Inclusion Criteria:

Subjects must meet all the following criteria to be eligible for randomization into the study:

1. Sign and date the tissue screening and main ICFs, prior to the start of any study-specific qualification procedures.
2. Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old).
3. HER2-positive breast cancer, meeting all of the following criteria:

- ✧ HER2-positive status will be based on pretreatment biopsy material and defined as an immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization(ISH) (as defined in 2018 American Society of Clinical Oncology – College of American Pathologists [ASCO-CAP] guidelines29) confirmed by a central laboratory prior to randomization. If sufficient material from the pretreatment biopsy is not available for submission, central HER2 determination for eligibility may be performed on residual tumor tissue from the time of definitive surgery.
- ✧ Formalin-fixed paraffin-embedded tumor tissue block or a partial block must be available for central evaluation of HER2 expression. If sites are unable to send a tissue block due to local regulations, at least 7 unstained slides should be sent for central testing, and in addition up to 5 slides for exploratory biomarker research. A central laboratory will perform both IHC and ISH assays for HER2.
- ✧ Patients with synchronous bilateral invasive disease are eligible if both primary tumors were confirmed to be HER2-positive.

4. Histologically confirmed invasive breast carcinoma at time of disease presentation. Subjects with inflammatory breast cancer are allowed providing all eligibility criteria are met.
5. Clinical stage at disease presentation of T1-4, N0-3, M0 prior to neoadjuvant therapy (Note: Patients presenting with T1N0 tumors will not be eligible).
6. Pathologic evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of neoadjuvant therapy meeting one of the following high-risk criteria.

- ✧ Inoperable breast cancer at presentation (prior to neoadjuvant therapy), defined as clinical stages T4,N0-3,M0 or T1-3,N2-3,M0. (See Section 10.6.1)
- ✧ Operable disease at presentation, defined as clinical stages T1-3,N0-1,M0, with axillary node positive disease (ypN1-3) following neoadjuvant therapy. (See Section 10.6.2).

7. Completion of neoadjuvant systemic chemotherapy and HER2-directed treatment:

- ✧ Systemic therapy must consist of at least 6 cycles of chemotherapy with a total duration of at least 16 weeks, including at least 9 weeks of trastuzumab

(± pertuzumab) and at least 9 weeks of taxane based chemotherapy. Patients may have received an anthracycline as part of neoadjuvant therapy in addition to taxane chemotherapy.

- ✧ Patients may have received more than one HER2-directed therapy.
- ✧ All planned chemotherapy must be completed prior to surgery as a component of neoadjuvant therapy.

8. Adequate excision as confirmed per medical records: surgical removal of all clinically evident disease in the breast and lymph nodes (see Section 8.1.2).
9. An interval of no more than 12 weeks between the date of last surgery and the date of randomization.
10. Known hormone receptor (HR) status, per local laboratory assessment, as defined by

ASCO-CAP guidelines (≥1%): HR-positive status defined by either positive estrogen receptor (ER) or positive progesterone receptor (PR) status. HR-negative status defined by both known negative ER and known negative PR.

11. Left ventricular ejection fraction (LVEF) ≥ 50% within 28 days prior to randomization.
12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
13. Has adequate organ function within 14 days before randomization;
14. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4 months for males and 7 months for females after the last dose of study drug.

- ✧ If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening before the first dose of study drug and must be willing to use highly effective birth control, as detailed in Section 10.3.4, upon randomization, during the Treatment Period, and for 7 months, following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy).
- ✧ If male, the subject must be surgically sterile or willing to use highly effective birth control (Section 10.3.4) upon enrollment, during the treatment period, and for 4 months following the last dose of study drug.

15. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to enrolment in this study.
16. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.