥2); the addition of LVEF assessments before and after treatment with anthracyclines; modifications to comply with the updated SmPCs of the IMPs. Moreover, some clarifications and updates were made to the study background, the duration for contraception, the thickness of FFPE slides of the pre-treatment tumor biopsy, and the commercial name of pertuzumab and trastuzumab FDC SC, among other changes for consistency and clarifications.

The second amendment, from 24 Sep 2021 (Protocol version 2.0), as made in response to the request for information in France and Belgium and included clarification on the primary objective and endpoint, as well as inclusion criterion (5. Moreover, a definition was added for childbearing potential and for reviewed postmenopausal status. Other changes were clarification on follow-up period and on wording at other passages.

Finally, the third amendment, dated 01 Sep 2022 (Protocol version 3.0), concerned reference updates in the study rationale and reference addition in the management of hematological toxicities; clarifications regarding timeframe, timepoints and delays for treatment (including surgery, delays between consecutive treatments); clarification of inclusion criteria 5, 6, and 15; modifications to comply with the updated SmPCs of the IMPs; addition of a possible switch in the neoadjuvant chemotherapy in case of toxicity; clarification regarding T-DM1 dose reduction in case of toxicity; updated in the management of LVEF decrease; allowance for flexibility regarding paclitaxel weekly treatment; clarification regarding recurrent/new cancer assessment during the neoadjuvant and adjuvant phases; clarification regarding LVEF pre- and post-anthracycline-based chemotherapy; clarification regarding timing of the first

Independent Data Monitoring Committee meeting; clarification regarding LVEF assessment in the sub-study; and wording clarifications.

Due to low recruitment, the study was discontinued early. When the study was discontinued, the sample size was 138 enrolled subjects. For that reason, most efficacy outcomes were not analyzed; only the rates of pCR and recurrence according to RCB were analyzed.

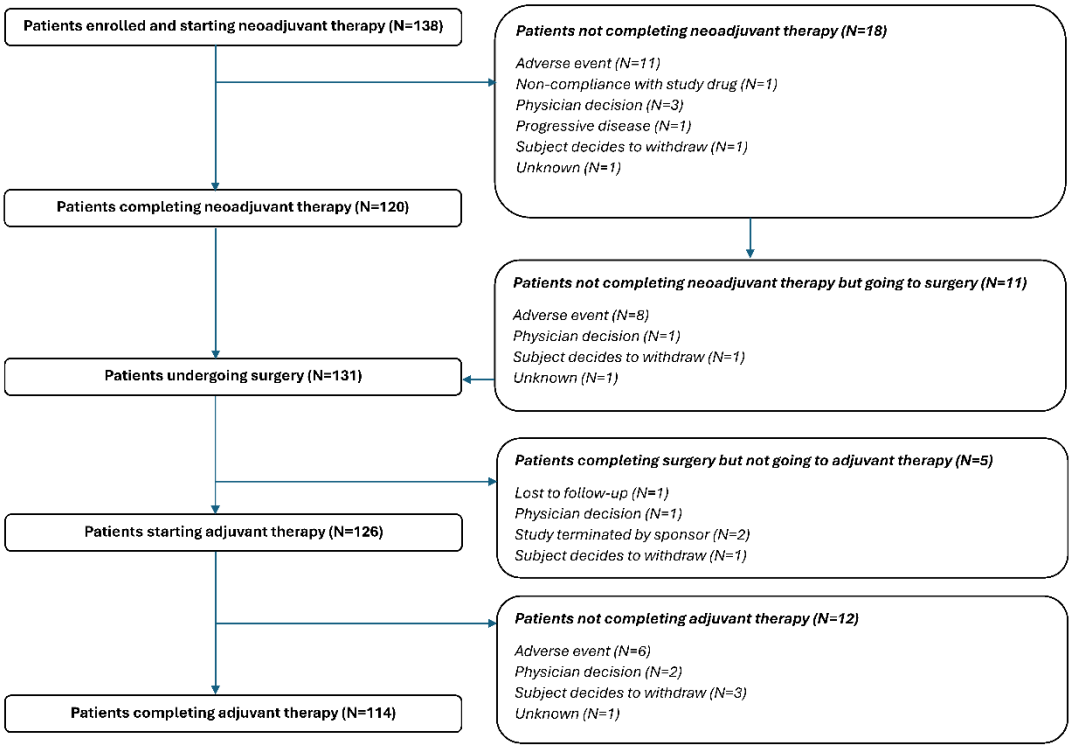
For statistical analysis, MedDRA version 25.1 (instead of 28.0) was used. In comparison with the planned analyses, a summary was added on TEAEs according to SOC (i.e., without showing Preferred Terms or grades).

# 10. STUDY SUBJECTS

## 10.1 DISPOSITION OF SUBJECTS

Between 17 Jan 2022 and 24 Jul 2023, 138 subjects were enrolled at 51 sites in Australia (n=22 subjects), Belgium (n=24), France (n=77), Israel (n=4), South Korea (n=9), and Switzerland (n=3). Enrolment was stopped in October 2023 due to low recruitment, and the study was terminated by the Sponsor. Both the ITT Population and the Safety Population comprised all 138 subjects. Of note, one subject (ID 0082; out of an initial number of 139) was considered by the site as a screen failure, did not start any treatment, and was therefore discontinued. **Figure 2** displays the study flowchart, and **Table 10** displays the disposition of subjects across the various components of study treatment.

***Figure 2. Patient disposition in the DECRESCENDO study.***



Of 138 subjects starting neoadjuvant treatment, 131 (94.9%) underwent surgery, and 126 (91.3%) started adjuvant treatment. The table also shows the number of subjects starting and completing each treatment component. Except for T-DM1, study treatment (IMP) completion was above 80% regarding subjects who started each treatment (11/15 subjects completed T-DM1). No subjects withdrew their consent, but four decided to withdraw from the study. Three subjects were lost to follow-up.

*Table 10.* ***Subject disposition (ITT Population).***

| Disposition according to treatment | N (%) |
|---|---|
| Subjects starting neoadjuvant treatment | 138 (100%) |
| Subjects undergoing surgery | 131 (94.9%) |
| Subjects starting adjuvant treatment | 126 (91.3%) |
| Subjects deciding to withdraw | 4 (2.9%) |
| Subjects lost to follow-up | 3 (2.2%) |
| Subjects starting paclitaxel | 129 (93.5%) |
| Subjects completing paclitaxel | 114 (82.6%) |
| Subjects starting docetaxel | 11 (8.0%) |
| Subjects completing docetaxel | 9 (6.5%) |
| Subjects starting pertuzumab and trastuzumab FDC SC | 138 (100%) |
| Subjects completing pertuzumab and trastuzumab FDC SC | 121 (87.7%) |
| Subjects starting T-DM1 | 15 (10.9%) |
| Subjects completing T-DM1 | 11 (8.0%) |

## 10.2 PROTOCOL DEVIATIONS

No tables or listings were produced for protocol deviations.

# 11. EFFICACY EVALUATION

Due to low accrual, a decision was made to not carry out a complete efficacy evaluation, and only selected and available outcomes were analyzed. All analyses of baseline data and efficacy were carried out on the database locked on 11 Mar 2025.

## 11.1 DATA SETS ANALYZED

The analyses of baseline data and of the only two efficacy measures analyzed were carried out on the ITT Population (N=138).

## 11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

**Table 11** displays selected baseline demographic characteristics. All subjects were women, and their mean age (± SD) was 58.2 (± 11.86) years. The youngest subject was 29, and the oldest was 86 years old. Most (89.1%) subjects had an ECOG performance status of 0, and slightly more than two-thirds were postmenopausal.

*Table 11.* ***Baseline demographic characteristics (ITT Population).***

| Characteristic | N (%) or value |
|---|---|
| Age (Years) | |

| Characteristic | N (%) or value |
|---|---|
| Mean (SD) | 58.2 (11.86) |
| Median (Min – Max) | 58 (29 – 86) |
| Sex | |
| Female | 138 (100%) |
| ECOG performance status | |
| 0 | 123 (89.1%) |
| 1 | 15 (10.9%) |
| Menopausal status | |
| Premenopausal | 44 (31.9%) |
| Postmenopausal | 94 (68.1%) |

ECOG, Eastern Cooperative Oncology Group.

**Table 12** displays selected baseline disease-related characteristics. Slightly over two-thirds of subjects had T2 tumors, and the lymph-node status was N0 in 136 subjects; two subjects had missing information for these two variables. The distribution of histological type and grade was typical of this population, with the predominance of invasive carcinoma of no special type (85.5%) and of grade 2 and grade 3 tumors (39.9% and 52.2%, respectively). Of subjects with available information, three were reported as having ER-positive tumors, and six as having PR-positive tumors. Upon contact with sites, all confirmed that these subjects had very low expression, were considered as having negative ER and PR for the sake of clinical practice and were therefore considered eligible for the study. All subjects in the study had a positive HER2 status, considering HER2 positivity as 3+ staining by IHC or a positive ISH (ratio of HER2 copy number/chromosome 17 ≥ 2) or an average HER2 copy number ≥6.

***Table 12.*** ***Baseline disease-related characteristics (ITT Population).***

| Characteristic | N (%) or value |
|---|---|
| Tumor laterality | |
| Left | 67 (48.6%) |
| Right | 71 (51.4%) |
| Tumor stage | |
| T1c | 43 (31.2%) |
| T2 | 93 (67.4%) |
| Missing | 2 (1.4%) |
| Lymph-node status | |
| N0 | 136 (98.6%) |
| Missing | 2 (1.4%) |
| Histological type | |
| Invasive carcinoma of no special type | 118 (85.5%) |
| Invasive lobular carcinoma | 14 (10.1%) |
| Other | 5 (3.6%) |
| Missing | 1 (0.7%) |
| Histological grade | |
| Gx: Differentiation cannot be assessed | 1 (0.7%) |

| Characteristic | N (%) or value |
|---|---|
| G1: Well differentiated | 6 (4.3%) |
| G2: Moderately differentiated | 55 (39.9%) |
| G3: Poorly differentiated/undifferentiated | 72 (52.2%) |
| Unknown | 1 (0.7%) |
| Missing | 3 (2.2%) |
| Estrogen-receptor status | |
| Positive* | 3 (2.2%) |
| Negative | 133 (96.4%) |
| Missing | 2 (1.4%) |
| Progesterone-receptor status | |
| Positive* | 6 (4.3%) |
| Negative | 130 (94.2%) |
| Missing | 2 (1.4%) |
| HER2 status assessment | |
| HER2 status assessed by IHC | 76 (55.1%) |
| HER2 status assessed by ISH | 8 (5.8%) |
| HER2 status assessed by ISH and IHC | 54 (39.1%) |

* Three subjects were reported as having ER-positive tumors, and six as having PR-positive tumors. Contact with sites confirmed that these subjects had very low expression and were considered as having negative ER and PR.

IHC, immunohistochemistry; ISH, in-situ hybridization; SD, standard deviation.

## 11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

There were no measurements of treatment compliance. Exposure to study treatment is described in Section **12.1**.

## 11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

### 11.4.1 Analysis of efficacy

Only two efficacy outcomes were analyzed: pCR rates and progression/recurrence events according to the RCB score.

**Table 13** displays the results of pathological analysis of surgical specimens for the 138 subjects in the Safety Population and the 131 subjects who underwent surgery. Considering the Safety Population, a pCR (i.e., RCB=0, corresponding to ypT0/TisN0 or subjects with missing information but receiving adjuvant pertuzumab and trastuzumab FDC SC) was reported in 113 of 138 subjects (81.9%); 10 subjects (7.2%) had an RCB score of 1, and eight (5.8%) had an RCB score of 2 or greater. Among subjects undergoing surgery, a pCR was reported in 113 of 131 subjects (86.3%); 10 subjects (7.6%) had an RCB score of 1, and eight (6.1%) had an RCB score of 2 or greater. In the latter group, the rates of pCR were relatively similar between subjects with T1 (36/41, or 87.8%) and T2 (75/88, or 85.2%) tumors. On the other hand, the pCR rate was numerically higher among subjects with HER2-enriched (88.8%) than among those with non-HER2-enriched (78.8%) tumors.

***Table 13.*** ***Pathological response (Safety Population N=138] and subjects undergoing surgery [N=131]).***

| Groups of subjects and response categories | Safety Population (N=138) | Patients undergoing surgery (N=131) |
|---|---|---|
| Subjects overall | | |
| RCB=0 | 113 (81.9%) | 113 (86.3%) |
| RCB=1 | 10 (7.2%) | 10 (7.6%) |
| RCB≥2 | 8 (5.8%) | 8 (6.1%) |
| Patients not undergoing surgery | 7 (5.1%) | Not applicable |
| According to tumor stage | | |
| T1, number of subjects | 43 (32.2%) | 41 (31.3%) |
| T1 with RCB=0 | 36/43 (83.7%) | 36/41 (87.8%) |
| T2, number of subjects | 93 (67.4%) | 88 (67.2%) |
| T2 with RCB=0 | 75/93 (80.6%) | 75/88 (85.2%) |
| According to PAM50 results | | |
| HER2-enriched, number of subjects | 98 (71.0%) | 98 (74.8%) |
| HER2-enriched with RCB=0 | 87/98 (88.8%) | 87/98 (88.8%) |
| Non-HER2-enriched, number of subjects | 40 (29.0%) | 33 (25.2%) |
| Basal-like | 19/40 (47.5%) | 19/33 (57.6%) |
| Luminal A | 7/40 (17.5%) | 7/33 (21.2%) |
| Other | 5/40 (12.5%) | 5/33 (15.2%) |
| Missing | 9/40 (22.5%) | 2/33 (6.1%) |
| Non-HER2-enriched with RCB=0 | 26/40 (65.0%) | 26/33 (78.8%) |
| Basal-like | 13/19 (68.4%) | 13/19 (68.4%) |
| Luminal A | 7/7 (100.0%) | 7/7 (100.0%) |
| Other | 4/5 (80.0%) | 4/5 (80.0%) |
| Missing | 2/9 (22.2%) | 2/2 (100.0%) |

Regarding tumor progression or recurrence, this was reported as progression (in the brain) in only one subject (ID 0088) with an RCB score of 0. Moreover, two subjects not described in that table (IDs 0010 and 0125) did not have surgery (and hence no ascertainment of RCB) and had progression reported (one in liver [ID 0010], the other without specific details).

### 11.4.2 Statistical/analytical issues

Not applicable for this study.

#### 11.4.2.1 Adjustments for covariates

Not applicable for this study.

#### 11.4.2.2 Handling of dropouts or missing data

There was no data imputation, except for missing dates, as foreseen in the SAP.

#### 11.4.2.3 Interim analyses and data monitoring

There were no formal interim analyses for efficacy. There were four meetings of the IDMC to ensure subject safety during the study.

#### 11.4.2.4 Multicenter studies

The study was conducted in 51 sites in six countries, but no analyses were carried out to assess baseline or efficacy results according to site or country, given the relatively small number of subjects included in the study.

#### 11.4.2.5 Multiple comparison/multiplicity

There was no need for adjustment for multiplicity, given the absence of inferential analyses or comparisons between groups.

#### 11.4.2.6 Use of an "efficacy subset" of subjects

Not applicable for this study.

#### 11.4.2.7 Active-control studies intended to show equivalence

Not applicable for this study.

#### 11.4.2.8 Examination of subgroups

No subgroup analyses were carried out other than the computation of pCR rates according to tumor stage and PAM50 subtypes (see Section **11.4.1**).

### 11.4.3 Tabulation of individual response data

Not applicable for this study.

### 11.4.4 Drug dose, drug concentration, and relationships to response

Not applicable for this study.

### 11.4.5 Drug-drug and drug-disease interactions

Not applicable for this study.

### 11.4.6 By-subject displays

Display of individual patient data, other than data provided in Appendix **16**, has not been considered necessary.

### 11.4.7 Efficacy conclusions

After enrolment of 138 subjects, the study had to be stopped due to low accrual, and only two efficacy outcomes could be analyzed. Among the 131 subjects who underwent surgery, a pCR rate of 86.3% (113/131) was achieved, higher than expected even considering only HER2-enriched tumors, for which a pCR rate of 70% was predicted and a pCR rate of 88.8% (87/98) was observed. For those with non-HER2-enriched tumors, a pCR rate of 30% was predicted and a pCR rate of 78.8% (26/33) was observed. Overall, three subjects had a report of tumor progression or recurrence until database lock, but RFS was not calculated due to the small number of subjects enrolled.

The available efficacy results from the current study suggest that the anthracycline-free neoadjuvant strategy tested here, with pertuzumab and trastuzumab FDC SC combined with

a taxane, is efficacious in terms of pCR rates in subjects with HER2-positive/ER- and PR-negative, node-negative, early breast cancer. Given the prognostic role of pCR in this setting, further research is warranted in order to establish the long-term benefit of this treatment, particularly with regard to tailoring adjuvant treatment to the pathological assessment of surgical specimens.

## 12. SAFETY EVALUATION

All analyses of safety data, carried out on the database locked on 11 Mar 2025. These analyses were carried out on the Safety Population (N=138).

### 12.1 EXTENT OF EXPOSURE

**Table 15** displays information on neoadjuvant treatment. Of 138 subjects starting neoadjuvant treatment, 129 were designated by investigators to receive paclitaxel as the chemotherapy partner to pertuzumab and trastuzumab FDC SC, and nine to receive docetaxel as such partner. No subject was still receiving treatment at the time of analysis. As indicated in the table, two subjects switched treatment from paclitaxel to docetaxel (Subject ID 0006 received eight administrations of paclitaxel and one of docetaxel, and Subject ID 0021 received one administration of paclitaxel and one of docetaxel). Moreover, one subject from the Safety Population (Subject ID 0152) was planned to receive paclitaxel in combination with pertuzumab and trastuzumab FDC SC, but did not receive paclitaxel, only the antibodies.

Subjects received a mean number of cycles of pertuzumab and trastuzumab FDC SC very close to the four planned neoadjuvant cycles. There were no dose interruptions of pertuzumab and trastuzumab FDC SC, and delayed administration of these antibodies was nominally less frequent, in relative terms, among subjects receiving paclitaxel than those receiving docetaxel. Among all subjects receiving paclitaxel, subjects received a mean of 11.3 of the planned 12 administrations; delayed administrations were reported for 31.0% of subjects, dose adjustments for 27.9%, and dose interruptions for 9.4%. Among the nine subjects receiving docetaxel, subjects received a mean of 3.9 of the planned four administrations; delayed administrations were reported for 33.0% of subjects, dose adjustments for 11.1%, and no dose interruptions were reported for docetaxel.

***Table 14.*** ***Exposure to neoadjuvant treatment according to taxane used (Safety Population).***

| Exposure | Pertuzumab and trastuzumab FDC SC plus paclitaxel (N=129) | Pertuzumab and trastuzumab FDC SC plus docetaxel (N=9) |
|---|---|---|
| **Subjects receiving at least one dose of pertuzumab and trastuzumab FDC SC** | **129 (100%)** | **9 (100%)** |
| Mean (SD) | 4.2 (0.75) | 3.9 (0.33) |
| Min ; Max | 1 ; 6 | 3 ; 4 |
| Number of subjects with delayed administration | 19 (14.7%) | 3 (33.3%) |
| Number of subjects with dose interruption | - | - |
| **Subjects receiving at least one dose of paclitaxel** | **128 (99.2%)** | **-** |
| Mean (SD) | 11.3 (2.04) | - |
| Min ; Max | 1 ; 12 | - |
| Number of subjects with delayed administration | 40 (31.0%) | - |

| Exposure | Pertuzumab and trastuzumab FDC SC plus paclitaxel (N=129) | Pertuzumab and trastuzumab FDC SC plus docetaxel (N=9) |
|---|---|---|
| Number of subjects with at least one dose adjustment | 36 (27.9%) | - |
| Number of subjects with dose interruption | 13 (10.1%) | - |
| **Subjects receiving at least one dose of docetaxel** | **2* (1.6%)** | **9 (100%)** |
| Mean (SD) | 1 | 3.9 (0.33) |
| Min ; Max | 1 ; 1 | 3 ; 4 |
| Number of subjects with delayed administration | - | 3 (33.3%) |
| Number of subjects with at least one dose adjustment | - | 1 (11.1%) |
| Number of subjects with dose interruption | 1 (0.8%) | - |

*Two subjects switched from paclitaxel to docetaxel.

SD, standard deviation.

**Table 15** displays information on adjuvant treatment. For pertuzumab and trastuzumab FDC SC, 110 subjects received a mean number of 13.2 of the 14 planned cycles of adjuvant treatment; for T-DM1, 15 subjects received a mean of 11.6 (with anthracyclines, n=5) to 12 (without anthracyclines, n=10) of the 14 planned cycles. Among these subjects, no delayed administrations, dose adjustments or dose interruptions were reported. Of note, one subject (ID 0067) received doxorubicin but not T-DM1 in the adjuvant period and therefore is not shown below.

***Table 15.** Exposure to adjuvant treatment (Safety Population).*

| | Pertuzumab and trastuzumab FDC SC (N=110) | T-DM1 (N=10) | Anthracyclines plus T-DM1 (N=5) |
|---|---|---|---|
| Subjects starting treatment | 110 | 10 | 5 |
| Number of subjects with at least one cycle | 110 | 10 | 5 |
| Mean (SD) | 13.2 (2.2) | 12 (3.5) | 11.6 (5.37) |
| Min ; Max | 2 ; 14 | 5 ; 14 | 2 ; 14 |
| Number of subjects with delayed administration | - | - | - |
| Number of subjects with at least one dose adjustment | - | - | - |
| Number of subjects with dose interruption | - | - | - |

*For anthracyclines plus T-DM1, shown are only the number of T-DM1 cycles.

SD, standard deviation.

## 12.2 ADVERSE EVENTS

### 12.2.1 Brief summary of adverse events

**Table 16** summarizes TEAEs reported for the Safety Population according to the component of study treatment (neoadjuvant, surgery, and adjuvant), and overall. The surgery period was defined as lasting from the date of surgery up to the start date of adjuvant treatment. Each event of a given type (Preferred Term) or of a given grade for a given subject was considered

separately for each part of the study (i.e., in the neoadjuvant, surgery or adjuvant period), according to the start date of the event. If an event spanned more than one period, it was counted only for the period in which it started (i.e., the earliest period). If it was reported in two periods with different start dates, it was counted twice. If two or more events of the same type (Preferred Term) but different grades were recorded for the same subject, the event with the worst grade was reported following the above rules. Moreover, TEAEs are reported for the whole study; in this case, each patient is counted only once, even if the same type of AE occurred in more than one part of the study. Of note, “serious TEAE” denotes SAEs that were treatment-emergent.

Overall, all subjects had at least one TEAE, which were more frequently reported in the neoadjuvant (100%) and adjuvant (89.7%) parts of the study than during the surgery period (22.1%), always in relation to the number of subjects receiving each of these treatment components. In nearly two-thirds of subjects, the highest grade of the TEAE was 1 or 2, and for the remaining one-third it was grade 3 or 4. Further considerations on grading of TEAEs are provided in Section **12.2.3**. At least one serious TEAE was reported for 23 (16.7%) subjects, again more often in the neoadjuvant (9.4%) and adjuvant (7.1%) parts of the study than during the surgery period (1.5%). Most of these serious TEAEs were considered as treatment-related (17/23), particularly during the neoadjuvant (11/13) and surgery (2/2) parts of the study. At least one TEAESI was reported for 32 (23.2%) subjects, and further details on these events are provided in Section **12.2.3**. Relatedness to study drug was always more frequent for paclitaxel than for the other three study drugs for TEAEs, serious TEAEs, TEAEs leading to study-drug dose reduction, and TEAEs leading to permanent treatment discontinuation.

***Table 16.*** ***Summary of TEAEs (Safety Population).***

| Category of TEAE | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Subjects with at least one TEAE | 138 (100%) | 29 (22.1%) | 113 (89.7%) | 138 (100%) |
| All TEAEs (severity) | | | | |
| Grade 1-2 | 104 (75.4%) | 26 (19.8%) | 95 (75.4%) | 88 (63.8%) |
| Grade 3-4 | 34 (24.6%) | 3 (2.3%) | 17 (13.5%) | 50 (36.2%) |
| Subjects with at least one serious TEAE | 13 (9.4%) | 2 (1.5%) | 9 (7.1%) | 23 (16.7%) |
| Subjects with at least one treatment-related serious TEAE | 11 (8.0%) | 2 (1.5%) | 4 (3.2%) | 17 (12.3%) |
| Subjects with at least one TEAESI* | 27 (19.6%) | - | 7 (5.6%) | 32 (23.2%) |
| Subjects with any TEAE leading to death | - | - | - | - |
| Subjects with any TEAE related to study drug | | | | |
| Pertuzumab and trastuzumab FDC SC | 96 (69.6%) | 7 (5.3%) | 67 (53.2%) | 109 (79.0%) |
| Paclitaxel | 124 (89.9%) | 5 (3.8%) | 29 (23.0%) | 125 (90.6%) |
| Docetaxel | 12** (8.7%) | - | 4 (3.2%) | 13 (9.4%) |
| T-DM1 | - | - | 15 (11.9%) | 15 (10.9%) |
| Subjects with any serious TEAE related to study drug | | | | |
| Pertuzumab and trastuzumab FDC SC | 4 (2.9%) | - | 1 (0.8%) | 5 (3.6%) |
| Paclitaxel | 8 (5.8%) | - | 1 (0.8%) | 9 (6.5%) |

| Category of TEAE | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Docetaxel | 1 (0.7%) | - | - | 1 (0.7%) |
| T-DM1 | - | - | 2 (1.6%) | 2 (1.4%) |
| Subjects with any TEAE leading to study-drug dose reduction | | | | |
| Pertuzumab and trastuzumab FDC SC | 1 (0.7%) | - | - | 1 (0.7%) |
| Paclitaxel | 35 (25.4%) | - | - | 35 (25.4%) |
| Docetaxel | 1 (0.7%) | - | - | 1 (0.7%) |
| T-DM1 | - | - | 4 (3.2%) | 4 (2.9%) |
| Subjects with any TEAE leading to permanent treatment discontinuation | | | | |
| Pertuzumab and trastuzumab FDC SC | 4 (2.9%) | - | 3 (2.4%) | 7 (5.1%) |
| Paclitaxel | 7 (5.1%) | - | 2 (1.6%) | 9 (6.5%) |
| Docetaxel | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| T-DM1 | - | - | 2 (1.6%) | 2 (1.4%) |

TEAE, treatment-emergent adverse event(s); TEAESI, treatment-emergent adverse event(s) of special interest.

*Three adverse events of special interest, two in the neoadjuvant part and one in the adjuvant part of the study are not included because they did not fulfil the definition of potential drug-induced liver injury.

** Subject IDs 0044, 0106 and 0134 had AEs reported as related to docetaxel while in fact receiving paclitaxel.

**Table 17** displays a summary of TEAEs by SOC according to the component of study treatment (neoadjuvant, surgery, and adjuvant), and overall, whereas details on Preferred Terms are shown in Section **12.2.2**. Overall in the study, the most commonly reported SOCs (in more than 70% of subjects) were “gastrointestinal disorders”, “skin and subcutaneous tissue disorders”, and “general disorders and administration site conditions”. Of note, TEAEs under the SOC “cardiac disorders” were reported in only 10 (7.2%) subjects overall, five each in the neoadjuvant and adjuvant parts of the study. One TEAE was reported in the SOC category “neoplasms benign, malignant and unspecified (incl. cysts and polyps)”: this was a case of tumor pain.

***Table 17.** Summary of TEAEs by SOC (Safety Population).*

| System Organ Class | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Overall | 138 (100%) | 29 (22.1%) | 113 (89.7%) | 138 (100%) |
| Blood and lymphatic system disorders | 32 (23.2%) | - | 12 (9.5%) | 41 (29.7%) |
| Cardiac disorders | 5 (3.6%) | - | 5 (4.0%) | 10 (7.2%) |
| Ear and labyrinth disorders | 2 (1.4%) | - | 8 (6.3%) | 10 (7.2%) |
| Endocrine disorders | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Eye disorders | 16 (11.6%) | 1 (0.8%) | 7 (5.6%) | 23 (16.7%) |
| Gastrointestinal disorders | 119 (86.2%) | 3 (2.3%) | 52 (41.3%) | 125 (90.6%) |
| General disorders and administration site conditions | 99 (71.7%) | 6 (4.6%) | 43 (34.1%) | 109 (79.0%) |
| Hepatobiliary disorders | 9 (6.5%) | - | 5 (4.0%) | 11 (8.0%) |
| Immune system disorders | 11 (8.0%) | 1 (0.8%) | 1 (0.8%) | 13 (9.4%) |
| Infections and infestations | 43 (31.2%) | 8 (6.1%) | 47 (37.3%) | 74 (53.6%) |

| System Organ Class | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Injury, poisoning and procedural complications | 8 (5.8%) | 2 (1.5%) | 29 (23.0%) | 36 (26.1%) |
| Investigations | 24 (17.4%) | 2 (1.5%) | 9 (7.1%) | 34 (24.6%) |
| Metabolism and nutrition disorders | 21 (15.2%) | 1 (0.8%) | 12 (9.5%) | 31 (22.5%) |
| Musculoskeletal and connective tissue disorders | 33 (23.9%) | 4 (3.1%) | 36 (28.6%) | 63 (45.7%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.7%) | - | - | 1 (0.7%) |
| Nervous system disorders | 85 (61.6%) | - | 28 (22.2%) | 96 (69.6%) |
| Psychiatric disorders | 11 (8.0%) | 1 (0.8%) | 15 (11.9%) | 24 (17.4%) |
| Renal and urinary disorders | 9 (6.5%) | - | 4 (3.2%) | 11 (8.0%) |
| Reproductive system and breast disorders | 4 (2.9%) | 1 (0.8%) | 12 (9.5%) | 17 (12.3%) |
| Respiratory, thoracic and mediastinal disorders | 49 (35.5%) | - | 23 (18.3%) | 66 (47.8%) |
| Skin and subcutaneous tissue disorders | 97 (70.3%) | 7 (5.3%) | 41 (32.5%) | 112 (81.2%) |
| Vascular disorders | 20 (14.5%) | 1 (0.8%) | 16 (12.7%) | 32 (23.2%) |
| Not coded (fatigue) | 1 (0.7%) | - | - | 1 (0.7%) |

### 12.2.2 Display of adverse events

**Table 18** displays the number of subjects with all TEAEs reported until database lock, according to SOC and Preferred Term. A short summary considering the worst grade per subject is provided below in Section **12.2.3**.

Overall in the study, the SOC categories with the largest number of subjects with reported TEAEs were "gastrointestinal disorders" (n=125; 90.6%), "skin and subcutaneous tissue disorders" (n=112; 81.2%), "general disorders and administration site conditions" (n=109; 79.0%), "nervous system disorders" (n=96; 69.6%), and "infections and infestations" (n=74; 53.6%). The most frequently reported Preferred Terms in the study overall were "diarrhea" (n=108 subjects; 78.3%), "alopecia" (n=57; 41.3%), "asthenia" (n=51; 37.0%), "fatigue" (n=45; 32.6%), "neuropathy, peripheral" (n=44; 31.9%; with 14 additional reports of "peripheral sensory neuropathy", 10 of "paresthesia", two of "dysesthesia", two of "neurotoxicity", and two of "peripheral motor neuropathy"), "nausea" (n=41; 29.7%), "epistaxis" (n=33; 23.9%), "rash" (n=28; 20.3%; with 12 additional reports of different types of skin rash), "arthralgia" (n=26; 18.8%; with one additional case each of "arthritis" and "polyarthritis"); "radiation skin injury" (n=24; 17.4%), and "anemia" (n=22; 15.9%). In addition to these events, Preferred Terms reported in at least 10% of subjects in the study overall were "muscle spasms" (n=18; 13.0%), "cough" (n=17; 12.3%), "dry skin" (n=17; 12.3%), "headache" (n=20; 14.5%), "dysgeusia" (n=17; 12.3%; with one additional report of "hypogeusia"), "pruritus" (n=17; 12.3%), "stomatitis" (n=17; 12.3%; with 25 additional reports of "mucosal inflammation" and one of "mucosal pain"), "COVID-19" (n=16; 11.6%); with one additional report of "COVID pneumonia"), "neutropenia" (n=16; 11.6%), "abdominal pain" (n=14; 10.1%; with 9 additional reports of "abdominal pain, upper"), "gastroesophageal reflux disease" (n=14; 10.1%), "myalgia" (n=14; 10.1%), and "hot flush" (n=14; 10.1%).

Considering only the neoadjuvant part of the study, the most frequently reported SOC categories were "gastrointestinal disorders" (n=119; 86.2%), "general disorders and administration site conditions" (n=99; 71.7%), "skin and subcutaneous tissue disorders" (n=97; 70.3%), "nervous system disorders" (n=85; 61.6%), “respiratory, thoracic and mediastinal disorders” (n=49; 35.5%), and "infections and infestations" (n=43; 31.2%). The most frequently

reported Preferred Terms were "diarrhea" (n=100; 72.5%), "alopecia" (n=55; 39.9%), "asthenia" (n=44; 31.9%), "neuropathy, peripheral" (n=40; 29.0%; with 12 additional reports of "peripheral sensory neuropathy", 10 of "paresthesia", two of "neurotoxicity", and one of "peripheral motor neuropathy"), "fatigue" (n=37; 26.8%), "nausea" (n=34; 24.6%), "epistaxis" (n=30; 21.7%), "rash" (n=25; 18.1%; with 10 additional reports of different types of skin rash), “mucosal inflammation” (n=23; 16.7%), and "anemia" (n=21; 15.2%).

Twenty-nine (22.1%) of 131 subjects undergoing surgery had at least one TEAE reported, more frequently under the SOC categories "infections and infestations" (n=8; 6.1%), "skin and subcutaneous tissue disorders" (n=7; 5.3%), and "general disorders and administration site conditions" (n=6; 4.6%).

Considering only the adjuvant part of the study, the SOC categories with the largest number of subjects with reported TEAEs were "gastrointestinal disorders" (n=52; 41.3%),"infections and infestations" (n=47; 37.3%), "general disorders and administration site conditions" (n=43; 34.1%), and "skin and subcutaneous tissue disorders" (n=41; 32.5%). The Preferred Terms reported for at least 10% of the 126 subjects were "diarrhea" (n=34; 27.0%), "radiation skin injury" (n=24; 19.0%), "asthenia" (n=20; 15.9%), "fatigue" (n=14; 11.1%), and "arthralgia" (n=13; 10.3%; with one additional case of "polyarthritis").

***Table 18.*** ***Summary of TEAEs by SOC and Preferred Term (Safety Population).***

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Overall | 138 (100%) | 29 (22.1%) | 113 (89.7%) | 138 (100%) |
| Blood and lymphatic system disorders | 32 (23.2%) | - | 12 (9.5%) | 41 (29.7%) |
| Anaemia | 21 (15.2%) | - | 2 (1.6%) | 22 (15.9%) |
| Hyperleukocytosis | - | - | 1 (0.8%) | 1 (0.7%) |
| Iron deficiency anaemia | - | - | 1 (0.8%) | 1 (0.7%) |
| Leukopenia | 1 (0.7%) | - | - | 1 (0.7%) |
| Lymphadenitis | - | - | 1 (0.8%) | 1 (0.7%) |
| Lymphopenia | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Neutropenia | 14 (10.1%) | - | 2 (1.6%) | 16 (11.6%) |
| Thrombocytopenia | - | - | 3 (2.4%) | 3 (2.2%) |
| Thrombocytosis | - | - | 2 (1.6%) | 2 (1.4%) |
| Cardiac disorders | 5 (3.6%) | - | 5 (4.0%) | 10 (7.2%) |
| Atrial thrombosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Cardiac aneurysm | - | - | 1 (0.8%) | 1 (0.7%) |
| Left atrial dilatation | - | - | 1 (0.8%) | 1 (0.7%) |
| Palpitations | 2 (1.4%) | - | 3 (2.4%) | 5 (3.6%) |
| Tachycardia | 2 (1.4%) | - | - | 2 (1.4%) |
| Ear and labyrinth disorders | 2 (1.4%) | - | 8 (6.3%) | 10 (7.2%) |
| Hypoacusis | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Meniere's disease | - | - | 1 (0.8%) | 1 (0.7%) |
| Vertigo | 1 (0.7%) | - | 5 (4.0%) | 6 (4.3%) |
| Endocrine disorders | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Hyperthyroidism | - | - | 1 (0.8%) | 1 (0.7%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Hypothyroidism | 1 (0.7%) | - | - | 1 (0.7%) |
| Eye disorders | 16 (11.6%) | 1 (0.8%) | 7 (5.6%) | 23 (16.7%) |
| Blepharitis | - | - | 1 (0.8%) | 1 (0.7%) |
| Chalazion | 1 (0.7%) | - | - | 1 (0.7%) |
| Conjunctival haemorrhage | 1 (0.7%) | - | - | 1 (0.7%) |
| Dry eye | 7 (5.1%) | 1 (0.8%) | 3 (2.4%) | 11 (8.0%) |
| Eye irritation | 1 (0.7%) | - | - | 1 (0.7%) |
| Eye pain | 1 (0.7%) | - | - | 1 (0.7%) |
| Keratitis | - | - | 1 (0.8%) | 1 (0.7%) |
| Lacrimation increased | 2 (1.4%) | - | 2 (1.6%) | 4 (2.9%) |
| Vision blurred | 1 (0.7%) | - | - | 1 (0.7%) |
| Visual acuity reduced | 1 (0.7%) | - | - | 1 (0.7%) |
| Xerophthalmia | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Gastrointestinal disorders | 119 (86.2%) | 3 (2.3%) | 52 (41.3%) | 125 (90.6%) |
| Abdominal discomfort | 1 (0.7%) | - | - | 1 (0.7%) |
| Abdominal pain | 11 (8.0%) | - | 4 (3.2%) | 14 (10.1%) |
| Abdominal pain upper | 7 (5.1%) | - | 2 (1.6%) | 9 (6.5%) |
| Aerophagia | 1 (0.7%) | - | - | 1 (0.7%) |
| Anal fissure | 1 (0.7%) | - | - | 1 (0.7%) |
| Angular cheilitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Anorectal discomfort | 1 (0.7%) | - | - | 1 (0.7%) |
| Aphthous ulcer | 3 (2.2%) | - | 1 (0.8%) | 3 (2.2%) |
| Colitis | 3 (2.2%) | - | - | 3 (2.2%) |
| Constipation | 3 (2.2%) | 1 (0.8%) | 8 (6.3%) | 12 (8.7%) |
| Diarrhoea | 100 (72.5%) | - | 34 (27.0%) | 108 (78.3%) |
| Dry mouth | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Dyspepsia | 10 (7.2%) | - | 2 (1.6%) | 11 (8.0%) |
| Dysphagia | - | - | 1 (0.8%) | 1 (0.7%) |
| Food poisoning | - | - | 1 (0.8%) | 1 (0.7%) |
| Gastritis | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Gastrointestinal disorder | - | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| Gastrointestinal motility disorder | - | 1 (0.8%) | - | 1 (0.7%) |
| Gastrointestinal pain | - | - | 1 (0.8%) | 1 (0.7%) |
| Gastrooesophageal reflux disease | 13 (9.4%) | - | 2 (1.6%) | 14 (10.1%) |
| Gingival bleeding | 1 (0.7%) | - | - | 1 (0.7%) |
| Gingival pain | 1 (0.7%) | - | - | 1 (0.7%) |
| Haemorrhoidal haemorrhage | 1 (0.7%) | - | - | 1 (0.7%) |
| Haemorrhoids | 5 (3.6%) | - | 4 (3.2%) | 8 (5.8%) |
| Lip dry | 1 (0.7%) | - | - | 1 (0.7%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Mouth ulceration | 2 (1.4%) | - | 1 (0.8%) | 2 (1.4%) |
| Nausea | 34 (24.6%) | - | 12 (9.5%) | 41 (29.7%) |
| Odynophagia | 1 (0.7%) | - | - | 1 (0.7%) |
| Proctalgia | 2 (1.4%) | - | - | 2 (1.4%) |
| Stomatitis | 17 (12.3%) | - | 2 (1.6%) | 17 (12.3%) |
| Toothache | 1 (0.7%) | - | - | 1 (0.7%) |
| Vomiting | 6 (4.3%) | - | 1 (0.8%) | 7 (5.1%) |
| General disorders and administration site conditions | 99 (71.7%) | 6 (4.6%) | 43 (34.1%) | 109 (79.0%) |
| Asthenia | 44 (31.9%) | 1 (0.8%) | 20 (15.9%) | 51 (37.0%) |
| Axillary pain | 1 (0.7%) | 1 (0.8%) | 1 (0.8%) | 3 (2.2%) |
| Catheter site scar | 1 (0.7%) | - | - | 1 (0.7%) |
| Chest pain | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Chills | - | 1 (0.8%) | - | 1 (0.7%) |
| Device related thrombosis | - | - | 1 (0.8%) | 1 (0.7%) |
| Epithelitis | - | - | 2 (1.6%) | 2 (1.4%) |
| Fatigue | 37 (26.8%) | - | 14 (11.1%) | 45 (32.6%) |
| Hyperthermia | 1 (0.7%) | - | - | 1 (0.7%) |
| Influenza like illness | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Injection site bruising | 1 (0.7%) | - | - | 1 (0.7%) |
| Injection site pain | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Injection site pruritus | - | 1 (0.8%) | - | 1 (0.7%) |
| Injection site rash | 1 (0.7%) | - | - | 1 (0.7%) |
| Injection site reaction | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Localised oedema | 1 (0.7%) | - | - | 1 (0.7%) |
| Mucosal dryness | 1 (0.7%) | - | - | 1 (0.7%) |
| Mucosal inflammation | 23 (16.7%) | - | 4 (3.2%) | 25 (18.1%) |
| Mucosal pain | 1 (0.7%) | - | - | 1 (0.7%) |
| Non-cardiac chest pain | - | 1 (0.8%) | - | 1 (0.7%) |
| Oedema | 1 (0.7%) | - | - | 1 (0.7%) |
| Oedema peripheral | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Pain | 6 (4.3%) | - | 3 (2.4%) | 9 (6.5%) |
| Pyrexia | 6 (4.3%) | 1 (0.8%) | 4 (3.2%) | 10 (7.2%) |
| Xerosis | 3 (2.2%) | - | - | 3 (2.2%) |
| Hepatobiliary disorders | 9 (6.5%) | - | 5 (4.0%) | 11 (8.0%) |
| Cholelithiasis | - | - | 1 (0.8%) | 1 (0.7%) |
| Cholestasis | 2 (1.4%) | - | - | 2 (1.4%) |
| Hepatic cirrhosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Hepatic cytolysis | 7 (5.1%) | - | 2 (1.6%) | 7 (5.1%) |
| Hypertransaminasaemia | - | - | 1 (0.8%) | 1 (0.7%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Jaundice | 1 (0.7%) | - | - | 1 (0.7%) |
| Porto-sinusoidal vascular disorder | - | - | 1 (0.8%) | 1 (0.7%) |
| Immune system disorders | 11 (8.0%) | 1 (0.8%) | 1 (0.8%) | 13 (9.4%) |
| Anaphylactic reaction | 2 (1.4%) | - | - | 2 (1.4%) |
| Anaphylactoid reaction | 1 (0.7%) | - | - | 1 (0.7%) |
| Drug hypersensitivity | 3 (2.2%) | 1 (0.8%) | - | 4 (2.9%) |
| Hypersensitivity | 6 (4.3%) | - | 1 (0.8%) | 7 (5.1%) |
| Infections and infestations | 43 (31.2%) | 8 (6.1%) | 47 (37.3%) | 74 (53.6%) |
| Appendicitis | - | - | 1 (0.8%) | 1 (0.7%) |
| Bartholinitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Breast abscess | 1 (0.7%) | - | - | 1 (0.7%) |
| Bronchitis | 2 (1.4%) | - | 3 (2.4%) | 5 (3.6%) |
| COVID-19 | 2 (1.4%) | 2 (1.5%) | 12 (9.5%) | 16 (11.6%) |
| COVID-19 pneumonia | 1 (0.7%) | - | - | 1 (0.7%) |
| Cellulitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Conjunctivitis | 3 (2.2%) | - | 1 (0.8%) | 4 (2.9%) |
| Cystitis | 5 (3.6%) | - | 2 (1.6%) | 6 (4.3%) |
| Eye infection | 1 (0.7%) | - | - | 1 (0.7%) |
| Folliculitis | 6 (4.3%) | - | 1 (0.8%) | 7 (5.1%) |
| Fungal infection | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Gastroenteritis | - | - | 1 (0.8%) | 1 (0.7%) |
| Gastroenteritis viral | - | - | 1 (0.8%) | 1 (0.7%) |
| Gastrointestinal viral infection | - | - | 1 (0.8%) | 1 (0.7%) |
| Genital herpes | 1 (0.7%) | - | - | 1 (0.7%) |
| Gingivitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Helicobacter gastritis | - | - | 1 (0.8%) | 1 (0.7%) |
| Herpes simplex reactivation | - | - | 1 (0.8%) | 1 (0.7%) |
| Hordeolum | 1 (0.7%) | - | - | 1 (0.7%) |
| Influenza | - | - | 2 (1.6%) | 2 (1.4%) |
| Laryngitis | - | - | 1 (0.8%) | 1 (0.7%) |
| Localised infection | - | - | 1 (0.8%) | 1 (0.7%) |
| Lower respiratory tract infection | - | - | 1 (0.8%) | 1 (0.7%) |
| Mastitis | - | 1 (0.8%) | - | 1 (0.7%) |
| Myringitis | - | - | 1 (0.8%) | 1 (0.7%) |
| Nasopharyngitis | 1 (0.7%) | - | 5 (4.0%) | 6 (4.3%) |
| Onychomycosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Oral candidiasis | 1 (0.7%) | - | - | 1 (0.7%) |
| Oral fungal infection | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Oral herpes | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Otitis media | - | - | 1 (0.8%) | 1 (0.7%) |
| Paronychia | 2 (1.4%) | - | 5 (4.0%) | 7 (5.1%) |
| Parotitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Pharyngitis | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Pneumonia | 1 (0.7%) | - | 3 (2.4%) | 4 (2.9%) |
| Postoperative wound infection | - | 1 (0.8%) | - | 1 (0.7%) |
| Pyelonephritis acute | 1 (0.7%) | - | - | 1 (0.7%) |
| Rash pustular | 1 (0.7%) | - | - | 1 (0.7%) |
| Respiratory tract infection | 1 (0.7%) | - | - | 1 (0.7%) |
| Rhinitis | 4 (2.9%) | 1 (0.8%) | 1 (0.8%) | 6 (4.3%) |
| Sepsis | 1 (0.7%) | - | - | 1 (0.7%) |
| Sinusitis | - | - | 2 (1.6%) | 2 (1.4%) |
| Tinea infection | - | - | 1 (0.8%) | 1 (0.7%) |
| Tooth abscess | - | - | 2 (1.6%) | 2 (1.4%) |
| Tooth infection | - | 1 (0.8%) | - | 1 (0.7%) |
| Tracheitis | - | 1 (0.8%) | - | 1 (0.7%) |
| Upper respiratory tract infection | 1 (0.7%) | - | 4 (3.2%) | 5 (3.6%) |
| Urinary tract infection | 5 (3.6%) | 1 (0.8%) | 7 (5.6%) | 11 (8.0%) |
| Viral infection | - | - | 1 (0.8%) | 1 (0.7%) |
| Vulvovaginal mycotic infection | 1 (0.7%) | - | - | 1 (0.7%) |
| Wound infection | - | 1 (0.8%) | - | 1 (0.7%) |
| Injury, poisoning and procedural complications | 8 (5.8%) | 2 (1.5%) | 29 (23.0%) | 36 (26.1%) |
| Ankle fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Clavicle fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Fall | - | - | 3 (2.4%) | 3 (2.2%) |
| Fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Infusion related reaction | 5 (3.6%) | - | - | 5 (3.6%) |
| Joint dislocation | - | - | 1 (0.8%) | 1 (0.7%) |
| Periorbital haematoma | 1 (0.7%) | - | - | 1 (0.7%) |
| Postoperative lymphocele | - | - | 1 (0.8%) | 1 (0.7%) |
| Procedural pain | - | 2 (1.5%) | - | 2 (1.4%) |
| Radiation skin injury | - | - | 24 (19.0%) | 24 (17.4%) |
| Recall phenomenon | - | - | 1 (0.8%) | 1 (0.7%) |
| Scar | 1 (0.7%) | - | - | 1 (0.7%) |
| Seroma | 1 (0.7%) | - | - | 1 (0.7%) |
| Skin abrasion | 1 (0.7%) | - | - | 1 (0.7%) |
| Wrist fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Investigations | 24 (17.4%) | 2 (1.5%) | 9 (7.1%) | 34 (24.6%) |
| Alanine aminotransferase increased | 11 (8.0%) | - | 1 (0.8%) | 12 (8.7%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Aspartate aminotransferase increased | 6 (4.3%) | - | 2 (1.6%) | 8 (5.8%) |
| Blood alkaline phosphatase increased | - | - | 1 (0.8%) | 1 (0.7%) |
| Blood bilirubin increased | 1 (0.7%) | - | - | 1 (0.7%) |
| Blood creatinine increased | 2 (1.4%) | - | - | 2 (1.4%) |
| Eastern Cooperative Oncology Group performance status worsened | - | - | 1 (0.8%) | 1 (0.7%) |
| Ejection fraction decreased | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Gamma-glutamyltransferase increased | 1 (0.7%) | 1 (0.8%) | 1 (0.8%) | 3 (2.2%) |
| Heart rate irregular | - | - | 1 (0.8%) | 1 (0.7%) |
| Neutrophil count decreased | 11 (8.0%) | - | - | 11 (8.0%) |
| Platelet count decreased | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Serum ferritin decreased | - | - | 1 (0.8%) | 1 (0.7%) |
| Transaminases increased | - | 1 (0.8%) | - | 1 (0.7%) |
| Weight decreased | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Weight increased | 1 (0.7%) | - | - | 1 (0.7%) |
| White blood cell count decreased | 1 (0.7%) | - | - | 1 (0.7%) |
| Metabolism and nutrition disorders | 21 (15.2%) | 1 (0.8%) | 12 (9.5%) | 31 (22.5%) |
| Cell death | - | - | 3 (2.4%) | 3 (2.2%) |
| Decreased appetite | 12 (8.7%) | - | 2 (1.6%) | 13 (9.4%) |
| Dehydration | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Hypercalcaemia | - | - | 1 (0.8%) | 1 (0.7%) |
| Hypercholesterolaemia | - | - | 2 (1.6%) | 2 (1.4%) |
| Hypokalaemia | 8 (5.8%) | - | 2 (1.6%) | 10 (7.2%) |
| Hypomagnesaemia | 3 (2.2%) | - | - | 3 (2.2%) |
| Hyponatraemia | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Hypophosphataemia | 2 (1.4%) | - | - | 2 (1.4%) |
| Iron deficiency | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Vitamin B12 deficiency | - | 1 (0.8%) | - | 1 (0.7%) |
| Musculoskeletal and connective tissue disorders | 33 (23.9%) | 4 (3.1%) | 36 (28.6%) | 63 (45.7%) |
| Arthralgia | 10 (7.2%) | 3 (2.3%) | 13 (10.3%) | 26 (18.8%) |
| Arthritis | 1 (0.7%) | - | - | 1 (0.7%) |
| Back pain | 3 (2.2%) | - | 4 (3.2%) | 6 (4.3%) |
| Bone pain | 1 (0.7%) | - | - | 1 (0.7%) |
| Flank pain | - | - | 1 (0.8%) | 1 (0.7%) |
| Joint ankylosis | - | - | 1 (0.8%) | 1 (0.7%) |
| Muscle spasms | 7 (5.1%) | - | 11 (8.7%) | 18 (13.0%) |
| Musculoskeletal chest pain | - | - | 3 (2.4%) | 3 (2.2%) |
| Myalgia | 8 (5.8%) | 1 (0.8%) | 7 (5.6%) | 14 (10.1%) |
| Osteoporosis | - | - | 1 (0.8%) | 1 (0.7%) |
| Pain in extremity | 5 (3.6%) | - | 2 (1.6%) | 7 (5.1%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Polyarthritis | - | - | 1 (0.8%) | 1 (0.7%) |
| Sacral pain | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.7%) | - | - | 1 (0.7%) |
| Tumor pain | 1 (0.7%) | - | - | 1 (0.7%) |
| Nervous system disorders | 85 (61.6%) | - | 28 (22.2%) | 96 (69.6%) |
| Ageusia | 2 (1.4%) | - | - | 2 (1.4%) |
| Amnesia | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Brain fog | - | - | 1 (0.8%) | 1 (0.7%) |
| Cognitive disorder | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Depressed level of consciousness | 1 (0.7%) | - | - | 1 (0.7%) |
| Disturbance in attention | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Dizziness | 2 (1.4%) | - | 3 (2.4%) | 5 (3.6%) |
| Dysaesthesia | - | - | 2 (1.6%) | 2 (1.4%) |
| Dysgeusia | 15 (10.9%) | - | 2 (1.6%) | 17 (12.3%) |
| Headache | 14 (10.1%) | - | 8 (6.3%) | 20 (14.5%) |
| Hypoaesthesia | 2 (1.4%) | - | - | 2 (1.4%) |
| Hypogeusia | 1 (0.7%) | - | - | 1 (0.7%) |
| Lethargy | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Memory impairment | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Neuralgia | 2 (1.4%) | - | 3 (2.4%) | 5 (3.6%) |
| Neuralgic amyotrophy | 1 (0.7%) | - | - | 1 (0.7%) |
| Neuropathy peripheral | 40 (29.0%) | - | 6 (4.8%) | 44 (31.9%) |
| Neurotoxicity | 2 (1.4%) | - | - | 2 (1.4%) |
| Paraesthesia | 10 (7.2%) | - | - | 10 (7.2%) |
| Peripheral motor neuropathy | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Peripheral sensory neuropathy | 12 (8.7%) | - | 2 (1.6%) | 14 (10.1%) |
| Presyncope | 1 (0.7%) | - | - | 1 (0.7%) |
| Radicular pain | - | - | 1 (0.8%) | 1 (0.7%) |
| Sciatica | - | - | 2 (1.6%) | 2 (1.4%) |
| Syncope | - | - | 1 (0.8%) | 1 (0.7%) |
| Taste disorder | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Psychiatric disorders | 11 (8.0%) | 1 (0.8%) | 15 (11.9%) | 24 (17.4%) |
| Anxiety | 4 (2.9%) | - | 5 (4.0%) | 8 (5.8%) |
| Depression | 1 (0.7%) | 1 (0.8%) | 4 (3.2%) | 6 (4.3%) |
| Insomnia | 4 (2.9%) | - | 8 (6.3%) | 12 (8.7%) |
| Libido decreased | - | - | 1 (0.8%) | 1 (0.7%) |
| Sleep disorder | 2 (1.4%) | - | - | 2 (1.4%) |
| Stress | - | - | 1 (0.8%) | 1 (0.7%) |
| Renal and urinary disorders | 9 (6.5%) | - | 4 (3.2%) | 11 (8.0%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Acute kidney injury | 2 (1.4%) | - | - | 2 (1.4%) |
| Dysuria | 3 (2.2%) | - | 2 (1.6%) | 4 (2.9%) |
| Haemorrhage urinary tract | 1 (0.7%) | - | - | 1 (0.7%) |
| Leukocyturia | 1 (0.7%) | - | - | 1 (0.7%) |
| Nephrolithiasis | - | - | 1 (0.8%) | 1 (0.7%) |
| Pollakiuria | 1 (0.7%) | - | - | 1 (0.7%) |
| Renal colic | 1 (0.7%) | - | - | 1 (0.7%) |
| Urinary incontinence | - | - | 1 (0.8%) | 1 (0.7%) |
| Urinary tract pain | 1 (0.7%) | - | - | 1 (0.7%) |
| Reproductive system and breast disorders | 4 (2.9%) | 1 (0.8%) | 12 (9.5%) | 17 (12.3%) |
| Breast induration | - | - | 1 (0.8%) | 1 (0.7%) |
| Breast oedema | - | - | 3 (2.4%) | 3 (2.2%) |
| Breast pain | 1 (0.7%) | - | 5 (4.0%) | 6 (4.3%) |
| Menometrorrhagia | - | - | 1 (0.8%) | 1 (0.7%) |
| Vaginal discharge | 1 (0.7%) | - | - | 1 (0.7%) |
| Vaginal haemorrhage | 1 (0.7%) | - | - | 1 (0.7%) |
| Vulvovaginal dryness | - | 1 (0.8%) | 2 (1.6%) | 3 (2.2%) |
| Vulvovaginal pruritus | 1 (0.7%) | - | - | 1 (0.7%) |
| Respiratory, thoracic and mediastinal disorders | 49 (35.5%) | - | 23 (18.3%) | 66 (47.8%) |
| Cough | 9 (6.5%) | - | 8 (6.3%) | 17 (12.3%) |
| Dysphonia | 2 (1.4%) | - | - | 2 (1.4%) |
| Dyspnoea | 2 (1.4%) | - | 4 (3.2%) | 6 (4.3%) |
| Dyspnoea exertional | 1 (0.7%) | - | - | 1 (0.7%) |
| Epistaxis | 30 (21.7%) | - | 4 (3.2%) | 33 (23.9%) |
| Lung disorder | - | - | 1 (0.8%) | 1 (0.7%) |
| Nasal dryness | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Oropharyngeal pain | 3 (2.2%) | - | 1 (0.8%) | 4 (2.9%) |
| Pulmonary embolism | 1 (0.7%) | - | - | 1 (0.7%) |
| Pulmonary hypertension | - | - | 1 (0.8%) | 1 (0.7%) |
| Rhinorrhoea | 6 (4.3%) | - | 7 (5.6%) | 13 (9.4%) |
| Skin and subcutaneous tissue disorders | 97 (70.3%) | 7 (5.3%) | 41 (32.5%) | 112 (81.2%) |
| Acne | 3 (2.2%) | - | 1 (0.8%) | 4 (2.9%) |
| Alopecia | 55 (39.9%) | 1 (0.8%) | 1 (0.8%) | 57 (41.3%) |
| Dermatitis | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Dermatitis acneiform | 6 (4.3%) | - | 1 (0.8%) | 7 (5.1%) |
| Dermatitis allergic | - | 1 (0.8%) | - | 1 (0.7%) |
| Drug eruption | - | - | 1 (0.8%) | 1 (0.7%) |
| Dry skin | 13 (9.4%) | - | 4 (3.2%) | 17 (12.3%) |
| Eczema asteatotic | 1 (0.7%) | - | - | 1 (0.7%) |

| System Organ Class and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Erythema | 4 (2.9%) | - | 3 (2.4%) | 7 (5.1%) |
| Hand dermatitis | 2 (1.4%) | - | - | 2 (1.4%) |
| Madarosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Nail discolouration | 2 (1.4%) | - | - | 2 (1.4%) |
| Nail disorder | 2 (1.4%) | - | 5 (4.0%) | 5 (3.6%) |
| Nail toxicity | 4 (2.9%) | - | 4 (3.2%) | 7 (5.1%) |
| Night sweats | 1 (0.7%) | - | - | 1 (0.7%) |
| Onychoclasis | 1 (0.7%) | - | 3 (2.4%) | 4 (2.9%) |
| Onycholysis | 3 (2.2%) | 1 (0.8%) | 2 (1.6%) | 6 (4.3%) |
| Onychomadesis | 1 (0.7%) | - | - | 1 (0.7%) |
| Pain of skin | 1 (0.7%) | - | - | 1 (0.7%) |
| Palmar-plantar erythrodysaesthesia syndrome | 2 (1.4%) | 1 (0.8%) | 1 (0.8%) | 4 (2.9%) |
| Papule | 1 (0.7%) | - | - | 1 (0.7%) |
| Photosensitivity reaction | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Pruritus | 8 (5.8%) | 2 (1.5%) | 10 (7.9%) | 17 (12.3%) |
| Rash | 25 (18.1%) | 1 (0.8%) | 3 (2.4%) | 28 (20.3%) |
| Rash erythematous | 1 (0.7%) | - | - | 1 (0.7%) |
| Rash maculo-papular | 7 (5.1%) | - | 3 (2.4%) | 10 (7.2%) |
| Rash pruritic | 1 (0.7%) | - | - | 1 (0.7%) |
| Skin hyperpigmentation | - | - | 1 (0.8%) | 1 (0.7%) |
| Skin irritation | - | - | 1 (0.8%) | 1 (0.7%) |
| Skin lesion | - | - | 1 (0.8%) | 1 (0.7%) |
| Skin toxicity | 1 (0.7%) | - | 2 (1.6%) | 3 (2.2%) |
| Urticaria | 3 (2.2%) | - | - | 3 (2.2%) |
| Vascular disorders | 20 (14.5%) | 1 (0.8%) | 16 (12.7%) | 32 (23.2%) |
| Flushing | 1 (0.7%) | - | - | 1 (0.7%) |
| Haematoma | 2 (1.4%) | - | 1 (0.8%) | 3 (2.2%) |
| Hot flush | 9 (6.5%) | - | 6 (4.8%) | 14 (10.1%) |
| Hypertension | 4 (2.9%) | - | 5 (4.0%) | 9 (6.5%) |
| Hypotension | 2 (1.4%) | - | - | 2 (1.4%) |
| Lymphocele | 3 (2.2%) | 1 (0.8%) | 2 (1.6%) | 6 (4.3%) |
| Lymphoedema | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Orthostatic hypotension | 1 (0.7%) | - | - | 1 (0.7%) |
| Peripheral vein thrombosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Phlebitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Venous thrombosis | - | - | 1 (0.8%) | 1 (0.7%) |
| Not coded | 1 (0.7%) | - | - | 1 (0.7%) |
| Fatigue | 1 (0.7%) | - | - | 1 (0.7%) |

### 12.2.3 Analysis of adverse events

**TEAESIs**

**Table 19** displays all cases of TEAESIs according to the component of study treatment (neoadjuvant, surgery, and adjuvant), and overall. Overall, 32 (23.2%) subjects had at least one TEAESI reported, more often in the neoadjuvant part of the treatment. The most frequent categories of TEAESI were grade ≥2 neuropathy (n=22;15.9%) and grade ≥3 diarrhea (n=8; 5.8%); grade ≥2 neuropathy was more often reported in the neoadjuvant part of the study, and grade ≥3 diarrhea exclusively in that part. There were two cases (1.4%) of LVEF decrease (absolute decrease >10% from baseline and/or LVEF value below 50%, excluding the baseline value). Of note, there were no cases of DILI as defined in the protocol. However, there were five cases in four subjects (2.9%) of liver abnormalities that did not fulfil Hy's law for DILI (shown below as "potential DILI"): two cases of "hepatic cytolysis" (one in the neoadjuvant phase and one in the adjuvant phase); two cases of "alanine aminotransferase increased" (in the neoadjuvant phase); and one case of "aspartate aminotransferase increased" (in the neoadjuvant phase).

***Table 19.*** ***TEAEs of special interest (Safety Population).***

| Treatment-emergent adverse event of special interest | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Subjects with at least one TEAESI | 27 (19.6%) | - | 7 (5.6%) | 32 (23.2%) |
| LVEF decrease >10%; or any value <50% | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Peripheral or motor neuropathy grade ≥2 | 17 (12.3%) | - | 5 (4.0%) | 22 (15.9%) |
| Diarrhea grade ≥3 | 8 (5.8%) | - | - | 8 (5.8%) |
| Thrombocytopenia grade ≥3 | - | - | - | - |
| Potential drug-induced liver injury* | 3 (2.2%) | - | 1 (0.8) | 4 (2.9%) |
| Suspected transmission of an infectious agent via pertuzumab and trastuzumab FDC SC or T-DM1 | - | - | - | - |

*Not fulfilling protocol-defined drug-induced liver injury.

TEAESI, treatment-emergent adverse event(s) of special interest.

Overall, across all SOC categories and study periods, the grade of the events for the 138 subjects with at least one TEAE reported was grade 1 in 13 subjects (9.4%), grade 2 in 75 subjects (54.3%), grade 3 in 42 subjects (30.4%), and grade 4 in eight subjects (5.8%). No fatal (i.e., grade 5) TEAEs were reported.

Listings of grade 3 and 4 TEAEs are provided in Appendix **16.2.7.**

### 12.2.4 Listing of adverse events by subject

Listings of AEs by subject are provided in Appendix **16.2.7.**

## 12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

One death was reported during the follow-up period before database lock. This death was not considered to be treatment-related. No fatal (i.e., grade 5) TEAEs were reported.

### 12.3.1 Listing of deaths, other serious adverse events and other significant adverse events

Listings of SAEs (i.e., serious TEAEs) are provided in Appendix **16.2.7**.

#### 12.3.1.1 Deaths

One subject died more than 1 year after completion of study treatment, and the causes of death were reported as natural and not related to the treatments received in the trial.

#### 12.3.1.2 Other serious adverse events

As shown in **Table 20**, a total of 23 (16.7%) subjects had at least one serious TEAE. This was more frequent in the neoadjuvant (13 subjects, 9.4%) and adjuvant (nine subjects, 7.1%) than in the surgery part of the study (two subjects, 1.5%).

The most frequent SOC category with at least one subject with a reported serious TEAE was "infections and infestations" (nine subjects), in which the only Preferred Terms reported for more than one subject were "pneumonia" (two subjects, both with grade 3 events) and "pneumonia related to coronavirus 2019 disease", in one subject. Four subjects had an event in the SOC category "hepatobiliary disorders": one each grade 2 "cholelithiasis", grade 3 "cholestasis", grade 3 "hepatic cirrhosis", and grade 2 "porto-sinusoidal vascular disorder". The only other individual Preferred Term reported as a serious TEAE in more than one subject was "anaphylactic reaction", reported in two subjects (one grade 3 and one grade 4), and all other individual Preferred Terms were reported in one subject each. The only subject with a report in the SOC "cardiac disorders" had a grade 2 left-atrial dilatation.

*Table 20. **Serious TEAEs by SOC, Preferred Term, grade, and study part (Safety Population).***

| System Organ Class, Preferred Term, and Grade | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Overall | 13 (9.4%) | 2 (1.5%) | 9 (7.1%) | 23 (16.7%) |
| Grade 2 | - | - | 4 (3.2%) | 4 (2.9%) |
| Grade 3 | 9 (6.5%) | 2 (1.5%) | 4 (3.2%) | 14 (10.1%) |
| Grade 4 | 4 (2.9%) | - | 1 (0.8%) | 5 (3.6%) |
| Cardiac disorders | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Left atrial dilatation | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Ear and labyrinth disorders | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 4 | - | - | 1 (0.8%) | 1 (0.7%) |
| Hypoacusis | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 4 | - | - | 1 (0.8%) | 1 (0.7%) |
| Gastrointestinal disorders | 2 (1.4%) | - | - | 2 (1.4%) |
| Grade 3 | 2 (1.4%) | - | - | 2 (1.4%) |
| Colitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Diarrhoea | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| General disorders and administration site conditions | 1 (0.7%) | 1 (0.8%) | - | 2 (1.4%) |
| Grade 1 | - | 1 (0.8%) | - | 1 (0.7%) |

| System Organ Class, Preferred Term, and Grade | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Hyperthermia | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Pyrexia | - | 1 (0.8%) | - | 1 (0.7%) |
| Grade 1 | - | 1 (0.8%) | - | 1 (0.7%) |
| Hepatobiliary disorders | 2 (1.4%) | - | 2 (1.6%) | 4 (2.9%) |
| Grade 2 | - | - | 2 (1.6%) | 2 (1.4%) |
| Grade 3 | 2 (1.4%) | - | - | 2 (1.4%) |
| Cholelithiasis | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Cholestasis | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Hepatic cirrhosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Porto-sinusoidal vascular disorder | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Immune system disorders | 2 (1.4%) | - | - | 2 (1.4%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Anaphylactic reaction | 2 (1.4%) | - | - | 2 (1.4%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Infections and infestations | 5 (3.6%) | 2 (1.5%) | 2 (1.6%) | 9 (6.5%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | 4 (2.9%) | 2 (1.5%) | 1 (0.8%) | 7 (5.1%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Breast abscess | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| COVID-19 pneumonia | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Cellulitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Helicobacter gastritis | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Mastitis | - | 1 (0.8%) | - | 1 (0.7%) |
| Grade 3 | - | 1 (0.8%) | - | 1 (0.7%) |
| Pneumonia | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Grade 3 | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Pyelonephritis acute | 1 (0.7%) | - | - | 1 (0.7%) |

| System Organ Class, Preferred Term, and Grade | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Sepsis | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Wound infection | - | 1 (0.8%) | - | 1 (0.7%) |
| Grade 3 | - | 1 (0.8%) | - | 1 (0.7%) |
| Injury, poisoning and procedural complications | - | - | 2 (1.6%) | 2 (1.4%) |
| Grade 3 | - | - | 2 (1.6%) | 2 (1.4%) |
| Clavicle fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | - | - | 1 (0.8%) | 1 (0.7%) |
| Fall | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | - | - | 1 (0.8%) | 1 (0.7%) |
| Joint dislocation | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | - | - | 1 (0.8%) | 1 (0.7%) |
| Wrist fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | - | - | 1 (0.8%) | 1 (0.7%) |
| Investigations | 2 (1.4%) | - | - | 2 (1.4%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Alanine aminotransferase increased | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Aspartate aminotransferase increased | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Ejection fraction decreased | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Metabolism and nutrition disorders | 2 (1.4%) | - | - | 2 (1.4%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Hypokalaemia | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Hyponatraemia | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Musculoskeletal and connective tissue disorders | 1 (0.7%) | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | 1 (0.8%) | 1 (0.7%) |
| Back pain | 1 (0.7%) | - | 1 (0.8%) | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | 1 (0.8%) | 1 (0.7%) |
| Psychiatric disorders | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Depression | 1 (0.7%) | - | - | 1 (0.7%) |

| System Organ Class, Preferred Term, and Grade | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| Grade 4 | 1 (0.7%) | - | - | 1 (0.7%) |
| Renal and urinary disorders | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Acute kidney injury | 1 (0.7%) | - | - | 1 (0.7%) |
| Grade 3 | 1 (0.7%) | - | - | 1 (0.7%) |
| Skin and subcutaneous tissue disorders | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |
| Drug eruption | - | - | 1 (0.8%) | 1 (0.7%) |
| Grade 2 | - | - | 1 (0.8%) | 1 (0.7%) |

Most subjects (14/23) with serious TEAEs had grade 3 events, five (of 23) had grade 4 events, and no grade 5 (i.e., fatal) events were reported. These grade 3 and grade 4 events are summarized in **Table 21** according to Preferred Terms. Of note, one subject may have had more than one of these events, both in different parts of the study and in the study as a whole.

***Table 21.*** ***Grade 3 and 4 serious TEAEs by Preferred Term and study part (Safety Population).***

| Grade and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| **Grade 3** | | | | |
| Acute kidney injury | 1 (0.7%) | - | - | 1 (0.7%) |
| Alanine aminotransferase increased | 1 (0.7%) | - | - | 1 (0.7%) |
| Anaphylactic reaction | 1 (0.7%) | - | - | 1 (0.7%) |
| Back pain | 1 (0.7%) | - | 1 (0.8%) | 1 (0.7%) |
| Breast abscess | 1 (0.7%) | - | - | 1 (0.7%) |
| Cellulitis | 1 (0.7%) | - | - | 1 (0.7%) |
| Cholestasis | 1 (0.7%) | - | - | 1 (0.7%) |
| Clavicle fracture | - | - | 1 (0.8%) | 1 (0.7%) |
| Colitis | 1 (0.7%) | - | - | 1 (0.7%) |
| COVID-19 pneumonia | 1 (0.7%) | - | - | 1 (0.7%) |
| Diarrhoea | 1 (0.7%) | - | - | 1 (0.7%) |
| Ejection fraction decreased | 1 (0.7%) | - | - | 1 (0.7%) |
| Fall | - | - | 1 (0.8%) | 1 (0.7%) |
| Hepatic cirrhosis | 1 (0.7%) | - | - | 1 (0.7%) |
| Hyperthermia | 1 (0.7%) | - | - | 1 (0.7%) |
| Hyponatraemia | 1 (0.7%) | - | - | 1 (0.7%) |
| Joint dislocation | - | - | 1 (0.8%) | 1 (0.7%) |
| Mastitis | - | 1 (0.8%) | - | 1 (0.7%) |
| Pneumonia | 1 (0.7%) | - | 1 (0.8%) | 2 (1.4%) |
| Pyelonephritis acute | 1 (0.7%) | - | - | 1 (0.7%) |
| Wound infection | - | 1 (0.8%) | - | 1 (0.7%) |
| Wrist fracture | - | - | 1 (0.8%) | 1 (0.7%) |

| Grade and Preferred Term | Neoadjuvant (N=138) | Surgery (N=131) | Adjuvant (N=126) | Whole period (N=138) |
|---|---|---|---|---|
| **Grade 4** | - | - | 1 (0.8%) | 1 (0.7%) |
| Anaphylactic reaction | 1 (0.7%) | - | - | 1 (0.7%) |
| Aspartate aminotransferase increased | 1 (0.7%) | - | - | 1 (0.7%) |
| Depression | 1 (0.7%) | - | - | 1 (0.7%) |
| Hypoacusis | - | - | 1 (0.8%) | 1 (0.7%) |
| Hypokalaemia | 1 (0.7%) | - | - | 1 (0.7%) |
| Sepsis | 1 (0.7%) | - | - | 1 (0.7%) |

#### 12.3.1.3 Other significant adverse events

There were no other significant AEs to present or discuss.

### 12.3.2 Narratives of deaths, other serious adverse events and certain other significant adverse events

Individual patient data are available upon request.

### 12.3.3 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

The frequency and profile of serious TEAEs and of other significant TEAEs observed in the study are those expected. No new safety signals have emerged.

## 12.4 CLINICAL LABORATORY EVALUATION

Abnormal laboratory findings (e.g. hematology, haemostatic function, blood chemistry and serology) that were judged by the investigator as clinically significant had to be recorded as AEs. All laboratory parameters were managed by the investigators at the respective sites in accordance with national and internal guidelines as per GCP.

### 12.4.1 Listing of individual laboratory measurements by subject and each abnormal laboratory value

Individual patient data are available upon request.

### 12.4.2 Evaluation of each laboratory parameter

All laboratory parameters were managed by the investigators at the respective sites in accordance with national and internal guidelines as per GCP.

### 12.4.3 Laboratory values over time

As reported in the protocol, abnormal laboratory findings (e.g., hematology, hemostatic function, blood chemistry, and serology) or other abnormal assessments (e.g., vital signs) that were judged by the investigator as clinically significant had to be recorded as AEs.

#### 12.4.3.1 Individual patient changes

Individual patient changes were not analyzed.

#### 12.4.3.2 Individual clinically significant abnormalities

Individual clinically significant abnormalities were not analyzed.

## 12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

As reported in the protocol, abnormal laboratory findings (e.g., hematology, hemostatic function, blood chemistry and serology) or other abnormal assessments (e.g., vital signs) that were judged by the investigator as clinically significant had to be recorded as AEs. Therefore, no specific analysis was conducted of vital signs, physical findings and other observations related to safety not reported as AEs. Moreover, these occurrences would be managed as per clinical practice at each site and following protocol provisions.

## 12.6 SAFETY CONCLUSIONS

Of 138 subjects starting neoadjuvant treatment, all received pertuzumab and trastuzumab FDC SC, and 137 received a taxane as part of neoadjuvant treatment (one subject did not receive paclitaxel, only the antibodies). Taxanes were paclitaxel only (n=128), docetaxel only (n=7), or both agents (n=2); these two subjects switched treatment from paclitaxel to docetaxel). Among all subjects receiving paclitaxel, there was a mean of 11.3 of the planned 12 administrations; delayed administrations were reported for 31.0% of subjects, dose adjustments for 27.9%, and dose interruptions for 9.4%. Among the nine subjects receiving docetaxel, there was a mean of 3.9 of the planned four administrations; delayed administrations were reported for 33.0% of subjects, dose adjustments for 11.1%, and no dose interruptions were reported for docetaxel. Subjects received a mean number of 4.2 cycles of pertuzumab and trastuzumab FDC SC in the neoadjuvant phase, and a mean of 13.2 cycles in the adjuvant phase. These means are very close to the planned number of four doses panned in the neoadjuvant phase and 14 planned in the adjuvant phase. For T-DM1, subjects received a mean of 11.6 (with anthracyclines) to 12 (without anthracyclines) of the planned 14 adjuvant cycles. There were no dose interruptions of pertuzumab and trastuzumab FDC SC, and delayed administration of these antibodies was infrequent. No delayed administrations, dose adjustments or dose interruptions were reported in the adjuvant phase. These results indicate adequate exposure to the anti-HER2 antibodies and to the planned chemotherapy, suggesting good tolerability of the study treatment.

Overall, all subjects had at least one TEAE, which were more frequently reported in the neoadjuvant and adjuvant parts of the study than during the surgery period. Beyond the general AEs related to fatigue and alopecia, diarrhea and peripheral neuropathy were frequent occurrences, as expected given the nature of study treatment. No unusual AEs were reported, and the severity of AEs overall was also in line with what is known for the agents administered. Of note, cardiac events were infrequently reported in the neoadjuvant and adjuvant parts (7.2% of subjects). At least one TEAESI was reported for 31 (22.5%) subjects. Among cardiac events predefined as TEAESIs, there were two cases of LVEF decrease, but none of the cases led to a reduction in LVEF below 50%. Other TEAESIs were generally neuropathy or diarrhea, and there were no confirmed cases of DILI according to Hy's law definition despite the fact that five subjects had liver abnormalities reported as TEAESIs. Relatedness to study drug was more frequently attributed to paclitaxel than for the other three study drugs for TEAEs in general, serious TEAEs, TEAEs leading to study-drug dose reduction, and TEAEs leading to permanent treatment discontinuation. In nearly two-thirds of subjects, the highest grade of TEAEs was 1 or 2, and there were no fatal TEAEs. Twenty-three (16.7%) subjects had at least one serious TEAE, more often in the neoadjuvant (9.4%) and adjuvant (7.1%) parts of the study than during surgery (1.5%). Most of these serious TEAEs were considered as treatment-related (17/23). The only Preferred Terms reported as a serious TEAE in more than one subject were

"pneumonia" (including pneumonia related to coronavirus 2019) and "anaphylactic reaction". One death not related to treatment was reported during the follow-up period.

The above results suggest that the anthracycline-free neoadjuvant strategy tested here, with pertuzumab and trastuzumab FDC SC combined with a taxane, and the adjuvant strategy directed to observed pathological results after surgical resection are both safe in subjects with HER2-positive/ER- and PR-negative, node-negative early breast cancer. Overall, the profile of TEAEs reported in the study regarding SOC categories, Preferred Terms and grades were as expected, given the patient population and treatment types, and no new safety signals have emerged.

## 13. DISCUSSION AND OVERALL CONCLUSIONS

The DECRESCENDO study had to be stopped due to low accrual. Nevertheless, the observed pCR rate (86.3% among 131 patients undergoing surgery) was higher than expected even considering only HER2-enriched tumors, for which a pCR rate of 70% was predicted and a pCR rate of 88.8% was observed. Likewise, a pCR rate of 30% was predicted and a pCR rate of 78.8% was observed among subjects with non-HER2-enriched tumors. These results suggest that neoadjuvant treatment with an anthracycline-free regimen in patients with HER2-positive, hormone receptor-negative, node-negative early breast cancer leads to a high rate of pCR, with the majority of patients achieving pCR having the HER2-enriched PAM50 subtype. Given the prognostic role of pCR in this setting, further research is warranted in order to establish the long-term benefit of this treatment, particularly regarding tailoring adjuvant treatment to the pathological assessment of surgical specimens.

Safety results from the DECRESECENDO study confirm the tolerability of the investigational regimen combining trastuzumab and pertuzumab with a de-escalated chemotherapy regimen. Grade 3–4 adverse events occurred in approximately one-third of patients (36%), with a low incidence of serious adverse events (16.7%) and no treatment-related deaths. Overall, no new safety concerns were observed, no unusual AEs were reported, and the severity of AEs overall was also in line with what is known for the agents administered. Of note, cardiac events were infrequently reported (7.2% of subjects) and among cardiac events predefined as TEAESIs, there were two cases of LVEF decrease. Other TEAESIs were generally neuropathy or diarrhea, and there were no confirmed cases of DILI.

## 14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

### 14.1 DEMOGRAPHIC DATA

### 14.2 EFFICACY DATA

### 14.3 SAFETY DATA

#### 14.3.1 Displays of adverse events

#### 14.3.2 Listings of deaths, other serious and certain adverse events

**14.3.3 Narratives of deaths, other serious and certain other significant adverse events**

**14.3.4 Abnormal laboratory value listing**

## 15. REFERENCE LIST

Hudis CA. Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J. Clin. Oncol. Off. J Clin Oncol 2007;25:2127-2132.

Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. Ann Oncol 2017;28(11):2768-2772.

Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372(2):134-141.

von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380(7):617-628.

## 16. APPENDICES

### 16.1 STUDY INFORMATION

**16.1.1 Protocol and protocol amendments**

**16.1.2 Sample case report form (unique pages only)**

**16.1.3 List of IECS or IRBS - representative written information for patient and sample consent forms**

**16.1.4 List and description of investigators and other important participants in the study, including brief CVs or equivalent summaries of training and experience relevant to the performance of the clinical study**

**16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer depending on the regulatory authority's requirement**

**16.1.6 Listing of patient receiving test drug(s)/investigational product(s) from specific batches where more than one batch was used**

**16.1.7 Randomization scheme and codes (patient identification and treatment assigned)**

**16.1.8 Audit certificates**

**16.1.9 Documentation of statistical methods**

**16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used**

**16.1.11 Publications based on the study**

**16.1.12 Important publications referenced in the report**

**16.2 PATIENT DATA LISTINGS**

**16.2.1 Discontinued patients**

**16.2.2 Protocol deviations**

**16.2.3 Patients excluded from the efficacy analysis**

**16.2.4 Demographic data**

**16.2.5 Compliance and/or drug concentration data**

**16.2.6 Individual efficacy response data**

**16.2.7 Adverse events listings**

**16.2.8 Listing of individual laboratory measurements by patient**

**16.3 CASE REPORT FORM**

**16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE**

**16.3.2 Other CRFs submitted**

**16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)**

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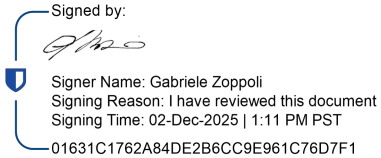
| Gabriele Zoppoli<br>gabriele.zoppoli@unige.it<br>Associate Professor & Senior Consultant<br>Security Level: Email, Account Authentication (Required), Logged in |  <br><br>Signature Adoption: Drawn on Device<br>Signature ID:<br>01631C17-62A8-4DE2-B6CC-9E961C76D7F1<br>Using IP Address: 93.47.220.56<br>Signed using mobile<br>With Signing Authentication via Docusign password<br>With Signing Reasons (on each tab):<br>I have reviewed this document | Sent: 12/2/2025 12:18:10 PM<br>Viewed: 12/2/2025 10:10:07 PM<br>Signed: 12/2/2025 10:11:57 PM |
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| Editor Delivery Events | Status | Timestamp |
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| Agent Delivery Events | Status | Timestamp |
|---|---|---|

| Intermediary Delivery Events | Status | Timestamp |
|---|---|---|

| Certified Delivery Events | Status | Timestamp |
|---|---|---|

| Carbon Copy Events | Status | Timestamp |
|---|---|---|

| Witness Events | Signature | Timestamp |
|---|---|---|

| Notary Events | Signature | Timestamp |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
|---|---|---|
| Envelope Sent | Hashed/Encrypted | 12/2/2025 12:18:12 PM |
| Certified Delivered | Security Checked | 12/2/2025 12:23:17 PM |
| Signing Complete | Security Checked | 12/3/2025 10:14:44 AM |
| Completed | Security Checked | 12/3/2025 10:14:44 AM |

| Payment Events | Status | Timestamps |
|---|---|---|

| Electronic Record and Signature Disclosure |
|---|

## ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, IDDI (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

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### Consequences of changing your mind

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### All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

**How to contact IDDI:**

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: fisseha.worku@iddi.com

**To advise IDDI of your new email address**

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at fisseha.worku@iddi.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

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i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to fisseha.worku@iddi.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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**Acknowledging your access and consent to receive and sign documents electronically**

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
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