

Intergroup Study 2129-BCG

Elacestrant for treating ER+/HER2- breast cancer patients with ctDNA relapse (TREAT ctDNA)

(EU trial number 2022-501453-36-00)
(NCT 05512364)

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Warning:

This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC template and is fully applicable to all **collaborative groups** (with the exception of EORTC specific chapters or other collaborative group(s) specific appendix and unless otherwise specified).

The [Appendix F](#), [Appendix J](#) and the PIS/IC are fully applicable to **EORTC investigators** only.

Corresponding items and contact addresses for non EORTC investigators are provided in their **Group specific appendix** that supersedes the contents of the [Appendix F](#) and [Appendix J](#).

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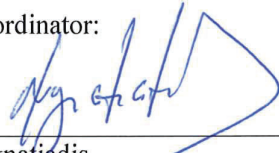
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Protocol summary

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| EU trial number and full title | <p>EU trial number: 2022-501453-36-00</p> <p>Elacestrant for treating ER+/HER2- breast cancer patients with ctDNA relapse (TREAT ctDNA)</p> |
| Rationale | <p>In patients with estrogen receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) early-stage breast cancer, the administration of adjuvant chemotherapy and endocrine treatment (ET) substantially reduces the recurrence rates. However, despite adjuvant systemic treatment, recurrences occur up to 20 years.</p> <p>ctDNA may be a useful biomarker after potentially curative treatment to identify individuals at high risk of relapse. The early diagnosis of recurrence by ctDNA analysis could allow effective therapies to be introduced at time when disease burden is still minimal.</p> <p>Elacestrant, a new oral selective estrogen receptor degrader, has shown significant clinical benefit in patients with ER+/HER2- advanced or metastatic breast cancer following progression on a CDK4/6-inhibitor and could be used at time of ctDNA relapse to delay the occurrence of distant metastasis.</p> |
| Objective(s) | <p><u>Primary objective</u></p> <ul style="list-style-type: none"> • To evaluate whether elacestrant can delay occurrence of distant metastasis or death when compared to standard endocrine therapy in ER+/HER2- breast cancer patients with ctDNA-relapse. <p><u>Secondary objectives</u></p> <ul style="list-style-type: none"> • To evaluate invasive disease-free survival (iDFS), relapse-free survival (RFS) and overall survival (OS) between the 2 treatment arms • To characterize the safety and the tolerability of the 2 treatment arms • To establish the patient-reported tolerability profile in each treatment arm • To compare the patient-reported benefit between the two treatment arms <p><u>Exploratory objectives</u></p> <ul style="list-style-type: none"> • To evaluate associations between ctDNA elimination at month 1 and DMFS according to treatment arm |

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| | <ul style="list-style-type: none"> • To evaluate associations between ctDNA elimination at month 4 and distant metastasis free survival (DMFS) according to treatment arm • To correlate ctDNA (as categorical variable) kinetics with DMFS, iDFS, RFS and OS according to treatment arm • To identify plasma circulating biomarkers associated with benefit from elacestrant |
| Endpoint(s) | <p><u>Primary endpoint</u></p> <ul style="list-style-type: none"> • DMFS defined as the time from randomisation until first distant metastatic recurrence or death from any cause, whichever occurs first <p><u>Secondary endpoints</u></p> <ul style="list-style-type: none"> • Invasive disease-free survival (iDFS) rate according to the STEEP criteria including locoregional recurrence, distant metastasis, invasive contralateral breast cancer and invasive non-breast second cancers, deaths from any cause as events • Relapse-free survival (RFS) rate according to the STEEP criteria, including locoregional recurrence, distant metastasis, deaths from any cause as events • Overall survival rate • Safety including but not limited to all adverse events, serious adverse events, laboratory abnormalities graded according to CTCAE version 5.0 • Patient reported outcomes: tolerability & benefit as measured by the QLQ-C30, QLQ-BR42 and EORTC IL46 <p><u>Exploratory endpoints</u></p> <ul style="list-style-type: none"> • ctDNA elimination rate at month 1, defined as the proportion of randomised patients who had a negative ctDNA test result at month 1 • ctDNA elimination rate at month 4, defined as the proportion of randomised patients who had a negative ctDNA test result at month 4 • ctDNA kinetics: ctDNA as categorical (negative versus positive) variable at different time points during the 3-year period post randomisation • To evaluate associations between plasma biomarkers with the treatment efficacy |
| Study design | International, multi-center, randomised, open label, superiority phase III trial of elacestrant vs standard endocrine therapy in patients with ER+/HER2- breast cancer and ctDNA relapse. |

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| | <p><u>1. ctDNA screening phase:</u> After verification of the eligibility criteria for screening, patients will enter the ctDNA screening phase of the study in which plasma samples will be collected and tested with the Signatera ctDNA assay to detect the presence of ctDNA. The test will be performed every 6 months from study entry until the end of accrual (approximately 5.7 years). During the screening phase, patients will be treated with standard adjuvant endocrine therapy [either tamoxifen or an aromatase inhibitor (exemestane, anastrozole or letrozole)] and followed up as per standard of care. The outcome of the serial ctDNA assessments performed during the screening phase will be disclosed to investigators.</p> <p>Patients who are found to be ctDNA-negative at the end of the screening period will not be followed further in this study.</p> <p>Patients who are found to be ctDNA-positive by Signatera at one of the screening time points, as well as patients who are found to be ctDNA positive by other ctDNA approved assay for diagnostic purposes, will undergo an imaging work-up to assess the presence of distant metastases or locoregional recurrence.</p> <p>Patients for whom the imaging work-up confirms no evidence of distant metastases or locoregional recurrence and/or new malignancy will be eligible for the randomised phase of the study provided they meet all other eligibility criteria. Patients for whom the imaging work-up shows evidence of distant metastases or locoregional recurrence will be excluded.</p> <p><u>2. Randomised trial:</u> Patients fulfilling the eligibility criteria of the randomised trial, will be randomised 1:1 within 4 weeks from the date of ctDNA detection (i.e., the date on which the results of the test are received) between standard endocrine treatment (the same they were receiving when tested ctDNA positive) versus elacestrant. The protocol treatment period will last 2 to 6 years (allowing for 7 years of ET at the end of the study treatment), detailed in the Treatment section. After completion of the protocol treatment period, treatment will be left at the discretion of the treating physician. For patients that discontinued study treatment for any other reason than relapse, treatment should be also as per standard of care.</p> <p>Patients in both arms will undergo intensive follow-up with yearly mammograms and bone scans and 16-weekly CT scans thorax and abdomen/pelvis for a maximum of 3 years after randomisation.</p> |
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| | <p>All randomised patients will be followed up until 3 years after the enrolment of the last patient.</p> <p>Blood will be collected for ctDNA test either within 3 days before start of treatment (elacestrant arm) or within 3 days after randomisation (standard endocrine treatment arm), at week 4 and week 16 after randomisation and every 16 weeks thereafter for a maximum of 3 years (36 months or 156 weeks) for the translational research program.</p> <p><u>End of study:</u> End of study occurs when all the following criteria have been satisfied:</p> <ul style="list-style-type: none"> • All patients have completed their end of study visit. If a patient discontinues the follow-up due to withdrawal of consent, loss to follow-up, or death, the end of study participation is defined as the time point when one of these events occurred. • The trial is mature for all analyses defined in the protocol and the database has been cleaned and frozen for these analyses. |
| <p>Number of patients</p> | <p><u>Number of events</u></p> <ul style="list-style-type: none"> • Considering 90% power and a two-sided alpha of 5% to detect an improvement in median DMFS from 12 months to 20.7 months (hazard ratio = 0.58), 146 events are required to compare DMFS distributions using a stratified two-sided log-rank test. • This number of events accounts for one interim analysis for futility (non-binding) and early efficacy at 50% events and for one interim analysis for early efficacy at 70% events. <p><u>Number of patients to be randomised</u></p> <ul style="list-style-type: none"> • It is expected to randomise 220 patients (110 per arm) to account for 5% annual drop out. <p><u>Number of patients to be successfully screened</u></p> <ul style="list-style-type: none"> • Assuming that 11.5% of screened patients will be ctDNA positive during the screening phase, approximately 1960 patients should be successfully screened (fulfilling eligibility criteria and having a successful ctDNA report test from the central laboratory). |

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| <p>Trial population</p> | <p><u>1. ctDNA screening phase:</u> Main inclusion criteria:</p> <ul style="list-style-type: none"> • Female (both pre- and postmenopausal) or male patients with histologically confirmed ER positive (regardless of PR), HER2 negative breast cancer, according to local pathologist: • ER-positive defined as $\geq 10\%$ of cells staining positive for ER or Allred proportion score ≥ 3 • HER2-negative defined as a score of 0, 1+ by immunohistochemistry (IHC) or a negative in situ hybridization (ISH) based on single-probe average HER2 copy number, as per American Society of Clinical Oncology guidelines • Intermediate to high risk of recurrence after definitive treatment for early breast cancer, defined as: FOR PATIENTS TREATED WITH PRIMARY SURGERY: <ul style="list-style-type: none"> • Any patient with ≥ 4 positive axillary lymph nodes (stage pN2-3). • 1-3 positive axillary lymph nodes (stage pN1) and either: <ul style="list-style-type: none"> • Tumour size ≥ 5 cm or/and • Histologic grade 3 or/and • Ki67$\geq 20\%$ or/and • High genomic risk defined as Oncotype Dx Recurrence Score ≥ 26, MammaPrint high risk, Prosigna score >40 or EPclin risk score ≥ 4.0. • Negative axillary lymph nodes (stage pN0) and tumour size ≥ 5 cm and either <ul style="list-style-type: none"> • Histologic grade 3 or/and • Ki67$\geq 20\%$ and/or • High genomic risk defined as Oncotype Dx Recurrence Score ≥ 26, MammaPrint high risk, Prosigna score >60 or EPclin risk score ≥ 4.0. • FOR PATIENTS TREATED WITH NEOADJUVANT SYSTEMIC TREATMENT FOLLOWED BY SURGERY: <ul style="list-style-type: none"> • Patient may have received neoadjuvant endocrine therapy or neoadjuvant chemotherapy provided that: <ul style="list-style-type: none"> • The initial tumour and/or the tumour after surgery meet the criteria above defined for patients treated with primary surgery or the initial tumour was staged as cT4anyN and • There is no pathological complete response, defined as no invasive disease in the breast and axilla (ypT0/is ypN0). • Age ≥ 18 years |
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| | <ul style="list-style-type: none"> • Patients must have received at least 1 year and up to 7.5 years of ET and planned to continue adjuvant ET during ctDNA screening phase • Previous adjuvant CDK4/6 inhibitor or PARP-inhibitor treatment is allowed provided it is completed • Invasive multicentric / multifocal disease is allowed provided that all the tested foci are ER+ HER2-. A sample from the highest-risk one, according to the investigator decision based on the size and grade, should be sent to Natera to build the patient ctDNA assay. • Available tumour sample from resected or biopsied tissue, with a tumour content of $\geq 20\%$ (30% preferred) either before or after macro dissection (if performed) and a cell viability of a minimum 100 cells. • Core Needle Biopsies (CNB): recommended minimum of four (4) cores per block • Fine Needle Aspirates (FNA) are <i>not</i> accepted • The following sample types are acceptable: <ul style="list-style-type: none"> • 6-10 unstained slides (charged and unbaked) of 10μm each (or 12-19 unstained slides at 5 μm each), PLUS one contiguous H&E slide. Minimum total tissue thickness must be 60μm OR • FFPE tissue block with 25mm² minimum surface area • Written informed consent must be given according to ICH/GCP, and national/local regulations. <p>Main exclusion criteria:</p> <ul style="list-style-type: none"> • Suspected recurrent disease or known conflicts with the inclusion and exclusion criteria for the randomised trial • Prior treatment with any SERD or investigational ER antagonist • Previous history of invasive breast cancer • Previous history of any other malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ. • Previous history of bone marrow and/or organ transplant • Bilateral breast cancer • Participation in another clinical study, with the exception of the SURVIVE study and observational (non-interventional) and non-drug intervention clinical studies. Note: patients participating in interventional studies may participate once they enter the follow-up period of the study • Blood transfusion within 3 months prior to registration or during the screening. |
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| | <p>2. Randomised trial:</p> <p>Main inclusion criteria:</p> <ul style="list-style-type: none"> • ctDNA positive according to the Signatera ctDNA assay (main study ctDNA test) or other ctDNA assay approved for diagnostic purposes. • Patients must meet the eligibility criteria for the screening phase, with the exception of the tissue sample requirements. • Patients must receive adjuvant ET at the time of the ctDNA positive test • Absence of locoregional and/or metastatic disease and/or new malignancy, as investigated by: <ul style="list-style-type: none"> • Mammogram (unilateral in case of mastectomy; not required in patients having undergone bilateral mastectomy) <p>NOTE: <i>if local investigator plans to use MRIs instead of mammograms during the study, MRI will have to be performed at baseline.</i></p> <ul style="list-style-type: none"> • CT thorax and abdomen/pelvis with IV contrast. In case of any contra-indications (medical or regulatory): CT thorax without contrast + MRI abdomen/pelvis. • Technetium-99m bone scintigraphy • Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 • Adequate organ function • Women of childbearing potential (WOCBP) must have a negative highly sensitive serum or urine pregnancy test within 7 days prior to randomisation. <p>Main exclusion criteria:</p> <ul style="list-style-type: none"> • Any unresolved toxic effect of prior therapies or surgical procedures of Grade ≥ 2 according to Common Terminology Criteria of Adverse Events (CTCAE) v5.0, with the exception of alopecia, peripheral neuropathy and other toxicities not considered a safety risk for the participant at investigator's discretion • Unable or unwilling to avoid over-the-counter medications, dietary/herbal supplements, and/or foods that are moderate/strong inhibitors or inducers of CYP3A4 activity • Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications • Any of the following cardiovascular disorders within 3 months before enrolment: <ul style="list-style-type: none"> • myocardial infarction • stroke • severe/unstable angina • symptomatic cardiac arrhythmia |
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| | <ul style="list-style-type: none"> • prolonged QTcF \geq Grade 3 (i.e., > 500 msec) • heart failure \geq Class III as defined by the New York Heart Association (NYHA) guidelines • Child-Pugh Score greater than Class A • Uncontrolled significant active infections (\geq grade 3 according to CTCAE version 5), including active hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency Virus (HIV) • Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism |
| Treatment | <p>Patients who are found to be ctDNA-positive and fulfill the eligibility criteria of the randomised trial will be centrally randomised (1:1) between:</p> <ul style="list-style-type: none"> • Experimental arm: elacestrant 400 mg/day orally once daily on a continuous dosing schedule • Control arm: standard endocrine treatment - the same they were receiving at the time of ctDNA detection <p>Patients in the experimental arm must start elacestrant between 7 to 10 days after randomisation, allowing a wash-out period of at least 1 week (i.e., 7 days) from the previous endocrine treatment (E.T).</p> <p>Patients in the control arm can continue their treatment without interruption.</p> <p>Pre-menopausal and perimenopausal women and men in the elacestrant arm will receive a GnRH analogue (goserelin, leuprorelin or triptorelin) as per site/ country availability for the duration of treatment.</p> <p>Those who were <i>not receiving it at the time of ctDNA detection</i> should be administered the GnRH analogue at the time of randomisation and continue their previous ET during the first 21 days, allowing for one week (i.e., 7 days) wash-out before - exceptionally- starting Elacestrant on Day 29 counting from the date of randomisation.</p> <p>If pre-menopausal and perimenopausal women or men in the control arm were receiving a GnRH analogue at the time of ctDNA detection, this should be continued after randomisation. If these patients were not receiving a GnRH analogue at the time of ctDNA detection, they are allowed, but not obliged, to receive this after randomisation upon discretion of the investigator.</p> |

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| | <p>In the absence of a withdrawal criteria, treatment in both arms will be administered for:</p> <ul style="list-style-type: none"> • For patients on ET between 1 to 5 years (12 to 60 months) at the time of randomisation: 2 to 6 years (allowing for 7 years of ET at the end of the study treatment) • For patients on ET between 5 to 7.5 years (60 to 90 months) at the time of randomisation: 2 years <p>After completion of the treatment phase of the randomised trial, patients will enter the follow-up phase. Of note, for patients still on treatment at 3 years after randomisation of the last patient, data will be collected until their end of treatment visit as per the schedule of assessments. During the follow-up phase patients can receive a treatment of investigator’s choice but there will be no option to continue elacestrant within the trial.</p> |
| <p>Reference Treatment</p> | <p>All patients with ER+ early breast cancer should receive at least 5 years of endocrine treatment (ET) after completion of local therapy.</p> <p>In premenopausal women, tamoxifen for 5–10 years is standard of care, with the option of adding ovarian function suppression (GnRH analogues) in high-risk patients, e.g., patients < 35 years or those requiring chemotherapy. For high-risk patients under effective ovarian function suppression the substitution of tamoxifen with an aromatase inhibitor (letrozole, anastrozole, exemestane) can be considered.</p> <p>For postmenopausal women both aromatase inhibitors and tamoxifen are considered standard treatments. Aromatase inhibitors can be used upfront, after 2–3 years of tamoxifen or as extended adjuvant therapy, after 5 years of tamoxifen (letrozole and anastrozole). Extended adjuvant therapy should be discussed with all patients, except those with a very low risk of relapse, but the optimal duration and regimen of adjuvant ET are currently unknown.</p> <p>The standard adjuvant ET for men with hormone receptor–positive breast cancer is 5 to 10 years of tamoxifen. For men who are not good candidates for tamoxifen, a GnRH analogue can be used as adjuvant therapy, with or without an aromatase inhibitor.</p> <p>There is lack of clear evidence on the most adequate follow-up schedule for patients treated for early breast cancer. Components mainly include regular history and physical examination and routine mammographic surveillance. More intensive laboratory and/or radiologic surveillance (e.g., tumour markers such as</p> |

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| | <p>cancer antigen 15-3 (CA15.3), chest X-rays, bone scans, liver US, CT scans, FDG-PET-CT) has failed to show a survival benefit over routine follow-up and is not generally recommended.</p> | | | | | | | | |
| <p>Statistical analyses</p> | <p>1:1 randomisation for patients who are ctDNA positive between standard endocrine treatment or elacestrant, stratified according to:</p> <ul style="list-style-type: none"> • Country • Duration of ET at the time of ctDNA detection (≤ 5 years vs. > 5 years) • Stage (II vs. III) • Prior treatment with CDK4/6 inhibitors (yes vs. no) • Prior (neo)adjuvant chemotherapy (yes vs. no) • ctDNA assay (Signatera from Natera versus others) <p><u>null hypothesis estimate for control group:</u> median DMFS: 12 months <u>alternative hypothesis as used for the power calculation:</u> HR = 0.58 corresponding to a median DMFS of 20.7 months <u>primary test:</u> two-sided stratified log-rank test. The stratification factor used at randomisation will be used for the stratified test (based on the actual distribution of number of events within strata, some stratification factors might not be included in the stratified test to minimize the risk of power loss).</p> <table border="1" data-bbox="613 1115 1463 1503"> <tr> <td>type I and type II errors</td> <td>2-sided Alpha 5% Beta 10%</td> </tr> <tr> <td>number of events/ patients</td> <td>146 events 220 patients randomised 1960 patients successfully screened</td> </tr> <tr> <td>expected duration of recruitment</td> <td>4.7 years for screening 5.7 years for randomised part</td> </tr> <tr> <td>expected duration of follow-up after last patient randomised*</td> <td>3 years for all patients</td> </tr> </table> <p>*After 3 years after the randomisation of last patient, some patients might still be on study treatment to complete at least 7 years of endocrine therapy. For these patients, data will be collected until their end of treatment as per the schedule of assessment. Therefore, the maximal study duration can be greater than 8.7 years.</p> <p><u>Assumptions</u></p> <ul style="list-style-type: none"> • The median lead time from ctDNA detection to occurrence of distant metastasis is approximately 11 months without treatment following ctDNA detection. • The recent results from the EMERALD study showed an observed HR of 0.70 (95%CI: 0.55;0.88) for the endpoint of PFS in the overall population of patients in second or | type I and type II errors | 2-sided Alpha 5% Beta 10% | number of events/ patients | 146 events 220 patients randomised 1960 patients successfully screened | expected duration of recruitment | 4.7 years for screening 5.7 years for randomised part | expected duration of follow-up after last patient randomised* | 3 years for all patients |
| type I and type II errors | 2-sided Alpha 5% Beta 10% | | | | | | | | |
| number of events/ patients | 146 events 220 patients randomised 1960 patients successfully screened | | | | | | | | |
| expected duration of recruitment | 4.7 years for screening 5.7 years for randomised part | | | | | | | | |
| expected duration of follow-up after last patient randomised* | 3 years for all patients | | | | | | | | |

third-line metastatic BC comparing elacestrant to standard of care as per physician's choice. In the metastatic setting, the PADA-1 trial has already shown that for patients treated with a CDK4/6 inhibitor in combination with an AI, switching to fulvestrant upon detection of an ESR1 mutation in the ctDNA, is associated with an improvement in PFS versus continuing the same treatment (median 11.9 vs. 5.7 months, HR 0.61, p=0.005). In the present study and since patients in the control arm will continue the same endocrine treatment, they were taken at the time of ctDNA detection, a large treatment effect (hazard ratio = 0.58) is considered for the power calculation.

Accrual duration

- Under the assumptions of an accrual rate of 40 patients successfully screened/month in 120 sites and a building up accrual rate during the first year, it is expected that the accrual duration for the screening period will be approximately 4.7 years and will be approximately **5.7 years for the randomised trial** to allow a minimum of 1-year screening period for all patients. (Note that each patient could have a minimum of 3 blood draws during the screening period (frequency every 6 months).

Timing of analysis of primary endpoint

- The required number of events for the final analysis of the primary endpoint is expected to be observed maximum **7 months after the last patient is randomised**, corresponding to approximately 6.25 years after the first patient randomised. The actual accumulation of events will be monitored throughout the study depending on the actual accrual rate, actual randomisation rate and event rate.

Follow-up analysis

- Follow-up analysis will be performed at 3 years after the last patient is randomised (corresponding to 8.7 years after the first patient randomised).
- The last analysis will be performed at the time of end of study if some patients are still on study treatment at 3 years after the last patient is randomised.

Interim analyses

- One interim analysis is planned to assess the futility (non-binding) and early efficacy of the experimental arm when 50% of the total number of events required have been observed (73 events). This interim analysis is expected to take place approximately at 4 years after start of accrual, when

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| | <p>approximately 140 (64%) patients would have been randomised. The results of this interim analysis will be made available before the end of accrual, this would allow not to expose patients to an ineffective drug in case of evidence of futility.</p> <p>To assess futility of the experimental arm, the stopping boundaries are derived based on the O’Brien and Fleming β-spending function depending on the actual number of events observed. For the experimental treatment group, the HR boundary is 0.954. Therefore, if the observed HR is >0.954, the experimental arm will be declared futile. In this scenario, there is a 55.4% probability to stop the study in case of futility of the experimental arm.</p> <p>To assess the early efficacy of the experimental arm, the stopping boundaries are derived based on the O’Brien and Fleming α-spending function. For the experimental treatment group, the HR boundary is 0.5, corresponding to a 2-sided p-value ≤ 0.0035. Under the alternative hypothesis, there is 26.3% probability to declare early efficacy of the experimental arm.</p> <ul style="list-style-type: none"> • One interim analysis planned to assess the early efficacy of the experimental arm when 70% of the total number of events required have been observed (102 events) for the primary endpoint DMFS. This interim analysis is expected to take place approximately at 4.9 years after start of accrual, when approximately 176 (80%) patients would have been randomised. The stopping boundaries are derived based on the O’Brien and Fleming α-spending function depending on the actual number of events observed. For the experimental treatment group, the corresponding HR boundary for early efficacy is 0.614 at 102 events (2-sided p-value ≤ 0.0137). Under the alternative hypothesis, there is a cumulative 61.7% probability to declare early efficacy of the experimental arm. • Four additional events were needed to perform the two interim analyses. |
| <p>Translational research</p> | <p>Translational research will be performed on all the leftovers and the randomised patients plasma samples collected during the study with the aim to identify plasma circulating biomarkers associated with benefit from elacestrant.</p> |

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| <p>Health Related Quality of Life</p> | <p>Health-related quality of life (HRQoL) is a secondary endpoint in this trial. HRQoL assessment aims at 1) establishing the patient-reported tolerability profile in each treatment arm and 2) comparing the patient-reported benefit between the two treatment arms.</p> <p>Assessments will be performed at 21 days before randomisation, 4 weeks, 16 weeks, 32 weeks, 48 weeks, 64 weeks, and 80 weeks after randomisation using the following measures: QLQ-C30, QLQ-BR42, & EORTC IL46.</p> |
| <p>Benefit-risk analysis</p> | <p>The adverse prognostic value of ctDNA detection has been demonstrated for multiple tumour types as well as in different disease settings (both early and advanced disease). Therefore, ctDNA may be a useful biomarker after potentially curative treatment to identify individuals at high risk of relapse. The early diagnosis of recurrence by ctDNA analysis in these high-risk patients could also allow effective therapies to be introduced at time when disease burden is still minimal. The Treat ctDNA study aims to evaluate whether elacestrant can delay the occurrence of distant metastasis compared to standard ET in patients with ctDNA relapse.</p> <p>Elacestrant has already demonstrated a significant benefit over standard endocrine treatment in pretreated patients with advanced breast cancer.</p> <p>Treating patients at the moment of ctDNA relapse rather than waiting for clinically and/or radiologically detectable disease recurrence has not been proven to be affective and puts patients at risk of being overtreated. Therefore, an interim analysis is planned at 50% of the total number of events required, with an early stopping rule to avoid exposing patients to an ineffective drug in case of evidence of futility.</p> <p>Elacestrant is mainly associated with low grade gastro-intestinal AEs, which are less frequent with the tablet formulation used in our trial in comparison to the capsules used in the phase 1 studies. No ocular or cardiac toxicity was observed and there were no treatment related deaths. Patients will be regularly monitored for the occurrence of toxicity during the randomised part of our trial, and specific guidelines for the prompt management of nausea and vomiting are provided by the study protocol. Since SERD agents in general are known to be teratogenic, pregnancy should be strictly avoided during treatment with elacestrant. In addition, in this trial, in premenopausal women on elacestrant, a menopausal status will be induced by ovarian function suppression.</p> |

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| | Overall, we believe that the benefit / risk ratio is favourable and justifies the inclusion of patients in the Treat ctDNA trial. |
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Trial organisation

- The EORTC, based in Belgium, is the Sponsor in all participating countries.
- This trial is an intergroup trial, jointly conducted by several national/international cancer clinical research groups under the umbrella of BIG (Breast International Group) and by SUCCESS.
- The EORTC is the coordinating group in this trial and therefore centrally manages trial design and activation, attribution of duties and responsibilities between participating research groups, data collection and quality control of data, statistical analyses and publication.
- This protocol is to be followed by all participating groups. Chapters 1 to 10 are fully applicable to all groups. Appendix F and Appendix J are specific to the EORTC participants (members of the EORTC covered by the sponsorship of the EORTC), all other appendices are applicable to all groups. All particularities of participation of each individual group are included in the Group Specific Appendices annexed at the end of the protocol.
- The participation to this trial is only possible through one of the participating clinical cancer research groups. For contacts and addresses please refer to the Group Specific Appendix of the group of your membership on which behalf you are going to participate (see below).
- Investigators who are members of several groups participating to the trial should select one of these groups for the framework of this trial and have to include all patients through this group. In some cases, because of the national legal framework the choice may be imposed. For EORTC members all patients will be accounted for the membership independently from the group they choose to participate through (see EORTC POL005). In case of any difficulties in a group selection, please contact the EORTC Headquarters.
- The investigational drug elacestrant will be supplied free of charge by Menarini.

This trial is an academic trial with a restricted educational grant support from Menarini. Natera is the provider for ctDNA testing in the screening phase.

1 Background and rationale

1.1 Early breast cancer, endocrine treatment, and risk of recurrence

Breast cancer is the leading cause of cancer and the leading cause of cancer deaths in women. Breast cancer accounts for approximately 24.5% of the total cancer cases and 15.5% of the cancer deaths in women. Worldwide, there were 2.3 million new cases and over 685,000 deaths from breast cancer in 2020 [1]. However, breast cancer incidence rates are relatively stable, while mortality rates due to breast cancer have declined by 40% from 1989 to 2017 [2].

Breast cancer is categorized based on tumour receptor status and is considered receptor positive (+) if the tumour expresses the oestrogen receptor (ER), the progesterone receptor (PgR) and/or the human epidermal growth factor receptor 2 (HER2). Alternatively, a tumour may not express one or more of these receptors and be considered receptor negative (-). Approximately, 80% of breast cancers express the ER at the time of diagnosis, while about 15% is HER2+. The subgroup of ER+/HER2- breast cancer comprises about 66% of all breast cancer diagnoses [2].

1.1.1 Endocrine treatment

Given that the ER drives the growth and survival of these ER+ tumours, international guidelines recommend endocrine treatment (ET) for ER+ breast cancer. Available endocrine treatments act as anti-oestrogens either by: 1) decreasing ligand levels (ovarian ablation, gonadotropin releasing hormone [GnRH] agonists, aromatase inhibitors [AIs]) or 2) antagonizing the receptor (selective oestrogen receptor modulators [SERMs]; e.g., tamoxifen, toremifene), or 3) acting as selective oestrogen receptor degraders [SERDs] (e.g., fulvestrant). In patients with ER+, HER2- early-stage breast cancer, the administration of adjuvant chemotherapy and ET substantially reduces the recurrence rates and improves survival [3–6].

All patients should receive at least 5 years of ET after completion of local therapy [7]. In premenopausal women, tamoxifen for 5–10 years is a standard of care (SOC), with the option of adding ovarian function suppression (OFS) in high-risk patients, e.g., patients < 35 years or those requiring chemotherapy [8]. For high-risk patients under effective OFS, the substitution of tamoxifen with an AI can be considered. For postmenopausal women both AIs (either the non-steroidal letrozole and anastrozole or the steroidal exemestane) and tamoxifen are considered standard treatments. AIs can be used upfront, after 2–3 years of tamoxifen or as extended adjuvant therapy, after 5 years of tamoxifen (letrozole and anastrozole). Extended adjuvant therapy should be discussed with all patients, except those with a very low risk of relapse. However, the optimal duration and regimen of extended adjuvant ET are currently unknown [9].

The standard adjuvant ET for men with ER+ breast cancer is 5 to 10 years of tamoxifen. The efficacy of AIs in men is not clear and may be lower in men than in women. Population-based series have shown inferior survival rates when men were treated with adjuvant AIs as compared with tamoxifen. Treatment with single-agent AIs is not considered to be a standard adjuvant approach. For men who are not good candidates for tamoxifen, a GnRH analogue can be used as adjuvant therapy, with or without an AI [10].

Despite adjuvant systemic treatment, recurrences occur up to 20 years from diagnosis and the risk is strongly associated with tumour size and nodal status [11,12]. Thus, there is an unmet medical need to improve outcomes for these patients at high risk of relapse. There is also a lack of clear evidence on the most adequate follow-up schedule for patients treated for early breast cancer. Components mainly include medical history and physical examination and routine mammographic surveillance. More intensive laboratory and/or radiologic surveillance (e.g., tumour markers such as cancer antigen 15-3 (CA15-3), chest X-rays, bone scans, liver ultrasound (US), CT scans, FDG-PET-CT) has failed to show a survival benefit over routine follow-up and is not generally recommended. In a meta-analysis first published in 2000 and last updated in 2016, no significant differences in overall survival (OS) (hazard ratio (HR) 0.98, 95% CI 0.84-1.15), disease-free survival (DFS) (HR 0.84, 95% CI 0.71-1.00) or quality of life were observed between more intensive and routine follow-up schedules [13,14]. The identification of early breast cancer patients at high risk of relapse would allow a tailored adjuvant therapy approach aiming to escalate the treatment only for those patients who will benefit from this intensification [15].

1.2 Circulating tumour DNA (ctDNA) as biomarker of relapse

ctDNA is tumour-derived fragmented DNA shed into a patient's bloodstream that is not associated with cells. ctDNA quantity can vary among individuals and depends on the type of tumour, location, stage, tumour burden, and response to therapy. ctDNA may be a useful biomarker after potentially curative treatment to identify individuals at high risk of relapse, allowing for effective therapies to be introduced at time when disease burden is still minimal [16].

ctDNA detection in plasma using different technologies has been evaluated in different studies including in total more than 800 patients with early breast cancer who have been treated with (neo)adjuvant chemotherapy [17]. In these studies, ctDNA detection during follow-up identified with high accuracy patients in biochemical relapse (ctDNA relapse) with a median lead time of 11 months over clinical relapse [18]. In a recent systematic review of trials performed in different tumour types, including breast cancer, a surveillance strategy involving longitudinal blood draws at multiple time points during follow-up was shown to have a superior sensitivity and specificity in comparison to a landmark analysis at a single, prespecified time point shortly after completion of treatment [19].

ctDNA plasma levels in patients with early-stage disease are usually lower than those found in patients with metastatic disease, which poses substantial challenges for the use of ctDNA surveillance to detect early relapse. Another biological hurdle is the complexity of differentiating ctDNA from clonal haematopoiesis of indeterminate potential, a well-known age-related process due to shedding of blood leukocytes with clonal mutations above a variant allele fraction (VAF) of 2% [20].

Recent progresses, especially in the use of “personalised” ctDNA assays probing multiple known mutations, have lowered the detection threshold and are showing promising data overcoming the technical and biological difficulties in the detection of ctDNA in early-stage disease. Tumour-informed panels are constructed by sequencing the tumour and then selecting a set of variants to follow in plasma ctDNA. Limitations of this approach includes the lag time between tumour testing and the construction of the ctDNA panel and that the sensitivity and specificity may depend on clinical cut-offs and on the analytical sensitivity of the device as well as on the number of tumour informed targets assayed.

1.2.1 The Signatera test

1.2.1.1 Intended Purpose

The Signatera test is a personalized, tumour-informed multiplex-PCR and next generation sequencing (NGS) based in-vitro diagnostic test. It is intended for the detection of circulating tumour DNA (ctDNA) isolated from anticoagulated peripheral whole blood from post-surgical patients previously diagnosed with localized or advanced solid tumours to aid physician assessment and treatment decision making, together with other clinical factors. The Signatera test is for monitoring minimal residual disease by detection of ctDNA in patients previously diagnosed with solid malignancies. Signatera is also used to detect cancer recurrence before, during, and after therapy.

1.2.1.2 Regulatory Status

Signatera test is CE marked under in-vitro diagnostics (IVD) Directives as of 30 July 2020. Signatera tissue collection is CE marked under IVD Regulations and blood collection kits under IVD Directives.

In the United States (US), Signatera test is certified by US Clinical Laboratory Improvement Amendments (CLIA) (42 CFR Part 493), accredited by College of American Pathologists (CAP) and holds a New York state permit (New York Statutes, Public Health, Article 5, Title V. Title 10 New York Codes, Rules and Regulations (NYCRR)). Signatera test is a breakthrough device granted by the US Food and Drug Administration (FDA). Signatera test is not US FDA approved or cleared.

1.2.1.3 Signatera Test Description

The Signatera test is a personalized, tumour-informed, NGS based clinical trial assay targeting 16 tumour-specific somatic single nucleotide variants (SNVs). The test involves the custom design and manufacture of a personalized assay for each patient, based on the unique mutations found in that patient's tumour tissue (the personalized tumour signature).

The test includes two primary components: (1) Whole Exome Sequencing (WES) component used to identify and select tumour-informed SNVs, and (2) Plasma component for detection of the prioritized SNVs in a patient's plasma. An overview of the process, sample sources, and informatics pipeline are shown in [Figure 1](#).

Briefly, DNA isolated from FFPE tumour tissue and DNA isolated from matched whole blood collected in K2EDTA blood collection tubes are processed for tumour tissue characterization using WES. Through the WES process, tumour specific SNVs are identified following elimination of germline and CHIP variants by subtraction from the matched normal genomic sequence. Depending on the tumour type and disease stage along with other clinicopathological factors, tens to thousands of tumour specific SNVs can be identified per patient. This subtraction process is represented in [Figure 2](#).

From these candidate variants, a panel of 16 SNVs are selected for detection of ctDNA based primarily on variant allelic frequency (VAF), low noise profile in the plasma sequencing step, and multiplex PCR compatibility between primers. ctDNA is analysed from cfDNA isolated from whole blood (plasma) samples collected using Streck (Blood Collection Tubes) BCTs. The WES component is performed once for variant selection while the plasma component is performed for routine analysis of a patient's cell free DNA.

A patient’s plasma sample is considered ctDNA-positive when at least 2 SNV targets out of 16 are measured above a predefined confidence threshold. Otherwise, the sample is considered ctDNA negative. The Signatera test is a qualitative test that reports the presence or absence of ctDNA as “ctDNA Positive” or “ctDNA Not Detected”.

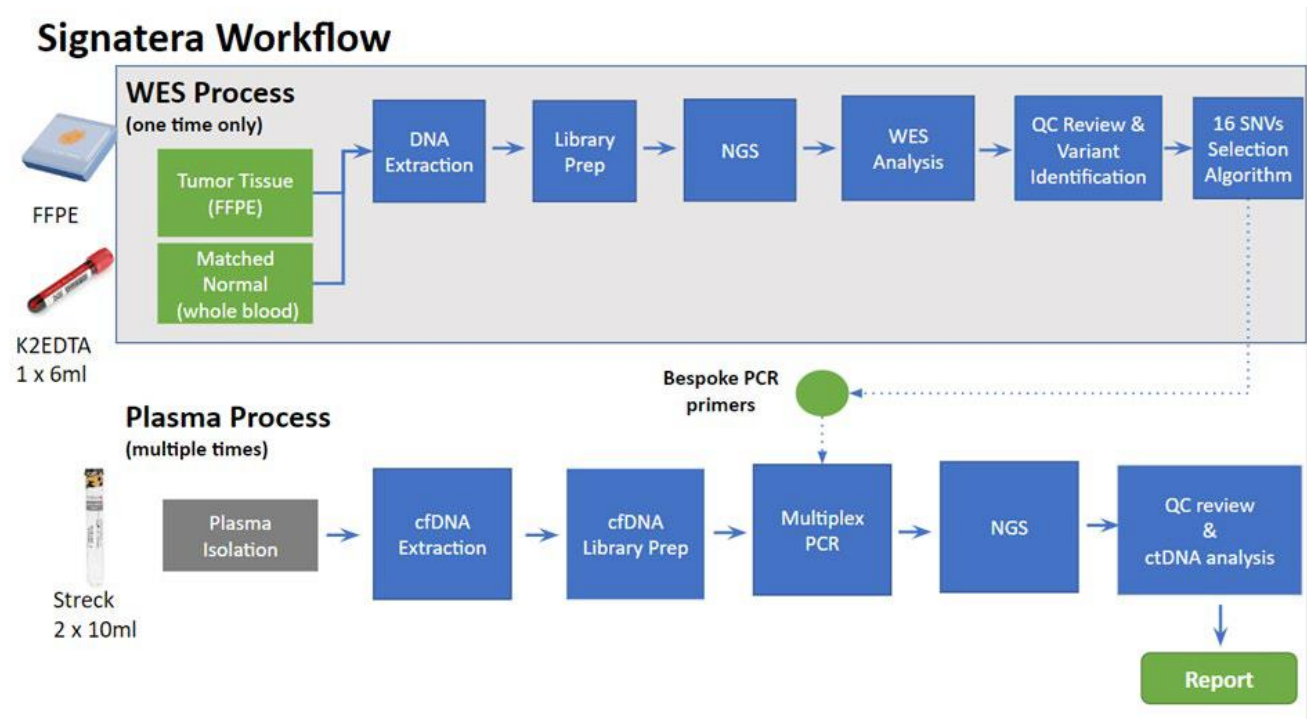


Figure 1: Signatera workflow

Signatera workflow consists of the WES component to identify and select a bespoke panel of tumour-informed variants and the Plasma component for routine NGS analysis for those variants from plasma samples.

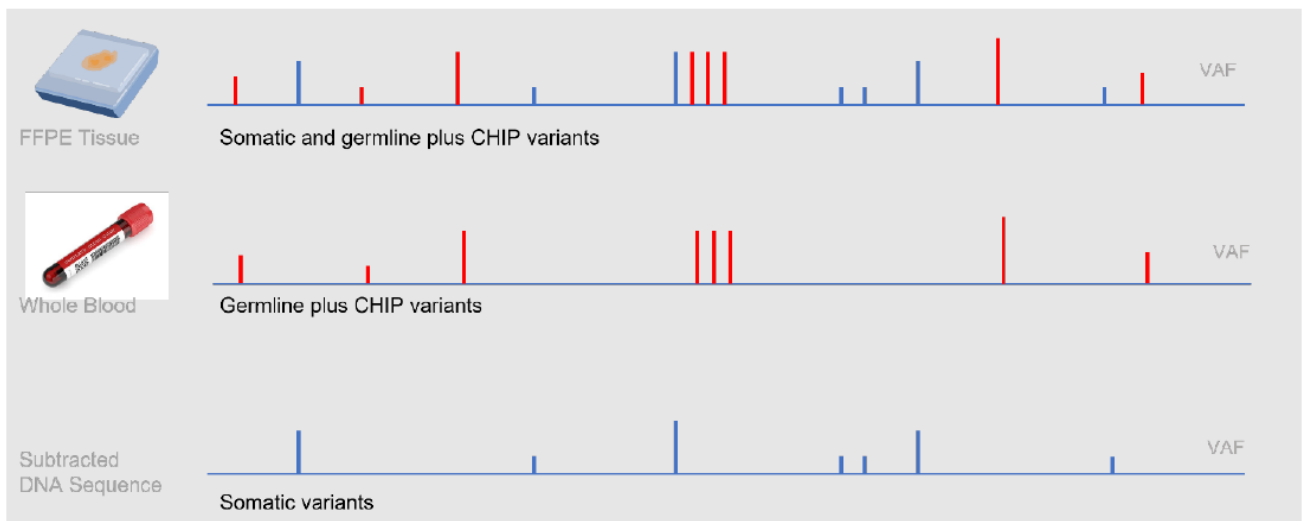


Figure 2: Subtraction process schematic representation

Schematic representation of the subtraction process of tumour tissue DNA sequence from germline DNA sequence to identify somatic, tumour-informed variants in the WES process.

Studies have shown that a positive Signatera result predicts relapse with an overall positive predictive value of more than 98% [4,9]. In early breast cancer, Shaw et al. showed that ctDNA detection with Signatera antedates clinical or radiologic relapse and metastatic disease with a lead time of up to 2 years (median 8.9 months, 0.5-24m; FPR=0)[4]. Patients who never became ctDNA positive during the four years of the study had been relapse-free. From two relapsed cases out of 49 patients, that had never been detected by the liquid biopsy (FNR=11%), the one had a local relapse and the other had bone metastasis and had chemotherapy before the blood draw. Similarly for the complete EBLIS cohort including a total of 156 patients with primary breast cancer followed with semi-annual blood samples for up to 12 years, patients with HR+/HER2- the median lead time was 15 months (2-39 months). Patients with positive test had poorer relapse-free survival (HR=47.5, 95%CI 18.5-161.4, P<0.001).

Of important note, history of bone marrow and/or organ transplant and/or of blood transfusions might affect the sensitivity of the test.

Patients who test positive with another ctDNA assay are candidates to be randomised provided that the ctDNA assay is validated for diagnostic purposes. One example is the follow-up SURVIVE-Study (Standard Surveillance vs. Intensive Surveillance in Early Breast Cancer), that was launched in Germany in 2022. In this study, patients with early breast cancer will be randomised to either standard surveillance or intensive liquid-biopsy guided surveillance, based on a different ctDNA assay, the RaDaR™ assay (Residual Disease and Recurrence). Upon detection of molecular recurrence, patients participating in SURVIVE will be offered the option to enter interventional trials such as the EORTC 2129-BCG, providing that the RaDaR test complies with IVDR requirements.

1.3 Selective oestrogen receptor degraders (SERDs)

1.3.1 Rationale and mechanism of action

SERDs have the ability to block endocrine-dependent and endocrine independent oestrogen receptor α (ER α) signalling by ablation of ER α and have been recognized to offer a therapeutic approach where other endocrine agents, such as tamoxifen or AIs have failed.

The only SERD currently approved for the treatment of ER+ patients is fulvestrant. Fulvestrant has shown clinical benefit in the treatment of patients with advanced breast cancer, both as a first line treatment and after progression under endocrine therapies such as tamoxifen or AIs [21–23]. Although fulvestrant has served as an important proof of concept for the SERD approach, this therapy is limited by its poor pharmaceutical properties which necessitate intramuscular administration and limits the applied dose, exposure, and receptor engagement.

The “new generation” of SERDs have shown improved route of administration (PO versus IM), bioavailability, and long-term maintenance of ER blockade combined with a strong antitumour activity and are currently tested in early and metastatic setting. Therefore, oral SERDs represent a novel treatment option for ER+ breast cancer with optimized characteristics [24].

1.3.2 Elacestrant

Elacestrant (RAD1901) is a tetrahydronaphthalene compound with a favourable tissue selective ER profile, acting as a SERD at higher doses and being developed as an oral formulation for the treatment of ER+ breast cancer. At lower doses, elacestrant was evaluated as a treatment for menopause-related vasomotor symptoms in women experiencing natural or surgically induced menopause [25].

1.3.2.1 Nonclinical studies

Elacestrant have been shown to exert anti-proliferative effects via a dose-dependent antagonism of E2 and degradation of the ER in cell lines. It also showed anti-tumour activity in mouse xenograft models with breast tumours. A number of nonclinical studies were also conducted in animal species to evaluate PKs. Minimal toxicity was observed in nonclinical safety pharmacology studies in mice, rats, and monkeys at doses exceeding the relevant clinical human exposure in patients with breast cancer. Maternal and foetal toxicity was observed in rats when elacestrant was administered daily through the period of organogenesis. However, to date, elacestrant has not demonstrated a mutagenic, clastogenic, aneuploidy, or genotoxic effect in any study performed. No carcinogenicity studies have been conducted. Elacestrant has demonstrated no phototoxic potential.

1.3.2.2 Clinical studies

As of the data cut-off date of 27 December 2021, 815 subjects were exposed to elacestrant across a total of 17 completed or ongoing clinical studies.

1.3.2.2.1 Pharmacokinetics

Administration of the elacestrant 400 mg tablet with a light, low-fat meal or a heavy, high-fat meal slightly increased the geometric mean elacestrant C_{max} by 32% and 36%, respectively, and AUC_{0-inf} by 16% and 26%, respectively, compared to elacestrant administered under fasted condition. A second study confirmed a food effect for the elacestrant 400 mg commercial tablet. Administration of elacestrant 400 mg commercial tablet with a high-fat meal led to a mean plasma exposure 22% (for AUCs) and 42% (for C_{max}) higher compared to elacestrant 400 mg commercial administered fasted. As the relative bioavailability of elacestrant tablets slightly increased when administered under a fed condition (light meal) compared to when administered under a fasted condition, it is recommended to administer elacestrant after a light meal to improve the gastrointestinal tolerability effects associated with fasted administration.

Faecal excretion is the predominant route of elimination. Elacestrant undergoes only minor renal excretion, and dosage adjustment is not needed based on impaired renal function. Elacestrant was shown to penetrate the blood-brain barrier (BBB) in a dose-dependent manner. Elacestrant plasma concentrations were similar between healthy postmenopausal women and postmenopausal women with advanced or metastatic breast cancer.

1.3.2.2.2 Efficacy in Advanced/Metastatic Breast Cancer

The efficacy of elacestrant in women with ER+/HER2- metastatic breast cancer (mBC) has been studied in 2 Phase 1/1b clinical studies (Studies RAD1901-106 and RAD1901-005) and a randomised, active-controlled, ongoing Phase 3 study (Study RAD1901-308, EMERALD).

Study RAD1901-005

Study RAD1901-005 was a Phase 1 study to determine the safety, PK, and maximum tolerated dose (MTD) and/or the recommended phase II dose (RP2D) of elacestrant in postmenopausal women with ER+/HER2- mBC [26]. The study consisted of 4 parts: dose escalation (Part A), safety expansion (Part B), tablet introduction (Part C), and dose expansion (Part D). Subjects received a median of 3.0 lines of prior anticancer therapies (inclusive of all types of therapies, regardless of setting); approximately half of the subjects had prior treatment with a CDK4/6 inhibitor and/or SERD; 28.0% of subjects had prior treatment with an mTOR inhibitor. Regardless of which study part they were enrolled in, for all subjects treated at the RP2D of elacestrant 400 mg once daily (QD) with RECIST measurable disease at baseline and with at least 1 postbaseline measurement the confirmed overall response rate (ORR) was 19.4% (N = 6/31); clinical benefit rate (CBR) at 24 weeks was 42.6% (N = 20/47), median duration of response (DoR) was 24.86 weeks, and median progression free survival (PFS) was 4.5 months.

Study RAD1901-106

Study RAD1901-106 was a Phase 1b study in postmenopausal women with ER+/HER2- mBC to evaluate the effect of elacestrant on the availability of ER binding sites using FES-PET imaging [27]. Overall, 16 subjects were enrolled; 8 received 200 mg QD of elacestrant that was increased to 400 mg QD after 14 days (200/400 mg group), and 8 subjects received 400 mg QD of elacestrant. The primary study endpoint was the percentage difference in FES uptake in tumour lesions (up to a maximum of 20 lesions) after 14 days of treatment with elacestrant compared with baseline. At baseline, subjects had received a median of 3.0 lines of prior anticancer therapies (inclusive of all types of therapy, regardless of setting) and a median of 1.0 line of prior chemotherapy. Elacestrant greatly reduced FES uptake from baseline to Day 14. All but one subject in the 400 mg cohort (7/8; 87.5%) and 57% of subjects (4/7) in the 200/400 mg cohort had a greater than 75% reduction in FES uptake. The overall median reduction in FES uptake was 88.0%. This reduction in FES uptake was similar in subjects with and without mutations in ESR1. For subjects receiving the RP2D of elacestrant of 400 mg QD, with or without a 14-day lead-in at 200 mg QD and having RECIST measurable disease at baseline and with at least one postbaseline measurement, the ORR was 11.1% (N = 1/9); CBR at 24 weeks was 30.8% (N = 4/13), DoR was 22.0 weeks, and median PFS was 5.3 months. No significant correlation was found between FES uptake and best overall response.

Study RAD1901-308 (EMERALD)

EMERALD trial is an international, multisite, randomised, open-label, active-controlled, event-driven, Phase 3 clinical study comparing the efficacy and safety of elacestrant to the SOC options of either fulvestrant or an AI in postmenopausal women and men with ER+/HER2- mBC whose disease had relapsed or progressed on one or two prior lines of endocrine therapy for mBC [28]. The prior lines of therapy must have included CDK4/6-I therapy in combination with fulvestrant or an AI. Subjects must have received no more than 1 line of cytotoxic chemotherapy for mBC. The primary objective was to demonstrate that elacestrant, is superior in prolonging PFS based on a blinded Imaging Review Committee (IRC) assessment either in subjects with ESR1 mutations (ESR1-mut subjects) or in all subjects, which includes subjects without detectable ESR1 mutations (ESR1 mut-nd). The secondary objectives were to compare OS between treatment groups in ESR1-mut subjects and to compare OS between treatment groups in all subjects (ESR1-mut + ESR1 mut-nd). In total, 477 subjects were randomised to treatment (466 treated), with 228 randomised subjects (221 treated) with the ESR1 mutation. A total of 239 subjects (of whom 237 subjects were treated) were

randomised to the elacestrant group. The key subject demographics, baseline characteristics, and use of prior anticancer therapies were comparable between treatment groups.

In all subjects group, PFS was statistically significantly improved in subjects randomised to the elacestrant group compared to the SOC group (HR 0.70, $p=0.0018$, stratified log-rank test). The median PFS was 2.79 months in the elacestrant group and 1.91 months in the SOC group. In the ESR1 mutation subgroup, PFS was statistically significantly improved in subjects randomised to the elacestrant group compared to the SOC group (HR 0.55, $p = 0.0005$, stratified log-rank test). The median PFS was 3.78 months in the elacestrant group and 1.87 months in the SOC group.

The prespecified interim OS analysis is a key secondary endpoint. Since the 2 primary PFS endpoints met statistical significance, OS was evaluated using an alpha level of 0.0001. With this alpha level, elacestrant treatment did not significantly prolong OS in either group (All, $p = 0.0821$, stratified log-rank test; ESR1-mut, $p = 0.0325$, stratified log-rank test). However, HRs are in favour of OS improvement in subjects randomised to elacestrant compared to those randomised to SOC in either group (All, 0.751; ESR1-mut, 0.592). The final OS analysis is currently projected for late 2022 to early 2023 when 50% of subjects are expected to have experienced an OS event. An alpha level of 0.0499 will be used for the final analysis.

The ORR and best overall response were evaluated as secondary objectives of this study. In both groups ‘all subjects’ and ‘subjects with the ESR1 mutation’ randomised to elacestrant, subjects did not display a statistically significant difference in ORR compared to the subjects randomised to SOC treatment (All, $p = 0.959$; ESR1-mut, $p = 0.499$). In addition, for the best overall response in both populations, there were very few reports of confirmed partial response (PR) and confirmed complete response (CR).

1.3.2.2.3 Safety

Safety in health volunteers:

Overall, the most frequently reported treatment emergent adverse events (TEAEs) in healthy volunteers enrolled in the eight Phase 1 studies of elacestrant in postmenopausal women and men were nausea (12.4%) and constipation (10.6%). There were no deaths or serious adverse events (SAEs). One subject in Study RAD1901-110 discontinued study drug and the study due to a TEAE of affect lability, related to study drug.

Safety in Advanced Metastatic Breast Cancer:

Among the subjects enrolled in Phase 1 studies, 66 subjects received 400 mg QD, the RP2D, and were treated for a maximum of approximately 43 months with capsules (mean 6.9 months), and approximately 25 months with tablets (mean 7.0 months). [Table 1](#) provides the most commonly reported ($\geq 10\%$) adverse events (AEs) for the RAD1901-106 and RAD1901-005 breast cancer studies. For both capsule and tablet 400 mg formulations, TEAEs occurred most frequently in the Gastrointestinal disorders SOC. Most subjects experienced TEAEs and treatment-related TEAEs. The most common ($\geq 25\%$) TEAEs in subjects receiving tablets (the formulation to be used in all future studies) were nausea, blood triglycerides increased, and blood phosphorus decreased.

Table 1: Most Common (> 10% Overall) Treatment-emergent Adverse Events by System Organ Class Using Combined Data from RAD1901-005 and RAD1901-106

| System Organ Class | Elacestrant 400 mg capsules (N = 42)^b | Elacestrant 400 mg tablets (N=24) | Overall (N=66)^b |
|--|---|--|-----------------------------------|
| Preferred Term^a | n (%) | n (%) | n (%) |
| Any TEAEs | 42 (100) | 22 (91.7) | 64 (97.0) |
| Gastrointestinal disorders | 38 (90.5) | 19 (79.2) | 57 (86.4) |
| Nausea | 28 (66.7) | 8 (33.3) | 36 (54.5) |
| Dyspepsia | 18 (42.9) | 5 (20.8) | 23 (34.8) |
| Vomiting | 17 (40.5) | 4 (16.7) | 21 (31.8) |
| Diarrhoea | 11 (26.2) | 3 (12.5) | 14 (21.2) |
| Constipation | 6 (14.3) | 5 (20.8) | 11 (16.7) |
| Gastro-oesophageal reflux disease | 8 (19.0) | 2 (8.3) | 10 (15.2) |
| Dysphagia | 7 (16.7) | 1 (4.2) | 8 (12.1) |
| Abdominal pain upper | 5 (11.9) | 2 (8.3) | 7 (10.6) |
| Flatulence | 6 (14.3) | 1 (4.2) | 7 (10.6) |
| Investigations | 19 (45.2) | 15 (62.5) | 34 (51.5) |
| SGOT increased | 9 (21.4) | 3 (12.5) | 12 (18.2) |
| SGPT increased | 6 (14.3) | 3 (12.5) | 9 (13.6) |
| Blood triglycerides increased | 6 (14.3) | 6 (25.0) | 12 (18.2) |
| Blood glucose increased | 7 (16.7) | 4 (16.7) | 11 (16.7) |
| Blood phosphorus decreased | 4 (9.5) | 6 (25.0) | 10 (15.2) |
| Blood Pressure Increased | 6 (14.3) | 2 (8.3) | 8 (12.1) |
| Blood cholesterol increased | 4 (9.5) | 4 (16.7) | 8 (12.1) |
| Blood potassium decreased | 2 (4.8) | 5 (20.8) | 7 (10.6) |
| General disorders | 23 (54.8) | 10 (41.7) | 33 (50.0) |
| Fatigue | 17 (40.5) | 5 (20.8) | 22 (33.3) |
| Oedema peripheral | 6 (14.3) | 1 (4.2) | 7 (10.6) |
| Musculoskeletal and connective tissue disorders | 19 (45.2) | 12 (50.0) | 31 (47.0) |
| Arthralgia | 7 (16.7) | 4 (16.7) | 11 (16.7) |
| Back pain | 7 (16.7) | 4 (16.7) | 11 (16.7) |
| Nervous system disorders | 12 (28.6) | 13 (54.2) | 25 (37.9) |
| Dizziness | 6 (14.3) | 2 (8.3) | 8 (12.1) |
| Headache | 3 (7.1) | 5 (20.8) | 8 (12.1) |
| Respiratory, thoracic and mediastinal disorders | 15 (35.7) | 8 (33.3) | 23 (34.8) |
| Cough | 6 (14.3) | 4 (16.7) | 10 (15.2) |
| Dyspnoea | 5 (11.9) | 2 (8.3) | 7 (10.6) |
| Infections and infestations | 13 (31.0) | 9 (37.5) | 22 (33.3) |
| Urinary tract infection | 2 (4.8) | 5 (20.8) | 7 (10.6) |
| Metabolism and nutrition disorders | 10 (23.8) | 8 (33.3) | 18 (27.3) |
| Decreased appetite | 6 (14.3) | 3 (12.5) | 9 (13.6) |

| System Organ Class | Elacestrant 400 mg capsules (N = 42)^b | Elacestrant 400 mg tablets (N=24) | Overall (N=66)^b |
|---|---|--|-----------------------------------|
| Preferred Term^a | n (%) | n (%) | n (%) |
| Vascular disorders | 9 (21.4) | 5 (20.8) | 14 (21.2) |
| Hot flush | 7 (16.7) | 4 (16.7) | 11 (16.7) |
| Blood and lymphatic system disorders | 8 (19.0) | 3 (12.5) | 11 (16.7) |
| Anaemia | 7 (16.7) | 3 (12.5) | 10 (15.2) |

SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; CSR = clinical study report; ITT = intent-to-treat; TEAE = treatment-emergent adverse event
TEAEs are those events that started on or after the first dose of study medication.
Each subject was counted once for the same system organ class and the same preferred term.
^a Preferred terms are grouped together across different SOCs using synonym terms.
^b Eight subjects initiated treatment at 200 mg for 14 days.

Table 2 presents an overall summary of TEAEs; 1 subject (4.2%) who received the tablet formulation had a TEAE of aorto-oesophageal fistula that led to discontinuation of study drug (this event was not considered to be related to treatment). Ten subjects (41.7%) had Grade 3 or 4 TEAEs most commonly including SGOT increased, and blood phosphorus decreased.

Table 2: Overall Summary of Treatment-emergent Adverse Events Using Combined Data from RAD1901-005 and RAD1901-106

| Adverse Event Category | Elacestrant 400 mg capsules (N = 42)^{a, b} | Elacestrant 400 mg tablets (N=24) | Overall (N=66)^{a, b} |
|--|--|--|--------------------------------------|
| | n (%) | n (%) | n (%) |
| TEAEs | 42 (100) | 22 (91.7) | 64 (97.0) |
| Treatment-related TEAEs | 40 (95.2) | 19 (79.2) | 59 (89.4) |
| Serious TEAEs | 8 (19.0) | 8 (33.3) | 16 (24.2) |
| Treatment-related Serious TEAEs | 2 (4.8) | 1 (4.2) | 3 (4.5) |
| TEAEs Leading to Dose Interruption | 13 (31.0) | 8 (33.3) | 21 (31.8) |
| Treatment-related TEAEs Leading to Dose Interruption | 9 (21.4) | 1 (4.2) | 10 (15.2) |
| TEAEs at Grade 3 or 4 | 16 (38.1) | 10 (41.7) | 26 (39.4) |
| Treatment-related TEAEs at Grade 3 or 4 | 9 (21.4) | 1 (4.2) | 10 (15.2) |
| TEAEs Leading to Death | 1 (2.4) | 1 (4.2) | 2 (3.0) |
| Treatment-related TEAEs Leading to Death | 0 | 0 | 0 |
| TEAEs Leading to Study Medication Discontinuation | 8 (19.0) | 1 (4.2) | 9 (13.6) |
| Treatment-related TEAEs Leading to Study Medication Discontinuation | 7 (16.7) | 0 | 7 (10.6) |

| Adverse Event Category | Elacestrant 400 mg capsules (N = 42) ^{a, b} n (%) | Elacestrant 400 mg tablets (N=24) n (%) | Overall (N=66) ^{a, b} n (%) |
|---|--|---|--|
| CSR = clinical study report; ITT = intent-to-treat; TEAE = treatment-emergent adverse event TEAEs are those events that started on or after the first dose of study medication. ^a Eight subjects initiated treatment at 200 mg for 14 days. ^b Includes 5 subjects who received capsules and then switched to tablets. | | | |

Based on the Phase 1 studies, 3 non serious adverse drug reactions (ADRs) have been identified in elacestrant-treated subjects with mBC: nausea, vomiting and dyspepsia. All of these ADRs were Grade 1 or Grade 2 in severity with the exception of 1 subject receiving 400 mg elacestrant who experienced Grade 3 nausea and 1 subject who experienced Grade 3 vomiting. Most of these events resolved with continued treatment.

An additional 477 subjects with ER+/HER2- mBC have been enrolled in Study EMERALD (RAD1901-308) [28]. The elacestrant safety profile was comparable to that of SOC, with 218 subjects (92.0%) and 197 subjects (86.0%) reporting at least 1 AE, respectively. A larger percentage of elacestrant-treated subjects (150 subjects [63.3%]) reported a treatment-related TEAE compared with the subjects who received SOC treatment (100 subjects [43.7%]). Similar to the overall TEAEs, the difference was primarily driven by treatment-related TEAEs classified as gastrointestinal disorders or metabolism and nutrition disorders (nausea, vomiting, diarrhoea, dyspepsia, constipation, and decreased appetite). Fifteen subjects (6.3%) receiving 400 mg QD had TEAEs leading to discontinuation of study drug. Treatment-emergent adverse events leading to discontinuation of study drug were driven by the SOC's musculoskeletal and connective tissue disorders, gastrointestinal disorders, metabolism and nutrition disorders, and investigations. As with the overall pattern for these AEs, the SOC's were of similar prevalence among treatment groups as well as for the ESR1-mut subgroup versus all subjects.

1.4 Rationale and relevance of the study

Patients with overt metastatic disease recurrence are considered incurable, and the objective of treatment in this setting is to prolong survival and improve or maintain quality of life. Despite improvement in prognosis over the past decades, the majority of patients with metastatic breast cancer still die from their disease [29].

We hypothesize that an effective systemic treatment at the moment of ctDNA relapse, when disease burden is more limited, could potentially lead to improved cure rates. In the metastatic setting, the PADA-1 trial has already shown that for patients treated with a CDK4/6 inhibitor in combination with an AI, switching to fulvestrant upon detection of an ESR1 mutation in the ctDNA, is associated with an improvement in PFS versus continuing the same treatment (median 11.9 vs. 5.7 mo, HR 0.61, p=0.005) [30]. The c-TRAK TN trial in patients who had completed treatment for early-stage triple negative breast cancer could not prove the value of treatment with pembrolizumab upon ctDNA detection. This trial had several limitations however, with a less sensitive assay used and many patients having metastatic disease on staging scans at time of ctDNA detection, which led to only 5 patients in total being treated with pembrolizumab [31].

Ongoing trials are testing the efficacy of a CDK4/6 inhibitor plus fulvestrant at ctDNA relapse in patients with ER+HER2- early breast cancer (DARE (NCT04567420); LEADER (NCT03285412); TRAK-ER (NCT04985266)). Ours is however the first trial testing a SERD in monotherapy in this setting. This is of particular interest since in the future a substantial proportion of patients will already have been treated with a CDK4/6-inhibitor in the immediate adjuvant setting, given the recent approval by the FDA of abemaciclib for HR-positive HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score $\geq 20\%$, based on the results of the MonarchE trial [32].

In addition to evaluation of efficacy and safety, patient self-reported health-related quality of life (HRQoL) is an essential part to ensure an understanding of the patients' perspective on the drug's tolerability and benefit. The assessment of patient-reported outcomes (PROs) in clinical research provides important insights into how therapies affect the daily lives of patients. Patient reports regarding HRQoL have proven more comprehensive than provider-collected data in breast cancer patients [33]. Because elacestrant is a new drug about which little is known regarding toxicity and impact on quality of life, questionnaires to assess overall quality of life, treatment burden and tolerability symptoms in each of the two study arms will be used. The main side effect described in the literature is nausea, reported at higher rates than typical with endocrine therapy. Other common side effects included fatigue and hot flashes, similar to other endocrine therapies [26,28]. In this study, patient-reported disease related symptoms and HRQoL will be evaluated using validated questionnaires.

2 Assessment of risks and benefits

2.1 Risks

The value of treating patients at the moment of ctDNA relapse rather than waiting for clinically and/or radiologically detectable disease recurrence has currently not been proven. This exposes patients to the risk of being overtreated. In order to mitigate this risk, an interim analysis is planned when 50% of the required total number of events is reached, with an early stopping rule to avoid exposing patients in the experimental arm to an ineffective drug in case of evidence of futility. Patients randomised to the control arm will continue the same ET as before ctDNA detection and will not be exposed to undue risk, as they would have received the same treatment if they had been followed up according to the standard of care. Patients with HER2+ breast cancer are excluded from this trial, as these are expected to be more responsive to HER2-directed treatment rather than endocrine treatment.

The dosage, regimen and administration route proposed for elacestrant in our trial are similar to those used in the EMERALD trial, where 237 patients were exposed to the drug. Based on the safety data from this trial as well as from the previous phase I trials, elacestrant is mainly associated with low grade gastro-intestinal AEs, which are less frequent with the tablet formulation used in our trial in comparison to the capsules used in the phase 1 studies. The most frequent AE in the elacestrant arm of the EMERALD trial was nausea (35.0%, grade 3/4 2.5%). Other AEs were similar between elacestrant and SOC endocrine treatment. No ocular or cardiac toxicity was observed and there were no treatment related deaths.

In order to minimize safety risks, patients will be regularly monitored for the occurrence of toxicity during the randomised part of our trial (see Chapter 7 - Study calendar), and specific guidelines for the prompt management of nausea and vomiting are provided by the study protocol. The effects of elacestrant on the growing foetus are unknown. Since SERD agents in general are known to be teratogenic, pregnancy should be strictly avoided during treatment with elacestrant. In addition, in this trial, in premenopausal women on elacestrant, a menopausal status will be induced by ovarian function suppression.

2.2 Benefit

The adverse prognostic value of ctDNA detection has been demonstrated for multiple tumour types as well as in different disease settings (both early and advanced disease) [19,34–37]. In patients with early breast cancer, detection of ctDNA during follow-up is associated with an elevated risk of relapse (HR 25.2; 95% CI, 6.7-95.6; $P < .001$) and a median lead time of 11 months to clinical relapse [17,18]. Therefore, ctDNA may be a useful biomarker after potentially curative treatment to identify individuals at high risk of relapse. The FDA has issued guidance on the use of ctDNA for early-stage solid tumour drug development and has identified the detection of ctDNA relapse as a valuable tool for patient enrichment [37]. The early diagnosis of recurrence by ctDNA analysis in high-risk patients could also allow effective therapies to be introduced at time when disease burden is still minimal [3]. In the RAD1901-308 trial Elacestrant has already demonstrated a significant benefit over standard ET in pre-treated patients with advanced breast cancer (100% after prior CDK4/6-inhibitors, > 40% after 2 prior lines of therapy), with a 30% relative improvement in PFS, extending up to 45% in patients with an ESR1 mutation [28].

As patients enrolled in our study are in the curative setting, never having recurred or progressed on endocrine therapy, they are therefore expected to be more endocrine sensitive than those in the EMERALD trial. Additionally, patients in our control arm will continue the same ET as before ctDNA detection, as opposed to EMERALD, wherein the large majority of patients in the control arm were treated with a different ET than the one received in the previous line. Furthermore, in the EMERALD trial it was observed that even in the elacestrant arm the majority of patients had progressive disease at the first imaging assessment. We estimate a larger treatment effect compared to what was observed in the EMERALD trial and target a more aggressive HR of 0.58.

2.3 Risk benefit conclusion

Overall, we believe that the benefit /risk ratio justifies the inclusion of patients in the Treat ctDNA trial aiming to evaluate whether elacestrant can improve distant metastasis free survival (DMFS) compared to standard ET in patients with ctDNA relapse.

2.4 COVID-19 risk and benefit assessment

In the context of this trial, no study-related risk minimization measures are recommended based on the favourable risk/ benefit balance of study population and anti-cancer treatment. The investigators should always exercise their medical judgement to individualize clinical decisions and adhere to national and institutional guidelines for SARS-CoV-2 infection prevention and vaccine administration.

3 Objectives and endpoints of the Study

3.1 Study objectives

3.1.1 Primary objective

- To evaluate whether elacestrant can delay the occurrence of distant metastasis or death when compared to standard endocrine therapy in ER+/HER2- breast cancer patients with ctDNA-relapse.

3.1.2 Secondary objectives

- To evaluate invasive disease-free survival (iDFS), relapse-free survival (RFS) and overall survival (OS) between the 2 treatment arms
- To characterize the safety and the tolerability of the two treatment arms
- To establish the patient-reported tolerability profile in each treatment arm
- To compare the patient-reported benefit between the two treatment arms

3.1.3 Exploratory objectives

- To evaluate associations between ctDNA elimination at month 1 and DMFS according to treatment arm
- To evaluate associations between ctDNA elimination at month 4 and DMFS according to treatment arm
- To correlate ctDNA (as categorical variable) kinetics with DMFS, iDFS, RFS and OS according to treatment arm,
- To identify plasma circulating biomarkers associated with benefit from elacestrant.

3.2 Endpoints

For each endpoint, an exact definition and the detailed method of assessment is provided in chapter 8 on "Criteria of evaluation".

3.2.1 Primary endpoint

- Distant metastasis free survival (DMFS) defined as the time from randomisation until first distant metastatic recurrence or death from any cause, whichever occurs first

3.2.2 Secondary endpoints

- Invasive disease-free survival (iDFS) rate according to the STEEP criteria [38], including locoregional recurrence, distant metastasis, invasive contralateral breast cancer and invasive non-breast second cancers, deaths from any cause as events
- Relapse-free survival (RFS) rate according to the STEEP criteria [38], including locoregional recurrence, distant metastasis, deaths from any cause as events
- Overall survival rate
- Safety including but not limited to all adverse events, serious adverse events, laboratory abnormalities graded according to CTCAE version 5.0
- Patient reported outcomes: tolerability & benefit as measured by the QLQ-C30, QLQ-BR42 and EORTC IL46.

3.2.3 Exploratory endpoints

- ctDNA elimination rate at month 1, defined as the proportion of randomised patients who had a negative ctDNA test result at month 1
- ctDNA elimination rate at month 4, defined as the proportion of randomised patients who had a negative ctDNA test result at month 4
- ctDNA kinetics: ctDNA as categorical (negative versus positive) variable at different time points during the 3-year period post randomisation,
- To evaluate associations between plasma biomarkers with the treatment efficacy.

4 Study Population

4.1 Accrual

The sample size requirement was primarily defined based on statistical considerations for the analysis of the primary endpoint (see Section 10.2.1). Approximately 1960 patients will be successfully screened (fulfilling eligibility criteria and having a successful ctDNA report test from the central laboratory) to randomise 220 patients to either elacestrant or continuation of the same endocrine therapy.

Under the assumptions of an accrual rate of 40 patients successfully screened/month in 120 sites and a building up accrual rate during the first year to account for the progressive activation of sites, it is expected that the accrual duration for the screening period will be approximately 4.7 years and will be approximately 5.7 years for the randomised part to allow a minimum of 1-year screening period for all patients, corresponding to a minimum of 3 blood draws during the screening period.

4.2 Patient selection criteria

Each patient must meet all inclusion criteria and none of the exclusion criteria to be registered in the ctDNA screening phase and enrolled in the randomised trial.

Patients undergoing ctDNA screening with other ctDNA approved assay for diagnostic purposes will not participate in the serial ctDNA screening phase. Such patients found to be ctDNA positive and who consent to participate in this trial, will enter directly in the randomised trial, provided they meet all eligibility criteria (both for the ctDNA screening phase, with the exception of the tissue sample requirements, and for the randomised trial).

4.2.1 ctDNA screening phase

4.2.1.1 Inclusion criteria

- Female (both pre- and postmenopausal) or male patients with histologically confirmed ER positive (regardless of PR), HER2 negative breast cancer, according to local pathologist:
 - ER-positive defined as $\geq 10\%$ of cells staining positive for ER or Allred proportion score ≥ 3
 - HER2-negative defined as a score of 0, 1+ by immunohistochemistry (IHC) or a negative in situ hybridization (ISH) based on single-probe average HER2 copy number, as per American Society of Clinical Oncology guidelines
- Intermediate to high risk of recurrence after definitive treatment for early breast cancer, defined as described below.

PATIENTS TREATED WITH PRIMARY SURGERY:

- Any patient with ≥ 4 positive axillary lymph nodes (stage pN2-N3)

- 1-3 positive axillary lymph nodes (stage pN1) and either:
 - Tumour size ≥ 5 cm or/and
 - Histologic grade 3 either on the biopsy or on the surgical specimen or/and
 - Ki67 $\geq 20\%$ either on the biopsy or on the surgical specimen and/or
 - high genomic risk defined as Oncotype Dx Recurrence Score ≥ 26 , Mammaprint high risk, Prosigna score >40 or EPclin risk score ≥ 4.0
- Negative axillary lymph nodes (stage pN0) and Tumour size ≥ 5 cm and either:
 - Histologic grade 3 either on the biopsy or on the surgical specimen or/and
 - Ki67 $\geq 20\%$ either on the biopsy or on the surgical specimen and/or
 - High genomic risk defined as Oncotype Dx Recurrence Score ≥ 26 , Mammaprint high risk, Prosigna score >60 or EPclin risk score ≥ 4.0

PATIENTS TREATED WITH NEOADJUVANT SYSTEMIC TREATMENT FOLLOWED BY SURGERY:

- Patient may have received neoadjuvant endocrine therapy or neoadjuvant chemotherapy provided that:
 - The initial tumour and/or the tumour after surgery meet the criteria above defined for patients treated with primary surgery or the initial tumour was staged as cT4 any cN and
 - There is no pathological complete response, defined as no invasive disease in the breast and axilla (ypT0/is ypN0).
- Age ≥ 18 years.
- Patients must have received at least 1 year and up to 7.5 years of ET
- Patients must have planned to continue adjuvant ET during ctDNA screening phase
- Previous neoadjuvant or adjuvant CDK4/6 inhibitor or PARP-inhibitor treatment is allowed provided it is completed.
- Invasive multicentric / multifocal disease is allowed provided that all the tested foci are ER+ HER2-. A sample from the highest-risk one, according to the investigator decision based on the size and grade, should be sent to Natera to build the patient ctDNA.
- Available tumour sample from resected or biopsied tissue, with a tumour content of $\geq 20\%$ (30% preferred) either before or after macro dissection (if performed) and a cell viability of a minimum 100 cells.
- If Core Needle Biopsies (CNB): recommended minimum of four (4) cores per block
- Fine Needle Aspirates (FNA) are *not* accepted
- The following sample types are acceptable:
 - 6-10 unstained slides (charged and unbaked) of 10 μm each (or 12-19 unstained slides at 5 μm each), PLUS one contiguous H&E slide. Minimum total tissue thickness must be 60 μm
 - OR**
 - FFPE tissue block with 25mm² minimum surface area.

Note: *Sequencing of tumour tissue is necessary to build a patient specific ctDNA assay. Patients from whom tumour tissue is not available cannot be registered in the study, unless they have already tested ctDNA positive with another assay for diagnostic purposes prior to entry in TREAT ctDNA.*
- Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations

4.2.1.2 Exclusion criteria

- Suspected recurrent disease or known conflicts with the inclusion and exclusion criteria for the randomised trial (Section 4.2.2)
- Prior treatment with any SERD or investigational ER antagonist
- Previous history of invasive breast cancer
- Previous history of any other malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
- Previous history of bone marrow and/or organ transplant
- Bilateral breast cancer
- Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients
- Participation in another clinical study, with the exception of the SURVIVE study and observational (non-interventional) clinical studies. Note: patients participating in interventional studies may participate once they enter the follow-up period of the study or in case of non-systemic drug intervention.
- Blood transfusion within 3 months prior to registration or during the screening period of the study

4.2.2 Randomised trial

4.2.2.1 Inclusion criteria

- ctDNA positive according to the central assessment with Signatera assay (main study ctDNA test) or other ctDNA assay approved for diagnostic purposes
- Patients must meet the eligibility criteria for the screening phase, with the exception of the tissue sample requirements
- Patients must receive adjuvant ET at the time of the ctDNA positive test
- Absence of locoregional and/or metastatic disease and/or new malignancy, as investigated by:
 - Mammogram (unilateral in case of mastectomy; not required in patients having undergone bilateral mastectomy)
Note: if local investigator plans to use breast MRI instead of mammograms during the study, MRI will have to be performed at baseline.
 - CT thorax and abdomen/pelvis with IV contrast. In case of any contra-indications (medical or regulatory): CT thorax without contrast + MRI abdomen/pelvis.
 - Technetium-99m bone scintigraphy
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 ([Appendix P](#))
- Adequate organ function as defined below:
 - Haematologic function:
 - Absolute neutrophil count $\geq 1.0 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$
 - Haemoglobin ≥ 9.0 g/dL
 - Renal function:
 - Glomerular filtration rate estimated via the MDRD equation of ≥ 30 mL/min/1.73m²
 - Hepatic function:
 - Alanine aminotransferase (SGPT) $\leq 3x$ upper limit of normal (ULN)
 - Aspartate aminotransferase (SGOT) $\leq 3x$ ULN

- Total bilirubin $\leq 1.5x$ ULN or total bilirubin $\leq 3x$ ULN with direct bilirubin \leq ULN of the laboratory in subjects with documented Gilbert's Syndrome
- Women of childbearing potential (WOCBP) must have a negative highly sensitive serum or urine pregnancy test within 7 days prior to randomisation.
Note: women of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e., females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrhoeic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antioestrogens, low body weight, ovarian suppression, or other reasons.
- WOCBP must agree to use highly effective birth control measures during the protocol treatment period and for at least:
 - 4 months after the last dose of elacestrant
 - 1 month after the last dose of an AI
 - 9 months after the last dose of tamoxifen
 A highly effective method of birth control is defined as a method which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods are listed in [Appendix T](#).
- Men must agree to use a condom during treatment and for at least:
 - 4 months after the last dose of elacestrant
 - 1 month after the last dose of an AI
 - 5.5 months after the last dose of tamoxifen
 when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. They should also refrain from donating sperm during the same period. Female partners of male patients must also use a highly effective form of contraception (see [Appendix T](#)) if they are of childbearing potential.
- Female subjects who are breast feeding should discontinue nursing during protocol treatment and until:
 - 1 month after the last dose of elacestrant or of an AI
 - 4 months after the last dose of tamoxifen

4.2.2.2 Exclusion criteria

- Any unresolved toxic effect of prior therapies or surgical procedures of Grade ≥ 2 according to Common Terminology Criteria of Adverse Events (CTCAE v5.0), with the exception of alopecia, peripheral neuropathy and other toxicities not considered a safety risk for the participant at investigator's discretion
- Major surgery < 28 days before randomisation
- Unable or unwilling to avoid over-the-counter medications, dietary/herbal supplements (e.g., St. John's wort), and/or foods (e.g., grapefruit, pomelos, star fruit, Seville oranges and their juices) that are moderate/strong inhibitors or inducers of CYP3A4 activity (see [Appendix W](#)). Participation will be allowed if the medication, supplements, and/or foods are discontinued for at least 14 days prior to randomisation
- Vaccination, including, but not limited to vaccination against COVID-19 within 7 days prior to randomisation
- Any of the following cardiovascular disorders within 3 months before enrolment:
 - myocardial infarction

- stroke
- severe/unstable angina
- symptomatic cardiac arrhythmia, i.e., atrial tachycardia with a heart rate > 110/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third-degree AV-block)
- prolonged QTcF \geq Grade 3 (i.e., > 500 msec)
- heart failure \geq Class III as defined by the New York Heart Association (NYHA) guidelines
- Child-Pugh Score greater than Class A ([Appendix S](#))
- Uncontrolled significant active infections (\geq grade 3 according to CTCAE version 5), including active hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency Virus (HIV)
 - Active HBV is defined by a positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible
 - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
 - Patients known to be positive for HIV are eligible if they demonstrate an undetectable viral load during screening (defined as <50 copies/mL)
- Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism. However, subjects with the following conditions will be allowed to participate:
 - Adequately treated catheter-related venous thrombosis occurring > 28 days prior to the first dose of study drug
 - Treatment with an anticoagulant, e.g., warfarin or heparin, or direct oral anticoagulants (DOAC; e.g., dabigatran, rivaroxaban) for a thrombotic event occurring > 6 months before enrolment, or for an otherwise stable and allowed medical condition, provided dose and coagulation parameters (as defined by local standard of care) are stable for at least 28 days prior to the first dose of study drug
- Uncontrolled intercurrent illness, including psychiatric conditions, that would, in the judgment of the investigator, limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications such as: uncontrolled nausea or vomiting (i.e., CTCAE \geq Grade 3 despite antiemetic therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass
- Evidence of ongoing alcohol or drug abuse.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol, understanding and completion of questionnaires and follow-up schedule; those conditions should be assessed and discussed with the patient before the enrolment in the trial.

5 Trial design

This is an international, multi-centre, randomised, open label, superiority phase III trial of elacestrant vs standard adjuvant endocrine therapy in patients with ER+/HER2- breast cancer and ctDNA-relapse.

5.1 ctDNA screening phase

After verification of the eligibility criteria for screening, patients will enter the ctDNA screening phase of the study in which plasma samples will be collected and tested with the Signatera ctDNA assay to detect the presence of ctDNA. The test will be performed every 6 months from study entry until the end of accrual (approximately 5.7 years). During the screening phase, patients will be treated with standard adjuvant endocrine therapy [either tamoxifen or an aromatase inhibitor (exemestane, anastrozole or letrozole)] and followed-up as per standard of care. The outcome of the serial ctDNA assessments performed during the screening phase will be disclosed to investigators by Natera.

Patients who are found to be ctDNA-negative at the end of the screening period will not be followed further in this study.

Patients who are found to be ctDNA-positive at one of the screening time points or outside of the TREAT ctDNA study, by a test approved for diagnosis, will undergo an imaging work-up to assess the presence of distant metastases, locoregional recurrence and/or new malignancy. The imaging work-up should be planned considering that patients must be randomised within 4 weeks from the date of ctDNA detection (i.e., the date on which the results of the test are received).

Patients for whom the imaging work-up confirms no evidence of distant metastases, locoregional recurrence and/or new malignancy will be eligible for the randomised phase of the study provided they meet all other eligibility criteria. Patients for whom the imaging work-up shows evidence of distant metastases, locoregional recurrence and/or new malignancy will not be followed further in this study.

5.2 Randomised trial

Patients will be randomised 1:1 within 4 weeks from the date of ctDNA detection (i.e., the date on which the results of the test are received) between standard endocrine treatment (the same they were receiving when tested ctDNA positive) versus elacestrant ([Figure 3](#)).

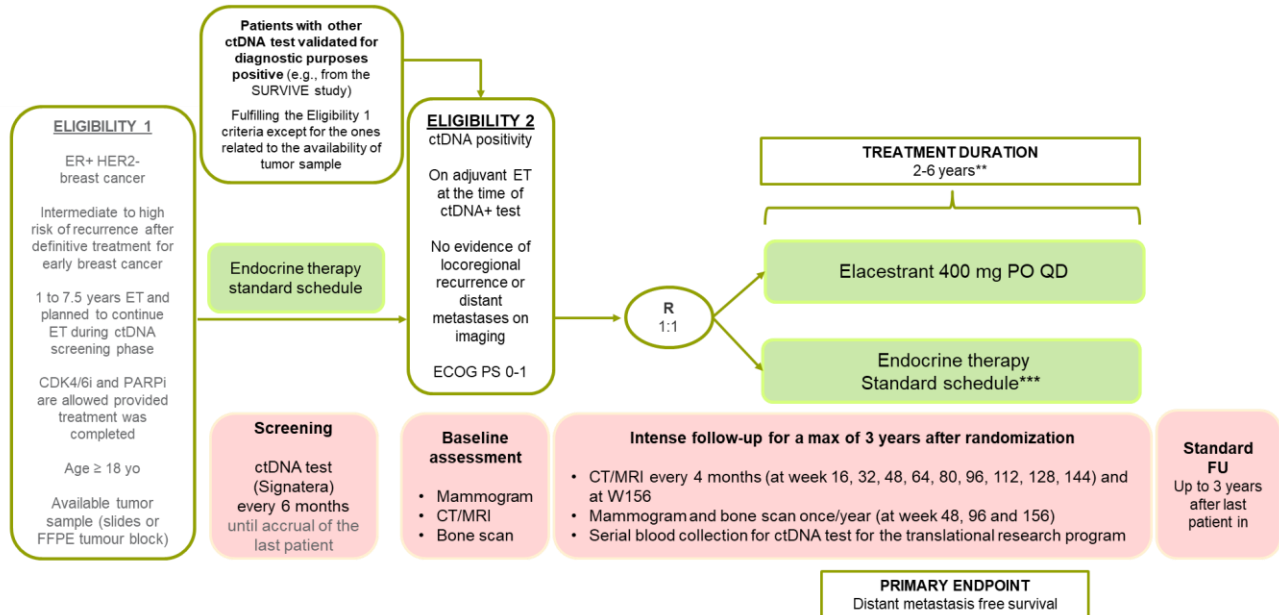
The protocol treatment period will last 2 to 6 years as described below ([Figure 4](#)):

- For patients on ET between 1 to 5 years (12 to 60 months) at the time of randomisation: 2 to 6 years (allowing for 7 years of ET at the end of the study treatment)
- For patients on ET between 5 to 7.5 years (60 to 90 months) at the time of randomisation: 2 years

After completion of the study treatment period, treatment will be left at the discretion of the treating physician. For patients that discontinued study treatment for any other reason than relapse, subsequent treatment should also be as per standard of care.

Patients in both arms will undergo intensive follow-up with yearly mammograms and bone scans and 16-weekly CT scans thorax and abdomen/pelvis for a maximum of 3 years after randomisation. During follow-up, treatment will continue as per standard of care. All randomised patients will be followed-up until 3 years after randomisation of the last patient. Of note, for patients still on treatment at 3 years after randomisation of the last patient, data will still be collected until their end of treatment visit as per the schedule of assessment described in [Section 7.4.5](#).

Blood will be collected for ctDNA test for the translational research program (see chapter 9) at: either within 3 days before start of treatment (elacestrant arm) or within 3 days after randomisation (standard endocrine treatment arm), week 4, and week 16 after randomisation and every 16 weeks thereafter for a maximum of 3 years (36 months or 156 weeks).



* Stratification factors: duration of ET at the time of ctDNA detection (≤5 vs >5 years); stage (II vs III); prior CDK4/6 inhibitors; prior (neo)adjuvant chemotherapy; country; ctDNA test (Signatera vs others)
 ** Depending on the duration of ET at the time of randomization: if 1-5 years, duration of 2-6 years to allow for 7 years of ET at the end of the study drug; if 5-7.5 years, duration of 2 years.
 *** Same endocrine therapy as received during the screening phase

Figure 3: Study scheme

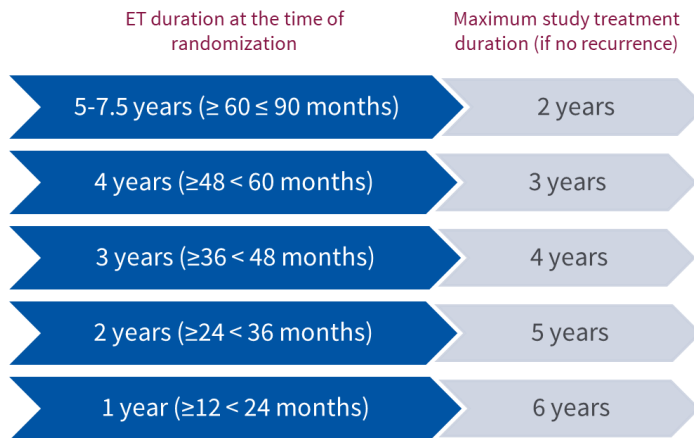


Figure 4: Maximum study treatment duration is dependent on the time patients are on ET (endocrine therapy) at the time of randomisation.

5.3 End of study

End of study occurs when all the following criteria have been satisfied:

- All patients have completed their end of study visit (see Section 7.4.9). If a patient discontinues the follow-up early due to withdrawal of consent, loss to follow-up, or death, the end of study participation is defined as the time point when one of these events occurred, whichever occurs first.
- The trial is mature for all analyses defined in the protocol and the database has been cleaned and frozen for these analyses (see Section 10.3.1).

Conditions of early study termination are described in [Appendix C](#).

6 Protocol treatment and Concomitant therapy

6.1 Drug information

6.1.1 General information

Table 3: Investigational medicinal products (IMPs) and auxiliary medical products (AMP) used in the study

| Drug name | IMP or AMP | Authorization status | Used in accordance with Marketing Authorisation (MA) |
|--|------------|----------------------|--|
| Elacestrant | IMP | Authorized | Not used in accordance with the MA indication but used in accordance with the MA posology. |
| Tamoxifen | IMP* | Authorized | Yes |
| Exemestane | IMP* | Authorized | Yes |
| Letrozole | IMP* | Authorized | Yes |
| Anastrozole | IMP* | Authorized | Yes |
| Goserelin, leuprorelin or triptorelin as per site/country availability | AMP | Authorized | Yes |

*The drugs used in the control arm will only be considered as IMPs during the treatment period of 24 months defined by the protocol.

6.1.1.1 Elacestrant

Elacestrant is a tetrahydronaphthalene compound that acts as a selective oestrogen receptor degrader (SERD) and is being developed for the treatment of ER+ advanced/metastatic breast cancer in men and women. Elacestrant is formulated as film-coated tablets containing elacestrant dihydrochloride as active pharmaceutical ingredient. 100 mg dosage is a light blue-coloured and round-shaped tablet that contains elacestrant dihydrochloride equivalent to elacestrant 86.3 mg, while 400 mg dosage is a light blue-coloured and oval-shaped tablet that contains elacestrant dihydrochloride equivalent to elacestrant 345 mg. The formulation is intended for once-daily (QD) oral dosing as a tablet. The dosage recommendation is 400 mg QD.

6.1.1.2 Tamoxifen

Tamoxifen is a non-steroidal, triphenylethylene-based drug indicated in the treatment of breast cancer. Tamoxifen displays a complex spectrum of oestrogen antagonist and oestrogen agonist-like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antioestrogen, preventing oestrogen binding to the oestrogen receptor.

Tamoxifen is marketed in the form of 20 mg film-coated tablets. The dosage range is 20 to 40 mg daily, administered orally either in divided doses twice daily or as a single dose once daily for at least 5 years.

6.1.1.3 Exemestane

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. Exemestane is used as hormonal treatment in post-menopausal women with breast cancer. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. Exemestane is marketed in the form of 25 mg coated tablets. The recommended dose of exemestane is 25 mg taken orally once daily, preferably after a meal.

6.1.1.4 Letrozole

Letrozole is a non-steroidal aromatase inhibitor that inhibits the aromatase enzyme by competitively binding to the haem of the aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present. Letrozole is indicated in the adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer, in the extended adjuvant treatment of hormone-dependent-invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years, in the first-line treatment in postmenopausal women with hormone-dependent advanced breast cancer, in advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens and in the neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated. Letrozole is marketed in the form of 2.5 mg film-coated tablets. The recommended dose is 2.5 mg once daily.

6.1.1.5 Anastrozole

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. Anastrozole is indicated for the treatment of hormone receptor-positive advanced breast cancer in postmenopausal women, for the adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women and for the adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen. Anastrozole is marketed in the form of 1 mg film-coated tablets. The recommended dose is one 1 mg tablet once a day.

6.1.1.6 Gonadotrophin releasing hormone analogues

Gonadotrophin releasing hormone (GnRH) analogues are synthetic analogues of naturally occurring luteinising hormone releasing hormone (LHRH). On chronic administration they result in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males and serum oestradiol concentrations in females. GnRH analogues are indicated in the management of breast

cancer in pre and perimenopausal women suitable for hormonal manipulation to suppress ovarian function and reduce the availability of natural hormone oestrogen to cancer cells.

Goserelin is a GnRH analogue marketed in the form of a 3.6 mg implant in a prefilled syringe. One 3.6 mg depot of goserelin is injected subcutaneously into the anterior abdominal wall every 28 days.

6.1.2 Stock management process

Elacestrant (400 and 100 mg) will be provided free of charge by Menarini Research & Business Service GmbH (A.MRBS). The company is responsible for distribution to the sites and each site will be provided with an initial supply of Elacestrant (400 mg and 100 mg) after confirmation of a first ctDNA-positive patient. Elacestrant stock will be managed via an Interactive Response Technology system, called iMedidata Rave RTSM (Randomisation and Trial Supply Management), administered by EORTC.

Endocrine therapy [tamoxifen or aromatase inhibitors (exemestane, anastrozole or letrozole)] and ovarian function suppression therapy (goserelin, leuprorelin or triptorelin) have to be taken from your local hospital pharmacy stock (taken from shelf) and/or from patient's local pharmacy according to site's standard of care.

Please refer to the study drug management guidelines (separate document) for further information on the drug supply in this study and on stock management.

6.1.3 Packaging, dispensing and storage

Elacestrant is packed in high-density polyethylene bottles (primary packaging). The bottles will be labelled as subject kits according to the study design in compliance with current valid international and corresponding national requirements.

All bottles are induction sealed and fitted with child-resistant caps. Elacestrant must be stored at the recommended storage conditions: controlled room temperature 15°C to 25°C.

In accordance with recital 57 and article 67 paragraph 2 of the Clinical Trials Regulation (EU) No 536/2014, all other study drugs (endocrine therapy [tamoxifen or aromatase inhibitors (exemestane, anastrozole or letrozole)] and ovarian function suppression therapy (goserelin, leuprorelin or triptorelin) will not be labelled. These drugs are taken from the local hospital pharmacy stock (taken from shelf) and/or from patient's local pharmacy and are considered as standard of care. Therefore, no additional particulars relating to the identification of the clinical trial and of the contact person are needed on the packaging of the study drugs to ensure subject safety and the reliability and robustness of data generated in clinical trials.

Nevertheless, all drug products must be stored, prepared, and administered according to the manufacturer's instructions and institutional policies for preparation of hazardous medications.

6.1.4 Drug reconciliation and destruction procedures

Accountability of the IMPs is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

The accountability of the study drug elacestrant should be maintained by each site. Accountability records should include:

- amount received and placed in storage area
- amount currently in stock (stock balance)
- batch numbers and expiry dates
- amount dispensed to and returned by each subject, including unique subject identifier (seqID)
- amount destroyed at study site, if applicable

EORTC study-specific accountability and destruction log can be used or alternatively, the site can use its own template, as long as the same information as the EORTC template are captured.

The study drug accountability and destruction logs will be verified during monitoring visits according to the monitoring plan or assessed remotely.

The unused IMP Elacestrant 100 mg and Elacestrant 400 mg, including expired medication, may be destroyed locally upon Sponsor's authorisation and in compliance with national regulations. A copy of the destruction log of Elacestrant must be sent to EORTC study team.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients enrolled in this study.

6.2 Initial dose and schedule

Patients who are found to be ctDNA-positive will be centrally randomised 1:1 between:

- Experimental arm: Elacestrant 400 mg QD
- Control arm: Standard Endocrine Treatment

6.2.1 Experimental arm: Elacestrant

Patients randomised to the experimental arm will take Elacestrant 400 mg QD orally on a continuous dosing schedule. They must start within 7 to 10 days after randomisation, allowing a wash-out period of at least 1 week from the previous endocrine treatment.

Elacestrant will be administered as follows:

- Patients should be instructed to take their study medication at approximately the same time each day, preferably in the morning. Treatment should be administered every day without interruption.
- Patients should be instructed to swallow the tablet(s) whole (unchewed), and 1 tablet at a time. Tablets should not be ingested if they are broken or cracked.
- In order to prevent or alleviate nausea, patients are recommended to have a light meal (e.g., juice, toast and jam or yogurt) at approximately 30 minutes prior to taking their study medication. Furthermore, they are recommended to take their study medication with a glass of water (at least 250 mL or 8 oz.), whereafter they should remain in an upright position for at least 2 hours after taking their dose(s). With the exception of water, subjects should fast for 1 hour after taking their dose(s).
- If vomiting occurs following a dose, the patient does not need to take a replacement dose but should attempt to take their next scheduled dose. Patients should be instructed that if they miss a dose, they should take it as soon as they remember.

- If the patient forgets to take a dose at the scheduled time, and more than 12 hours have passed after the scheduled time, that missed dose should be omitted, and the next dose should be taken at the usual time.

6.2.2 Control arm: Standard Endocrine Treatment

Patients randomised to the control arm will continue the same endocrine treatment they were receiving at the time of ctDNA detection without interruption, which can be either:

- Tamoxifen 20 mg QD orally on a continuous dosing schedule
- Letrozole 2.5 mg QD orally on a continuous dosing schedule
- Anastrozole 1 mg QD orally on a continuous dosing schedule
- Exemestane 25 mg QD orally on a continuous dosing schedule

Patients should be instructed that if they miss a dose, they should take it as soon as they remember. If the patient forgets to take a dose at the scheduled time, and more than 12 hours have passed after the scheduled time, that missed dose should be omitted, and the next dose should be taken at the usual time.

During the treatment period, the investigator may replace an aromatase inhibitor with another one, or with tamoxifen, and vice versa in the control arm, if needed for reasons of tolerability.

6.2.3 GnRH agonists (for pre/perimenopausal women and men)

6.2.3.1 Pre-menopausal and peri-menopausal women

Pre-menopausal and perimenopausal women, defined as women not meeting the criteria for being postmenopausal (see below), and men in the elacestrant arm will receive goserelin, leuprorelin or triptorelin as per site/country availability for the duration of treatment.

Pre-menopausal and perimenopausal women that were receiving tamoxifen without a GnRH analogue at the time of ctDNA detection should undergo ovarian function testing (follicle stimulating hormone (FSH), oestradiol (E2)) to confirm menopausal status.

Postmenopausal status is defined according to the following criteria:

- Documented bilateral surgical oophorectomy
- Age ≥ 60 years with amenorrhea ≥ 1 year since last menses
- Age < 60 years with amenorrhea ≥ 1 year since last menses with no alternative pathological or physiological cause (including ongoing or recent chemotherapy, treatment with tamoxifen or toremifene, or a GnRH agonist), and serum oestradiol and follicle stimulating hormone (FSH) levels within the laboratory reference range for post-menopausal women
- Age < 60 years with tamoxifen or toremifene therapy within the last 12 months, with documentation of 12 months of amenorrhea prior to tamoxifen or toremifene therapy and serum oestradiol and FSH levels within the laboratory reference range for post-menopausal women

6.2.3.2 Treatment with GnRH agonists

Pre-menopausal and perimenopausal women and men in the **experimental arm** will receive goserelin, leuprorelin or triptorelin as per site/ country availability for the duration of treatment. Pre-menopausal and perimenopausal women and men who were *not receiving a GnRH analogue at the*

time of ctDNA detection should be administered the GnRH analogue at the time of randomisation and continue their previous E.T during the first 21 days, allowing for one week (i.e., 7 days) wash-out before -exceptionally- starting Elacestrant on Day 29 counting from the date of randomisation.

If pre-menopausal and perimenopausal women or men **in the control arm** were receiving goserelin, leuprolerin or triptorelin at the time of ctDNA detection, this should be continued after randomisation. If these patients were not receiving a GnRH analogue at the time of ctDNA detection, they are allowed, but not obliged, to receive this after randomisation upon discretion of the investigator.

6.2.4 Treatment duration

The protocol treatment period will last 2 to 6 years as described below, or until the occurrence of a withdrawal criterion (as specified in section 6.4.2).

- For patients on ET between 1 to 5 years (12 to 60 months) at the time of randomisation: 2 to 6 years (allowing for 7 years of ET at the end of the study treatment)
- For patients on ET between 5 to 7.5 years (60 to 90 months) at the time of randomisation: 2 years

After completion of the treatment phase of the randomised trial, patients will enter the follow-up phase. Of note, for patients still on treatment at 3 years after randomisation of the last patient, data will still be collected until their end of treatment visit as per the schedule of assessment described in Section 7.4.5. In case patients in the control arm continue their standard endocrine treatment beyond the defined treatment period, this will not be considered as study treatment. During the follow-up phase, patients can receive a treatment of investigator's choice but there will be no option to continue elacestrant within the trial.

6.2.5 Study Intervention Compliance

Compliance with study intervention will be assessed by reviewing patient diary entries (i.e., dose, date, missed doses and the reason for missed dose), accounting of returned study intervention and documenting in the source documents and eCRF. Non-compliance from the prescribed dosage regimen should be recorded in the Source Documents and eCRF.

As patients self-administer study drugs at home, compliance with study intervention will be assessed at each visit at the study centre. Each patient will be reminded to bring back to the site at each study visit study intervention from the previous visit (used, partially used and unused boxes/blisters). I.e., a record of the number of tablets dispensed to and taken by each patient must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.2.6 Dose and schedule modifications

6.2.6.1 Elacestrant

Patients will be assessed for the development of any toxicity at each visit during the treatment period. Toxicity will be assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) v5.0. Patients should be monitored closely and receive supportive

care and agents to treat AEs (pain medications, antiemetics, antidiarrheals, etc.) as per local institutional guidance.

The most common adverse events related to elacestrant are nausea, dyspepsia, fatigue, vomiting, diarrhoea and SGOT increased.

Dose reductions of elacestrant due to AEs are allowed in this study; dose levels are provided in [Table 4](#). A dose reduction below 200 mg elacestrant QD is not allowed and with the exception of reduction to 100 mg due to the concomitant use of strong or moderated CYP3A4 inhibitor, as per section [6.3.4.1](#).

Dose interruptions of elacestrant of ≤ 14 consecutive days are permitted at any point during treatment. A dose interruption of >14 consecutive days requires discussion with the Sponsor (i.e., EORTC) prior to continuation on study.

No dose escalations above the starting dose of 400 mg QD are permitted.

Table 4: Dose reductions

| Dose Level | Elacestrant Dose |
|---|---|
| Starting dose | 400 mg QD |
| -1 (1 st dose reduction) | 300 mg QD (25% dose reduction) ^a |
| -2 (2 nd dose reduction) | 200 mg QD (50% dose reduction) ^b |
| QD = once daily a. Three 100 mg tablets b. Two 100 mg tablets | |

General guidelines regarding management and dose reduction for AEs considered by the investigator to be related to elacestrant treatment are provided in [Table 5](#). Dose reduction decisions should be based on the judgment of the investigator. Once a dose has been reduced, it may not be re-escalated to the original dose.

Table 5: Safety management guidelines

| | Action and Dose Modification |
|----------------|--|
| Grade 1 | Continue elacestrant treatment at current dose level |
| Grade 2 | <ul style="list-style-type: none"> Consider interruption of elacestrant treatment if clinically indicated When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment at current dose level |
| Grade 3 | <ul style="list-style-type: none"> Interrupt elacestrant treatment if clinically indicated When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment reduced by 1 dose level (refer to Table 4) If the Grade 3 toxicity recurs, interrupt elacestrant treatment When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment reduced by another dose level (refer to Table 4) |

| | Action and Dose Modification |
|----------------|--|
| Grade 4 | <ul style="list-style-type: none"> • Interrupt elacestrant treatment • When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment reduced by 1 dose level (refer to Table 4) • If the Grade 4 toxicity recurs either: <ul style="list-style-type: none"> • Permanently discontinue elacestrant treatment or • If the patient is clinically benefitting, elacestrant treatment may be reinitiated only if reduced by another dose level and with agreement of the Sponsor (i.e., EORTC) |

6.2.6.2 Standard endocrine treatment

The toxicities related to standard ET are well known, and all patients randomised to the control arm will continue the same ET they had been prescribed as per standard of care. Detailed information on undesirable effects can be found in the SmPCs of the drugs.

Dose reductions for patients in the control arm are not allowed.

Treatment interruptions and/or withdrawals due to AEs should be based on the Investigator's clinical judgment. Standard ET dose interruptions of ≤ 14 consecutive days are permitted at any point during treatment.

Dose interruptions of > 14 consecutive days requires discussion with the Sponsor (i.e., EORTC) prior to continuation on study. Note: During standard ET treatment the Investigator will follow any warnings or precautions for use as detailed in each SmPC.

6.3 Concomitant medications

Any concomitant medication(s) or vaccine, including over the counter or prescription medicines, vitamins, and/or herbal supplements, taken during the randomised phase of the study will be recorded in the CRF from 21 days prior to enrolment until the end of treatment visit.

6.3.1 Supportive care in case of toxicity

Supportive care is left at investigator's discretion.

Nausea and vomiting are the most frequent AEs observed with elacestrant treatment, occurring in 35% (2.5% \geq Grade 3) of patients treated with elacestrant in the EMERALD trial. Patients should be counselled on the occurrence of these symptoms, which can be reduced by correct administration of elacestrant after a light meal (Section [6.2.1](#)). Treatment with anti-emetic drugs of investigator's choice is recommended when needed. If symptoms persist, interruption of elacestrant treatment, or dose reduction in case of \geq Grade 3 toxicity, is allowed (Section [6.2.6.1](#)).

6.3.2 Prohibited medications

All patients are prohibited from taking any of the following medications:

- Hormonal medications or medications known to affect serum luteinizing hormone (LH), FSH (except spironolactone which is allowed if medically indicated), or oestradiol levels. This includes, but is not limited to medications, herbal remedies, and/or supplements for the treatment of vasomotor hot flush symptoms administered via any route, including topical or intravaginal administration.

- Any anti-cancer treatment other than those administered in this study, including cytotoxic chemotherapy, radiotherapy, immunotherapy, hormonal therapy, targeted anti-cancer therapy and other novel agents

In addition, **patients randomised to the elacestrant arm** are prohibited from taking:

- Over-the-counter medications, herbal preparations, supplements, and herbs or foods known to be moderate/strong inhibitors or inducers of CYP3A, because elacestrant undergoes biotransformation primarily by CYP3A.

With regards to the prescribed medications that are moderate/strong inhibitors or inducers of the CYP3A, the recommendations on Section 6.3.4 and [Appendix W](#) should be followed.

6.3.3 Permitted medications and vaccines

The following treatments are permitted during the study:

- H1 and H2 antagonists (e.g., dimetindene, ranitidine).
- Proton Pump Inhibitors (PPI) (e.g., omeprazole).
- Analgesics/anti-inflammatories (e.g., paracetamol/acetaminophen, ibuprofen, diclofenac, meperidine, opioids).
- Anti-emetics (metoclopramide, serotonin-antagonists, benzodiazepines etc).
- Medication to treat diarrhoea (e.g., loperamide).
- Anticoagulant therapy: patients who are taking warfarin may participate in this trial. However, prothrombin time (or INR) should be monitored in patients receiving elacestrant concurrently with warfarin or other coumarin derivatives. Subcutaneous heparin and low molecular weight heparin are permitted.
- Bisphosphonates may be used in the doses recommended for the treatment of osteoporosis and the prevention of recurrence in post-menopausal patients (including pre/peri menopausal women and men treated with GnRH analogues) as per local protocols.
- COVID-19 vaccines: if physicians decide to administer vaccines against SARS-CoV-2 in patients enrolled in the study, decisions should be individualized based on the risk of SARS-CoV-2 complications, the potential benefit from the vaccine, the general condition of the patient, the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label. Furthermore, country's guidelines and/or institutional guidelines, must be followed. Treatment schedule should not be altered because of the COVID-19 vaccination. The administration of a SARS-CoV-2 vaccine (including the brand name) shall be added in the concomitant medication form in the eCRFs and noted in the patient's medical file. Any vaccine-related AE(s) should be captured in the AE forms in the eCRFs.

6.3.4 Drug-Drug interaction

6.3.4.1 Elacestrant

Elacestrant is primarily eliminated in the liver via hepatic metabolism (CYP3A4) and biliary secretion. Elacestrant is neither an inhibitor nor an inducer of CYP3A4 or of any other isoform of cytochrome P450.

If a strong CYP3A4 inhibitor must be used, elacestrant dose should be reduced to 100 mg once daily with careful monitoring of tolerability.

If a moderate CYP3A4 inhibitor must be used, the elacestrant dose should be reduced to 200 mg once daily with careful monitoring of the tolerability. Subsequent dose reduction to 100 mg once daily may be considered with moderate CYP3A4 inhibitors based on tolerability.

A complete list of strong and moderate inhibitors and inducers of CYP3A4 can be found in [Appendix W](#).

There is no apparent drug-drug interaction between elacestrant and warfarin and between elacestrant and omeprazole. **Therefore, elacestrant may be administered without dose alteration in patients highly receiving protein-bound drugs and in patients receiving gastric pH–altering drugs.**

Elacestrant is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and may interact with sensitive P-gp and BCRP substrates in gastrointestinal tract increasing their exposure. Therefore, co-administration of P-gp and BCRP substrates such as digoxin or rosuvastatin with elacestrant should be monitored and dose should be reduced as necessary.

Elacestrant is also a substrate of the Organic Anion Transporting Polypeptide 2B1 (OATP2B1), thus caution is recommended for the concomitant administration of OATP2B1 inhibitors.

6.3.4.2 Standard endocrine treatment

Interactions with other medicinal products, other forms of interactions and contraindications are well known for standard endocrine treatment. Patients randomised to the control arm will continue the same endocrine treatment they had been prescribed as per standard of care. Detailed information on interactions, contraindications, special warnings, and precautions for use can be found in the SmPCs of the drugs.

6.3.5 Overdose

6.3.5.1 Elacestrant

There have been no known incidences of overdosage with elacestrant. Effects of overdose with elacestrant are unknown. There is no specific antidote for elacestrant. If overdose occurs, the subject should be treated supportively with appropriate monitoring as necessary.

6.3.5.2 Standard endocrine treatment

Effects of overdosage are well known for standard endocrine treatment. Patients randomised to the control arm will continue the same endocrine treatment they had been prescribed as per standard of care. Detailed information on overdosage can be found in the SmPCs of the drugs.

6.4 Withdrawal criteria

The primary reason for screening or study treatment discontinuation should be documented in the patient's medical notes and in the eCRFs.

If a patient fails to attend scheduled visits, several attempts should be made by the investigator to contact the subject or a responsible relative or the subject's general practitioner to obtain follow-up information. Only after sufficient unsuccessful attempts have been made to contact the patient (at least 1 phone call and 2 certified letters), this can be declared "lost to follow-up". The attempts to

contact the patient and collect data on their outcome should be documented in the patient's medical notes.

6.4.1 Treatment discontinuation

If the patient decides to prematurely discontinue study treatment, the investigator should ask her/him if he/she agrees to continue attending the study visits as per the schedule of assessments and/or to provide follow-up data (including safety, disease assessments, subsequent anticancer therapies, and survival). The outcome of the discussion between the investigator and the patient should be documented in the patient's medical notes.

Patients who discontinue study treatment prematurely will not be replaced. Patients who discontinue study treatment but remain on the study will return to the site for an end of treatment visit and will enter the follow-up period.

Every effort should be made to obtain information on patients who discontinued the study treatment but do not withdraw from the study.

If the sponsor or investigator recommends treatment discontinuation, the patient should continue attending the study visits as per the schedule of assessments.

The following conditions require permanent patient discontinuation from study treatment:

- Normal completion of the study treatment (see section 6.2.4).
- Locoregional or distant recurrence under current treatment (see section 8.1.1.1)
- Adverse event(s) or intercurrent illness that, in the opinion of the investigator, warrants the patient's withdrawal from study treatment [exceptional cases of patients in the control arm with the indication of switching ET due to AE (e.g., thromboembolic event during tamoxifen or osteoporotic fracture during AI) can continue in the study].
- Specific conditions described in the Safety Guidance (see section 6.2.6.1).
- Investigator's decision to withdraw the patient from treatment
- Noncompliance with study treatment schedule as defined by the investigator or the Sponsor
- Lost to follow up
- Patients of reproductive potential who refuse to use adequate birth control methods as described in the patient selection criteria and in Appendix T.
- A female patient inadvertently becomes pregnant
- Occurrence of a new malignancy whose natural history or treatment has the potential to interfere with the interventions and assessments of the trial. In case of occurrence of new malignancy with the exception of basal cell or squamous cell skin cancer, continuation of study treatment can occur only after discussing with the Sponsor (i.e., EORTC).
- Request by regulatory agencies for termination of treatment of an individual patient or all patients under the protocol
- Administrative reasons

After discontinuation of study treatment, further treatment will be left to the discretion of the treating physician. Any anti-cancer therapy other than the study drug will not be considered as part of the study treatment.

6.4.2 Study discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Other reasons leading to study discontinuation include, but are not limited to:

- Clinically/radiologically overt locoregional or distant breast cancer relapse during the ctDNA screening phase
- Occurrence of a new invasive malignancy, including a second breast cancer, during the ctDNA screening phase, with the exception of adequately treated basal cell or squamous cell skin cancer or an in-situ cancer.
- Administration of any other systemic anticancer treatment than ET (tamoxifen or aromatase inhibitor) or biphosphonates during the ctDNA screening phase
- Discontinuation of ET during the ctDNA screening phase
- Participation in another interventional clinical trial with an IMP during the ctDNA screening phase. In case of participation in an interventional trial without an IMP consultation with the study team is required.
- Significant noncompliance with the screening procedures, treatment schedule and evaluations as determined by the investigator or the Sponsor
- Lost to follow-up
- Administrative reasons
- Study termination or site closure

The primary reason for withdrawal from the study should be documented in the eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced. When a patient withdraws from the study and also withdraws consent for disclosure of future information and/or use of collected biological material, no further evaluations should be performed, no additional data should be collected and collected samples should be returned/destroyed. The study staff on site may use a public information source to obtain information about survival status.

After study discontinuation, patient care will be left at the discretion of the treating physician.

6.4.3 Site closure

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

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

7 Schedule of assessments and study calendar

7.1 General considerations

The patient's written informed consent to undergo screening for the clinical trial must be given prior to the performance of any protocol laboratory/imaging tests that are not part of local routine guidelines. Therefore, if a patient had laboratory/imaging tests as part of local routine guidelines (standard of care) prior to signing informed consent, the procedures will be acceptable for screening purposes if they are within the window required by the protocol.

The Study Calendar - Section 7.5 - summarizes the trial procedures to be performed at each designated visit.

Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature and thus local regulations may require that additional informed consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.2 ctDNA screening phase

7.2.1 General considerations

The patient's written informed consent to undergo screening must be given prior to the performance of any protocol procedures that are not part of local routine guidelines.

Once a subject has signed the screening period informed consent form, the patient should be registered in Rave EDC as soon as possible (preferably the same day), after which an identification number (Subject ID number) will be automatically assigned by the system and the study related screening procedures will start.

7.2.2 Within 28 days after registration

Within 28 days after the registration in Rave EDC, the following assessments need to be performed.

- Demographics (sex, age, year of birth)
- Malignant medical history
- History of current breast cancer
- Previous malignancies
- Breast cancer prior and current treatment
- Sample collection for DNA sequencing and building the Signatera assay (not applicable for patients who already tested ctDNA positive with another approved ctDNA assay for diagnostic purposes):
 - Tissue sample (either slides or FFPE) (see section 4.2.1.1 for details)
 - 2 Streck tubes of 10 ml of blood **AND** 1 EDTA tube of 6 mL for ctDNA detection
Additional samples might be requested in case of failed performed test mainly due to insufficient quality of the samples.

7.2.3 Every 6 months (+/- 4 weeks) after registration until the end of accrual

- Sample collection: 2 Streck tubes of 10 ml of blood for ctDNA detection per time point (applicable to all the patients successfully screened, not applicable to patients who already tested ctDNA positive with another approved ctDNA assay for diagnostic purposes)

7.3 Prior to randomisation

7.3.1 General considerations

The patient's written informed consent to enter the randomisation period must be given prior to the performance of any protocol procedures that are not part of local routine guidelines.

The following assessments need to be performed in all patients before randomisation, including patients who already tested ctDNA positive in the SURVIVE study or with another approved ctDNA assay for diagnostic purposes.

7.3.2 Within 28 days before randomisation

Disease evaluations to be performed considering that there must be a maximum of 4 weeks between ctDNA detection (the date on which the results of the ctDNA test are received) and randomisation:

- Mammogram (unilateral in case of mastectomy, not required in patients having undergone bilateral mastectomy)
 - Note:** *if local investigator plans to use breast MRI instead of mammograms during the study, MRI will have to be performed at baseline.*
- CT thorax and abdomen/pelvis with IV contrast. In case of any contra-indications (medical or regulatory): CT thorax without contrast + MRI abdomen/pelvis.
- Technetium-99m bone scintigraphy

For patients who tested ctDNA positive in the SURVIVE study or with another approved ctDNA assay for diagnostic purposes, the assessments listed on section 7.2.2 above must also be completed.

7.3.3 Within 21 days before randomisation

- Non-malignant medical history
- Review of prior/concomitant medications
- ECOG performance status
- Physical examination including breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions)
- Measurement of vital signs (blood pressure, pulse rate, temperature), weight and height
- Laboratory work-up:
 - Haematology: WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
 - Biochemistry: Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose (fasting), Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice). If total Bilirubin is >1.5xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
 - Estimated glomerular filtration rate with MDRD formula ([Appendix Q](#))

- Coagulation: prothrombin time (PT) / international normalized ratio (INR) and partial thromboplastin time (PTT)
- Serology: Hepatitis B surface antigen (HBsAg), hepatitis C antibody (and, if positive: PCR for HCV RNA).
- In patients known to be HIV-positive: PCR for HIV RNA (viral load)
- In women without prior history of bilateral surgical oophorectomy: follicle stimulating hormone (FSH), oestradiol (E2)
- Urine analysis: specific gravity, pH, proteins, glucose, and blood using dipsticks, elements and microscopic examinations if clinically indicated.
- Cardiac function: 12-lead ECG. The ECG should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 500 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
- G8 screening assessment for patient ≥ 70 years
- HRQoL: QLQ-C30 + QLQ-BR42 + EORTC IL46

7.3.4 Within 7 days before randomisation

- For WOCBP a negative pregnancy test (highly sensitive urine or serum beta HCG) must be documented no more than 7 days before randomisation.

Note: Since all pre- and perimenopausal women are required to take GnRH analogue in the experimental arm, and are allowed to take GnRH analogue in the control arm, and thus rendered medically post-menopausal, pregnancy tests after treatment start will only be done in the following situations:

- For the WOCBP not treated with GnRH analogue in the control arm, as per standard of care and local regulations
- Or if deemed necessary by the treating physician, suspicion of pregnancy or in cases of suspected non-compliance with GnRH analogue therapy

7.4 During protocol treatment and intense follow-up up to 36 months after randomisation

7.4.1 Within 3 days before the first treatment or after randomisation

- Sample collection: 2 Streck tubes of 10 ml of blood for ctDNA detection
 - Patients randomised in the **Experimental arm**: within 3 days before the first treatment.

Note 1: This also includes pre/peri-menopausal women and men who were not receiving GnRH analogue at the time of randomisation and who continue previous endocrine treatment during the first 21 days, allowing for one week (i.e., 7 days) wash-out before - exceptionally- starting Elacestrant on Day 29 counting from the date of randomisation.
 - Patients randomised in the **Control arm**: within 3 days after randomisation
 - For WOCBP in both arms, a negative pregnancy test (highly sensitive urine or serum beta HCG) must be documented within 3 days before the first dose of study drugs. Note: if the pregnancy test prior randomisation was done within 3 days before the first dose, there is no need to repeat the test.

7.4.2 At week 4 (+/- 3 days) after randomisation

- Review of concomitant medications
 - Physical examination including breast exam (palpation of breast/chest wall, axillae, supra and infraclavicular regions)
- Measurement of vital signs (blood pressure, pulse rate, temperature) and weight
- Adverse event assessment according to CTCAE version 5.0
- ECOG performance status
- Laboratory work-up:
 - Haematology: WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
 - Biochemistry: Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice) If clinically indicated: if total Bilirubin is $\geq 1.5 \times \text{ULN}$ (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
 - Estimated glomerular filtration rate with MDRD formula
- Sample collection: 2 Streck tubes of 10 ml of blood for ctDNA detection
- HRQoL: QLQ-C30 + QLQ-BR42 + EORTC IL46

7.4.3 During protocol treatment: at week 8, 24, 40, 56, 72, 88, 104 (+/- 1 week) after randomisation

The following examinations should only be performed for patients on protocol treatment. In case patients prematurely discontinue protocol treatment before week 104 (2 years), the patients should complete an end of treatment visit (Section 7.4.5) and will be assessed as per Section 7.4.4.

- Review of concomitant medications
 - Physical examination including breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions)
- Measurement of vital signs (blood pressure, pulse rate, temperature) and weight
- Adverse event assessment according to CTCAE version 5.0 and SAEs as per [Appendix I](#)
- ECOG performance status
- Laboratory work-up:
 - Haematology: WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
 - Biochemistry: Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice)
 - If clinically indicated: if total Bilirubin is $\geq 1.5 \times \text{ULN}$ (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
 - Estimated glomerular filtration rate with MDRD formula
 - In WOCBP, pregnancy test is to be renewed/repeated during protocol treatment if required by national regulations/institution guidelines.

The following examination should only be performed at **weeks 24 and 72**:

- Cardiac assessment: 12-lead ECG

7.4.4 During protocol treatment and follow-up: at week 16, 32, 48, 64, 80, 96, 112, 128, 144 and 156 (+/- 2 weeks) after randomisation

The following examinations should be performed **independent of treatment status** and until occurrence of distant breast cancer recurrence (after distant recurrence, refer to section 7.4.8).

- Physical examination including breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions)
- Measurement of vital signs (blood pressure, pulse rate, temperature) and weight
- Adverse event assessment according to CTCAE version 5.0.
 - During the follow-up period **only** new AEs of grade 3 and higher and all SAEs that are considered to be possibly related to protocol treatment (as per [Appendix I](#)) and follow-up of all adverse events that were ongoing at EoT visit (Section 7.4.5) should be collected.
- Sample collection: 2 Streck tubes of 10 ml of blood for ctDNA detection
- Disease evaluation:
 - CT thorax and abdomen/pelvis with IV contrast. In case of any contra-indications (medical or regulatory): CT thorax without contrast + MRI abdomen/pelvis
 - Mammogram (unilateral in case of mastectomy) (**only at week 48, 96 and 156**)
 - Note:** *Breast MRI instead of mammograms is an alternative during the study if an MRI was performed at baseline.*
 - Technetium-99m bone scintigraphy (**only at week 48, 96 and 156**)

The following examinations should be performed **independent of treatment status and regardless of distant recurrence**:

- HRQoL: QLQ-C30 + QLQ-BR42 + EORTC IL46 (**up to and including week 80**)

The following examinations should **only** be performed in **patients on protocol treatment** and should be discontinued after treatment discontinuation.

- Review of concomitant medications
- ECOG performance status
- Laboratory work-up:
 - Haematology: WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
 - Biochemistry: Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice)
 - If clinically indicated: if total Bilirubin is $\geq 1.5 \times \text{ULN}$ (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
 - Estimated glomerular filtration rate with MDRD formula

The following examination should only be performed at **week 48 in patients on protocol treatment**.

- Cardiac assessment: 12-lead ECG

The following examination should only be performed in **patients who have discontinued protocol treatment**.

- Subsequent anti-cancer therapy

7.4.5 During protocol treatment after year 3 [for patients on ET between 1 and 5 years (12 and 60 months) at randomisation]: at week 182, 208, 234, 260, 286, and 312 (+/- 4 weeks) after randomisation

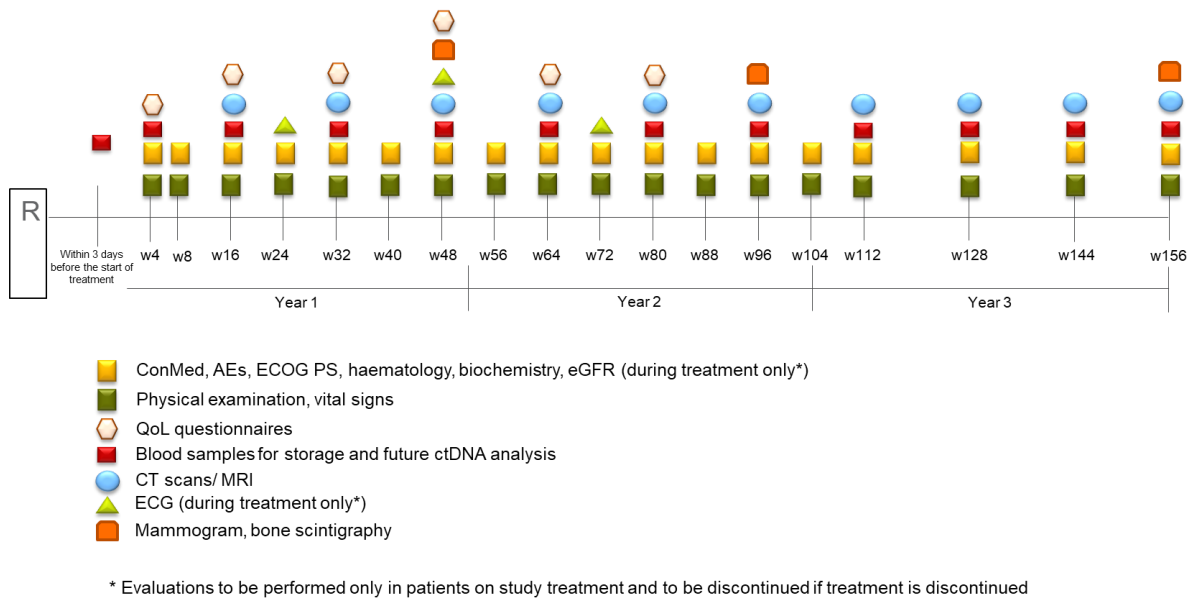
The following examinations should **only** be performed in **patients who are still on protocol treatment after year 3 in order to complete 7 years of ET in total** and should be stopped after treatment discontinuation.

- Review of concomitant medications
- Adverse event assessment according to CTCAE version 5.0.
 - During the follow-up period **only** new AEs of grade 3 and higher and all SAEs that are considered to be possibly related to protocol treatment (as per [Appendix I](#)) and follow-up of all adverse events that were ongoing at EoT visit (Section 7.4.5) should be collected.
- ECOG performance status
- Physical examination including breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions)
- Measurement of vital signs (blood pressure, pulse rate, temperature) and weight
- Laboratory work-up:
 - Haematology: WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
 - Biochemistry: Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice)
 - If clinically indicated: if total Bilirubin is $\geq 1.5 \times \text{ULN}$ (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
 - Estimated glomerular filtration rate with MDRD formula
 - In WOCBP, pregnancy test is to be renewed/repeated during protocol treatment if required by national regulations/institution guidelines.

7.4.6 End of treatment visit

The following assessments will be performed 30 days (+/-7 days) after last dose of protocol treatment (See Section 6.2.4):

- Adverse event assessment according to CTCAE version 5.0
- Physical examination including breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions)
- Measurement of vital signs (blood pressure, pulse rate, temperature) and weight
- ECOG performance status
- Laboratory work-up:
 - Haematology: WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
 - Biochemistry: Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice)
 - If clinically indicated: if total Bilirubin is $\geq 1.5 \times \text{ULN}$ (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
 - Estimated glomerular filtration rate with MDRD formula



Note: patients still on treatment at week 156 will have data collected as per section 7.4.5

Figure 5: Visit schedule during treatment and intense follow-up

7.4.7 Follow-up after year 3 (week 156)

After 3 years (week 156 after randomisation) the following information will be collected every 6 months (+/- 4 weeks) and for a maximum of 3 years after the randomisation of the last patient, unless prior occurrence of distant recurrence. For patients who receive study treatment for more than 3 years, this info should be collected every 6 months (+/- 4 weeks) after year 3 (week 156) until distant recurrence or 3 years after the randomisation of the last patient:

- Breast cancer recurrence (ipsilateral, locoregional or distant)
- Second primary malignancies
- Survival status (death and cause of death)
- Subsequent anti-cancer therapy
- Adverse event assessment according to CTCAE version 5.0: all SAEs that are considered to be possibly related to protocol treatment (as per [Appendix I](#)) and all adverse events that were ongoing at week 156

7.4.8 Follow-up after distant recurrence

For patients with distant breast cancer recurrence during treatment or follow-up, the following information should be collected every 6 months (+/- 4 weeks) from the date of recurrence (see Section [8.1.1.1](#)) and for a maximum of 3 years after the randomisation of the last patient:

- Second primary malignancies
- Survival status (death and cause of death)
- Subsequent anti-cancer therapy
- HRQoL: QLQ-C30 + QLQ-BR42 + EORTC IL46: at week 16, 32, 48, 64, and 80 (+/- 2 weeks) after randomisation.

- Adverse event assessment according to CTCAE version 5.0: all SAEs that are considered to be possibly related to protocol treatment as per [Appendix I](#) and all adverse events that were ongoing at EoT visit (Section [7.5](#))

7.4.9 End of study visit

When a patient completes the planned follow-up (for a maximum of 3 years after the randomisation of the last patient or at the time of EoT of the patient in question, in case she/he is still on treatment, whichever occurs last) or is discontinued from the study, the last follow-up visit is considered as the end of study visit.

7.5 Study calendar

7.5.1 ctDNA Screening phase

| | ctDNA screening phase | | |
|---|-----------------------|-----------------------------------|--|
| | Before registration | Within 28 days after registration | Every 6 months (± 4 weeks) after registration |
| Informed consent for the screening period | ◆ | | |
| Tumour sample (a) | | ◆ | |
| Blood samples for ctDNA (b) | | ◆ Plus one EDTA | ◆ |
| Medical history (c) | | ◆ | |
| Breast cancer prior and current treatment | | ◆ | |

- (a) **Tumour sample:** (1) Archival tumour tissue (FFPE tumour block with 25mm² minimum surface) or (2) Slides (6-10 unstained slides of 10µm each/12-19 unstained slides at 5µm each) **PLUS** one H&E slide from the baseline biopsy or from surgical specimen. Tumour cellularity must be $\geq 20\%$ (preferably $\geq 30\%$).
- (b) **Blood samples for ctDNA:** 2 Streck tubes of 10 ml of blood (AND one 6ml EDTA for ctDNA detection at registration).
- (c) Includes malignant medical history (history of current breast cancer and previous malignancies) and demographics (sex, age, year of birth)).

7.5.2 Randomisation phase

| | Within 21 days before randomisation | During protocol treatment period | | | | | End of Treatment visit |
|--|-------------------------------------|--|---|--|---|--|------------------------|
| | | Year 1 - 3 | | | | Year 4-6 (only applicable for patients continuing protocol treatment beyond 3 years) | |
| | | Within 3 days: before the first treatment (intervention arm) and after randomisation results (control arm) | At w4 (± 3 days) after randomisation | At w8, w24, w40, w56, w72, w88, w104 (± 7 days) after randomisation To be interrupted when treatment is discontinued prematurely | At w16, w32, w48, w64, w80, w96, w112, w128, w144 and w156 (± 2 weeks) after randomisation To be performed independent of treatment and until distant recurrence (unless otherwise specified) | At w182, w208, w234, w260, w286, w312 (± 4 weeks) after randomisation To be interrupted when treatment is discontinued | |
| Informed consent for the randomised phase | ◆ within 28 days | | | | | | |
| ctDNA Positive test | ◆ within 28 days | | | | | | |
| Blood sample for ctDNA to be biobanked (a) | | ◆ | ◆ | | ◆ | | |
| Medical history (b) | ◆ | | | | | | |
| Breast cancer prior and current treatment | ◆ | | | | | | |
| Concomitant Medications | ◆ | | ◆ | ◆ | ◆ interrupted when treatment is discontinued | ◆ | |
| Physical examination (c) | ◆ | | ◆ | ◆ | ◆ | ◆ | ◆ |
| ECOG performance status | ◆ | | ◆ | ◆ | ◆ interrupted when treatment is discontinued | ◆ | ◆ |
| Vital signs (d) and Weight | ◆ Plus height | | ◆ | ◆ | ◆ | ◆ | ◆ |
| Adverse events (e) | | | ◆ | ◆ | ◆ | ◆ | ◆ |
| Haematology (f) | ◆ | | ◆ | ◆ | ◆ | ◆ | ◆ |

| | Within 21 days before randomisation | During protocol treatment period | | | | | Year 4-6 (only applicable for patients continuing protocol treatment beyond 3 years) | End of Treatment visit |
|----------------------------------|-------------------------------------|--|---|--|---|--|---|------------------------|
| | | Year 1 - 3 | | | | | | |
| | | Within 3 days: before the first treatment (intervention arm) and after randomisation results (control arm) | At w4 (± 3 days) after randomisation | At w8, w24, w40, w56, w72, w88, w104 (± 7 days) after randomisation To be interrupted when treatment is discontinued prematurely | At w16, w32, w48, w64, w80, w96, w112, w128, w144 and w156 (± 2 weeks) after randomisation To be performed independent of treatment and until distant recurrence (unless otherwise specified) | At w182, w208, w234, w260, w286, w312 (± 4 weeks) after randomisation To be interrupted when treatment is discontinued | 30 days (+/-7 days) after last dose | |
| | | | | | interrupted when treatment is discontinued | | | |
| Biochemistry (g) and eGFR | ◆ | | ◆ | ◆ | ◆ interrupted when treatment is discontinued | ◆ | ◆ | |
| Serology (h) | ◆ | | | | | | | |
| FSH/E2 | ◆ | | | | | | | |
| Coagulation (i) | ◆ | | | | | | | |
| Urine analysis (j) | ◆ | | | | | | | |
| Pregnancy test (k) | ◆ within 7 days | | | | | | | |
| CT scan (l) | ◆ within 28 days | | | | ◆ | | | |
| Mammogram/MRI breast (m) | ◆ within 28 days | | | | ◆ only at w48, w96 and w156 | | | |
| Technetium-99m bone scintigraphy | ◆ within 28 days | | | | ◆ only at w48, w96 and w156 | | | |
| Cardiac function (n) | ◆ | | | ◆ only at w24 and w72 | ◆ only at w48 | | | |
| HRQoL (o) | ◆ | | ◆ | | ◆ only at w16, w32, w48, w64, w80 to be performed independent of patient's disease status | | | |
| G8 geriatric screening tool | ◆ | | | | | | | |

| | Within 21 days before randomisation | During protocol treatment period | | | | | Year 4-6 (only applicable for patients continuing protocol treatment beyond 3 years) | End of Treatment visit |
|---------------------------|-------------------------------------|--|---|--|---|--|---|------------------------|
| | | Year 1 - 3 | | | | | | |
| | | Within 3 days: before the first treatment (intervention arm) and after randomisation results (control arm) | At w4 (± 3 days) after randomisation | At w8, w24, w40, w56, w72, w88, w104 (± 7 days) after randomisation To be interrupted when treatment is discontinued prematurely | At w16, w32, w48, w64, w80, w96, w112, w128, w144 and w156 (± 2 weeks) after randomisation To be performed independent of treatment and until distant recurrence (unless otherwise specified) | At w182, w208, w234, w260, w286, w312 (± 4 weeks) after randomisation To be interrupted when treatment is discontinued | 30 days (+/-7 days) after last dose | |
| (patient ≥ 70 years) | | | | | | | | |

- (a) **Blood sample for ctDNA:** 2 Streck tubes of 10 ml of blood
- (b) **Medical history:** Included malignant medical history (history of current breast cancer, previous malignancies) and non-malignant medical history that includes non-malignant conditions prior to randomisation.
- (c) **Physical examination:** palpation of breast/chest wall, axillae, supra- and infraclavicular regions
- (d) **Vital signs:** Measurement of blood pressure, pulse rate, temperature
- (e) **Adverse events:** Assessment according to CTCAE version 5.0. During the follow-up period, only the following AEs will be collected: new AEs of grade 3 and higher that are considered to be possibly related to protocol treatment (collected until the end of treatment visit); follow-up of all adverse events that were ongoing at EoT visit; all SAEs that are considered to be possibly related to protocol treatment.
- (f) **Haematology:** WBC (including ANC, lymphocytes), RBC, haemoglobin, haematocrit and platelets
- (g) **Biochemistry:** Albumin, total protein, ALP, SGPT, SGOT, LDH, Bicarbonate, total Calcium, Chloride, Creatinine, Glucose (fasting), Potassium, Sodium, total Bilirubin, Urea or Blood urea nitrogen (depending on local practice). If total Bilirubin is $\geq 1.5 \times \text{ULN}$ (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
- (h) **Serology:** Hepatitis B surface antigen (HBsAg), hepatitis C antibody (and, if positive: PCR for HCV RNA); In patients known to be HIV-positive: PCR for HIV RNA (viral load)
- (i) **Coagulation:** prothrombin time (PT) / international normalized ratio (INR) and partial thromboplastin time (PTT)
- (j) **Urine analysis:** specific gravity, pH, proteins, glucose, and blood using dipsticks, elements and microscopic examinations if clinically indicated.
- (k) **Pregnancy test:** For women of child-bearing potential (WOCBP) a negative pregnancy test (highly sensitive urine or serum beta HCG) must be documented no more than 7 days before randomisation and within 3 days before the first dose of study drugs. Note 1: if the pregnancy test prior randomisation was done within 3 days before the first dose, there is no need to repeat the test. Note 2: In Switzerland, the only option for the pregnancy test is the serum beta HCG. Note 3: In WOCBP, pregnancy test is to be renewed/repeated during protocol treatment if required by national regulations/institution guidelines.
- (l) **CT scan:** CT thorax and abdomen/pelvis with IV contrast. In case of any contra-indications (medical or regulatory): CT thorax without contrast + MRI abdomen/pelvis
- (m) **Mammogram or MRI breast:** Note that Breast MRI instead of mammograms is an alternative during the study if an MRI was performed at baseline.

-
- (n) **Cardiac function:** A 12-lead ECG should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 500 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
 - (o) **HRQoL:** The following questionnaires should be completed: QLQ-C30, QLQ-BR42 and EORTC IL46

8 Criteria of evaluation

For each endpoint, the definition and the detailed method of assessment is provided in this chapter. The estimands (population-level summary of treatment effect) corresponding to the study objectives are precisely described in section 10.1 on "Statistical considerations" as well as how main and sensitivity estimators will be calculated.

8.1 Evaluation of efficacy

8.1.1 Disease recurrence and second cancers

8.1.1.1 Definitions

- Local recurrence is defined as an evidence of invasive breast cancer in the ipsilateral breast or chest wall.
- Regional recurrence is defined as an evidence of disease recurrence in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or an evidence of disease in the soft tissues in the ipsilateral axilla.
- Distant metastatic recurrence is defined as an evidence of disease recurrence in locations other than local or regional metastasis, for example recurrence in the not local or regional subcutaneous tissues, not regional lymph nodes, lung, bone, liver, brain, etc. Distant metastatic recurrence has either been biopsies confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Invasive contralateral breast cancer is defined as the histological evidence of invasive breast cancer in the contralateral breast, or chest wall.
- Invasive non-breast second cancer is defined as the evidence of any invasive non-breast second cancer other than any new in situ carcinomas of any site or non-metastatic non-melanomatous skin cancers.

8.1.1.2 Methods of assessment

- Mammogram (unilateral in case of mastectomy), or breast MRI (if MRI are used instead of mammograms, an MRI must be performed at baseline), not required in patients having undergone bilateral mastectomy
- CT thorax and abdomen/pelvis with IV contrast. In case of any contra-indications (medical or regulatory): CT thorax without contrast + MRI abdomen/pelvis.
- Technetium-99m bone scintigraphy
- Physical examination including breast exam (palpation of breast/chest wall, axillae, supra- and infraclavicular regions). In case recurrence is suspected based on physical examination, this should either be confirmed on pathology (through tumour biopsy) or by one of the imaging modalities above.

Any suspicion of recurrence or second cancer, either based on imaging or physical examination, should be confirmed through biopsy whenever possible.

Schedule of assessments and study calendar are summarized in Chapter 7.

8.1.2 Definition of efficacy endpoints

8.1.2.1 Date of recurrence

The first date when recurrence was observed is taken into account regardless of the method of assessment. For example, if both pathology and imaging indicate a recurrence, the date of the first of these two examinations is considered as the date of recurrence. If a clinical examination indicates a recurrence which is later confirmed by a pathology, the date of the clinical examination is considered as the date of recurrence.

8.1.2.2 Distant metastasis-free survival (DMFS)

DMFS is defined as the time between the date of randomisation and the date of the first occurrence of one of the following events (calculated as the difference between the two dates in days + 1):

- Distant metastasis
- Date of death from any cause

For participants who remain alive and distant metastasis-free, DMFS will be censored on the date of last adequate disease assessment.

DMFS will be based on the disease assessment and date of death provided by the local investigator.

8.1.2.3 Invasive disease-free survival (IDFS)

IDFS is defined as per the STEEP criteria and will be computed as the time between the date of randomisation and the date of the first occurrence of one of the following events (calculated as the difference between the two dates in days + 1):

- Loco-regional disease recurrence
- Distant metastasis
- Invasive contralateral breast cancer
- Invasive non-breast second cancer
- Date of death from any cause

For participants who remain alive and without disease recurrence or second cancer, IDFS will be censored on the date of last adequate disease assessment.

IDFS will be based on the disease assessment and date of death provided by the local investigator.

8.1.2.4 Relapse-free survival (RFS)

RFS is defined as per the STEEP criteria [38] and will be computed as the time between the date of randomisation and the date of the first occurrence of one of the following events (calculated as the difference between the two dates in days + 1):

- Loco-regional disease recurrence
- Distant metastasis
- Date of death from any cause

For participants who remain alive and without disease recurrence, RFS will be censored on the date of last adequate disease assessment.

RFS will be based on the disease assessment and date of death provided by the local investigator.

8.1.2.5 Overall survival (OS)

Overall survival will be computed from the date of randomisation to the date of death (calculated as the difference between the two dates in days + 1).

Patients still alive at the analysis cut-off date will be censored at the last date known to be alive (before the analysis cut-off date).

8.2 Evaluation of ctDNA

8.2.1 Signatera assay

In this study, a personalized ctDNA assay will be performed based on the whole exome sequencing of the primary tumour in the screening phase patients (see section 1.2.1). A primary tumour sample obtained prior to any treatment is preferred. If no such sample is available, a primary tumour sample obtained post neoadjuvant treatment is the next preferred option. If no sample from the primary tumour is available at all for testing, then tissue from involved regional lymph nodes (least preferred option) is acceptable as well for the set-up of the ctDNA assay.

During the screening phase of the study, the ctDNA assay will be performed on plasma collected every 6 months from study entry until ctDNA detection (ctDNA relapse) or until the end of accrual (approximately 5.7 years) for the translational research program. For patients who are eligible for the randomised part of the study, the translational research program on ctDNA assay will be performed on plasma collected either within 3 days before the start of the treatment (patients in experimental arm) or 3 days after randomisation (patients in control arm), at week 4 after randomisation and every 4 months thereafter for a maximum of 3 years to possibly assess ctDNA kinetics (see section 9.3.1).

The Signatera assay will be performed at the NATERA Labs (USA). For building the personalized Signatera assay, the first ctDNA assessment will take at maximum 6 weeks, counting from the date that the last required sample is received at the NATERA lab *up to* the date the results are shared with the investigator. For the subsequent ctDNA assessments the turnover period will be a maximum of 2 weeks, counting from the date the sample arrived at the NATERA lab *up to* the date the results are shared with the investigator.

8.3 Evaluation of safety

8.3.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

The collection period of adverse events will start from registration. Between registration and randomization, only SAEs will be collected. Starting from randomisation until 30 days after end of study treatment all AEs including SAEs will be collected.

After 30 days after end of study treatment, only the following AEs will be collected:

- follow-up of all adverse events that were ongoing at end of treatment visit
- all SAEs that are possibly related to protocol treatment

All adverse events must be followed until resolution or stabilization.

8.3.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page <https://www.eortc.be/services/doc/ctc/>.

Planned safety analysis and tabulations are described in section 10.3.4 on "Statistical considerations".

8.3.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events)

8.3.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

8.3.5 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

8.4 Health Related Quality of Life assessment

Health Related Quality of Life (HRQoL) will be assessed with 3 different questionnaires: QLQ-C30, QLQ-BR42 (only female patients) and EORTC IL46 (item Q168 from the EORTC Item Library (IL)). The order of the questionnaires should be first the EORTC QLQ-C30, then the EORTC QLQ-BR42 and IL46. The baseline questionnaires must be completed following ctDNA detection and before randomisation, to avoid biasing the patient's responses to the questions. The assessment schedule is specified in chapter 7. The total number of questions is 73 and can be completed within 30-40 mins.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (e.g., a research nurse, study coordinator) and if possible, assign a back-up person to cover if that individual is absent. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the HRQoL questionnaires are detailed in [Appendix U](#) while the English language version of the questionnaires themselves are included in [Appendix X](#). The administration of these questionnaires will be paper-based.

Patient reported data will not be used for clinical monitoring of patients' functioning and symptoms (e.g., PRO alerts). In the patient informed consent, patients are informed that there are no right or wrong answers to these questions and their answers will not affect their subsequent treatment or relationship with their treating physician or the hospital staff in any way.

8.4.1 QLQ-C30

The EORTC Quality of Life Questionnaire (QLQ-C30) version 3 [39] is valid for any cancer population and is composed of thirty distinct questions that are scored into fifteen scales [40]. These include five functional scales (physical, role, emotional, social, and cognitive), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and a global health status/QoL scale. The questionnaire employs 28 4-point Likert scales with responses from “not at all” to “very much” and two 7-point Likert scales for global health and overall HRQoL. The scale scores are converted to fall between 0 and 100 [40]. For functional and global HRQoL scales, higher scores represent a better level of functioning. For symptom-oriented scales, a higher score represents more severe symptoms. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups. [41,42] The EORTC QLQ-C30 version 3 has been translated in over 100 languages according to a standardized translation procedure [43].

8.4.2 QLQ-BR42

The EORTC measurement strategy is to supplement the generic EORTC QLQ-C30 with disease-specific modules. Over the last years, a comprehensive update of the EORTC QLQ breast module has been conducted to provide a more accurate and comprehensive assessment of the impact of new treatments on patients' quality of life taking into account the evolution of the therapeutic landscape. The updated EORTC-QLQ breast cancer module has recently completed validation [44]. In line with this strategy, all female patients should additionally complete the EORTC QLQ-BR42.

The 42-item EORTC QLQ-BR45 contains ten multi-item scales to assess body image, sexual functioning, systemic chemotherapy side effects, endocrine therapy symptoms, arm symptoms, breast symptoms, hand/feet/neuropathy symptoms, skeletal scale, vaginal symptoms and breast satisfaction scale, and three single items to assess sexual enjoyment, future perspective and weight gain.

The multi-item scales and single items are divided into two groups, namely (i) functional scales: body image, sexual functioning, sexual enjoyment future perspective and breast satisfaction and (ii) symptom scales/items: systemic chemotherapy side effects, breast symptoms, arm symptoms, weight gain, endocrine therapy symptoms, hand/feet/neuropathy symptoms, skeletal scale, vaginal symptoms. The scoring approach for the QLQ-BR42 is identical to that of the QLQ-C30 [40].

The EORTC QLQ-BR42 has been translated in several languages according to a standardized translation procedure [43].

8.4.3 EORTC IL46

In addition to the QLQ-C30, the EORTC Item Library [45] was used to construct an ad-hoc item list specific to this study named EORTC IL46. The aim was to add items from the EORTC Item Library

to cover overall treatment burden which is not covered by the previous questionnaires. The following single item was selected to include self-assessment on treatment burden:

- To what extent have you been troubled with side-effects from your treatment? (Item Q168 from EORTC IL)

This question is recommended by the US FDA to assess overall treatment side effect burden [46]. This item can be found in the module for pancreatic patients, QLQ-PAN26 and Cholangiocarcinoma & Gall Bladder, QLQ-BIL21 [47,48]. Although this Item List is not a validated instrument, it is an ad-hoc instrument optimized for this specific setting and composed of integral parts of validated HRQoL questionnaires. The question follows the same structure using a 4-point Likert scales with responses from “not at all” to “very much” and translated in more than 80 languages according to a standardized translation procedure [43]. The scoring approach for this item is identical to that for the symptom scales of the QLQ-C30 [40].

8.5 Evaluation of frailty

Older cancer patients have a much more heterogeneous general health status compared to young cancer patients. Presence of frailty can be detected by a so-called (Comprehensive) Geriatric Assessment (GA). Performance of GA is advised in older cancer patients by the International Society of Geriatric Oncology, (SIOG) [49]. GA is time consuming (takes about 30 minutes). Therefore, short geriatric screening tools such as the G8 have been developed as a short and easy to use measurement of general health status. The G8 score has been specifically developed in oncology, includes 8 items, takes a few minutes to complete, and can be completed by any health care worker [50].

G8 will be measured in all patients aged 70 years and above at baseline of the randomised trial. G8 has to be completed by the clinician, the nurse or the trained coder. This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient. The English version of G8 is included as a protocol [Appendix V](#).

9 Collection and analysis of Human Biological Material

9.1 General scope

This project, in compliance with the applicable ethical, legal and technical requirements, involves the collection, storage and use of

- Human Biological Material (HBM) listed in the Summary Table (section [9.3.1](#))
- residual biological material (“leftovers”)
- and/or derivatives

HBM, leftovers, derivatives and corresponding raw data and results will be stored at a central biobank (IBBL, the integrated biobank of the LIH, Luxembourg) for a maximum of 25 years after End of Trial, depending on the sample type, stability, scope and in compliance with the applicable legislation.

The analysis will be performed by a central laboratory when an analysis plan is set up and defined by EORTC Headquarters Translational Research Unit (HQ TRU) and the study team.

Depending on the research project and the required expertise, several laboratories in the European Union (EU) and potentially outside EU may be involved in the analysis of the samples. EORTC will select them after the evaluation of their quality, which is based on:

- Their expertise in the relevant field
- The availability of appropriate facilities and/or techniques for HBM handling and processing
- Their compliance with applicable laws and ICH-GCP.

EORTC Headquarters will perform quality control visits at the laboratories. Relevant assessors, including but not limited to EORTC Headquarters, according to EORTC standard process, will monitor compliance with relevant national and international quality standards.

Raw data and results, if applicable, will be sent to EORTC Headquarters for storage and correlation with the clinical outcome.

Molecular data will be stored at the European Genome-Phenome Archive (EGA) or a similar database with controlled access. The reporting of any genetic findings from any translational research projects will follow the EORTC POL022.

The data and HBM transfer for further use purposes will comply with the applicable legislation, EORTC policies (EORTC L-01-POL-01 and POL020) and the approved data transfer charters.

9.2 Research project(s)

All the described pre-defined research projects below are potential projects which feasibility will be evaluated during the trial and can be updated with new techniques developed on the course of the trial (subject to the project feasibility, samples availability and additional funding).

9.2.1 Pre-defined Research Project 1

9.2.1.1 Background and rationale

SERDs have the ability to block endocrine-dependent and endocrine independent ER α signalling by ablation of ER α and have been recognized to offer a therapeutic approach where other endocrine agents, such as tamoxifen or AIs have failed. Predictive plasma biomarkers and their evolution are getting popular. Amongst the most promising biomarkers, in this set of patients, ESR1 mutations are a common cause of acquired resistance to estrogenic deprivation by AIs [51]. We will further study the associations between new ctDNA biomarkers with the patient's outcome in breast cancer.

Please note that the methods to test the above hypothesis will be defined in the future.

9.2.1.2 Hypothesis/objectives

- To evaluate in plasma the associations between plasma biomarkers with the treatment efficacy at all timepoints.

9.2.2 Pre-defined Research Project 2

9.2.2.1 Background and rationale

ctDNA elimination or clearance is defined as lack of detectable mutation. Previous studies shows that ctDNA elimination of driving and not driving mutations at different points of the course of a treatment seems to be associated with longer PFS and OS in different tumour types [52,53]. We will further study the prognostic and predictive value of the ctDNA elimination in the patient's outcome in breast cancer.

In this study, ctDNA elimination rate will be defined as the proportion of randomised patients, i.e., with a ctDNA-positive test who have a ctDNA-negative test at the pre-specified time point (month 1 and month 4). Patients who developed a distant recurrence prior to the pre-specified time points and for whom sample collection will be stopped as per Section 7.4.8 will be considered as not having a ctDNA elimination.

Please note that the methods to test the above hypothesis will be defined in the future.

9.2.2.2 Hypothesis/objectives

- To evaluate associations between ctDNA elimination and DMFS (but not limited to it) according to treatment arm.

9.2.3 Undefined further usage of clinical trial data and samples

9.2.3.1 Background and rationale

Despite recent progress, there is still a lot to learn about cancer. The scientific examination of tissues, blood samples and other body fluids, in combination with medical data, is today one of the most important sources of knowledge. It is the only way to understand how cancer develops and spreads and it supports the development of new methods for its diagnosis, prevention and treatment.

The summary table describes the HBM, specifically collected for further research projects. All leftover biological material can also be used for further research projects, i.e.,

- The leftovers from Human Biological Material (HBM) listed in the Summary Table (section 9.3.1)
- Produced derivatives.

HBM and relevant data can be transferred from the central biobank to other research laboratories, which perform molecular analyses, or which are involved in translational research projects. This includes the incidence of certain molecular markers in a certain patient population or biomarker discovery.

HBM and relevant data can be further used either by EORTC alone or in collaboration with other partners or can be transferred to other researchers, including commercial partners, in the EU and potentially outside EU.

All leftover material from the undefined research studies, will be sent back to the central biobank if sufficient quantity and quality remains for usage in further research on breast cancer.

9.2.3.2 Objectives

The potential objectives are:

- To collect and/or use and/or re-use clinical-pathologically annotated HBM and clinical data, as well as patient-reported outcomes from patients with cancer diagnosis. The purpose is to support biospecimen-based translational research and biomarker discovery, as well as to improve the understanding of tumour biology and cancer patients' care, including long-term effects on health and social life.
- To perform biospecimen- and data-based high-quality research, aiming to better understand the biology of cancer, and/or how it is currently managed and/or how to better diagnose and treat it in the future;
- To investigate, from a biological point of view, the molecular pathways related to the development of specific tumours. Such pathways include, but are not limited to tumour cell proliferation, growth, invasion and metastasis, metabolism, angiogenesis, apoptosis, immune response, inflammation, and genomic instability.
- To collect large series of homogeneous clinical data, in order to analyse the disease course and the performed treatment;
- To investigate the prevalence and to validate the prognostic or predictive value of novel biomarkers in cancers;
- To perform biospecimen- and data-based high-quality research, aiming to facilitate the establishment of validated tests for tumour biomarkers;
- To identify the patients with molecular alterations in their tumour that can be matched to biomarker-driven clinical trials.
- To facilitate the enrolment of cancer patients in biomarker-driven clinical trials;
- To learn more about cancer prevention, diagnostics and treatment, including its long-term effects on health and social life
- To develop and/or validate new cancer research methodologies in order to evaluate/adapt therapies more rapidly, for example, by looking into the appropriate use of earlier signals
- To corroborate / consolidate other stakeholders' research results:
 - by using data that are gathered to either reproduce results others obtained or to increase the knowledge / the level of evidence
 - by pooling the obtained data with data from other research projects

9.2.4 Sample collection

We will collect 2 blood samples (Streck tubes) at each time point (with the exception of baseline timepoint where an extra EDTA blood tube will be collected from the patients) and an archival tumour FFPE material (see section 9.3.1) for the Signatera assay in all patients who enter the ctDNA screening phase, and 2 blood samples (Streck tubes) for all randomised patients for the translational research. All unused plasma samples and leftovers will be stored for defined and undefined breast cancer translational research (sections 9.2.1 and 9.2.3).

9.3 Summary tables

9.3.1 Sample summary table

All instructions pertaining to HBM management can be found in the separate HBM guidelines.

| Mandatory for site yes/no? | Patient's choice yes*/no**? | Specimen type(s) | Specimen amount | Collection time point(s) | Estimated/expected sample size |
|--|-----------------------------|--|--|--|--|
| All screened patients[§] | | | | | |
| Yes | No | Blood sample for monitoring ctDNA relapse | 2 Streck tubes of 10 ml | Registration, months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 (± 4 weeks). | 1610 ¹ X 2 tubes X 12 time points = 38,640 tubes |
| Yes | No | Blood sample for building the ctDNA test | 1 EDTA tube of 6ml | Registration | 1610 ¹ X 1 tube X 1 timepoint = 1610 tubes |
| Yes | No | From baseline biopsy or surgical specimen: FFPE sample OR Slides | 1 block of 25mm ² minimum surface OR 6-10 unstained slides of 10 μ m each (+ 1 H&E slide) (preferred) OR 12-20 unstained slides at 5 μ m each (+ 1 H&E slide) (preferred) | Registration | 1610 ¹ blocks OR sets of 6-10 slides of 10 μ m (+ 1 H&E slide for each set) OR 12-20 unstained slides at 5 μ m each (+1 H&E slide for each set) |
| Randomised patients | | | | | |
| Yes | No | Blood sample for ctDNA | 2 Streck tubes of 10 ml | Within 3 days before treatment start (experimental arm) or within 3 days after randomisation (control arm) and at weeks 4 (± 3 days), 16, 32, 48, 64, 80, 96, 112, 128, 144, 156 (± 2 weeks) | 220 X 2 tubes X 12 time points= 5280 tubes |

Table 6: Sample summary table

*"yes" means that the collection of this material is optional, as patients are given the choice in the Informed Consent Form (ICF). EORTC will not collect this type of material from patients not having specifically consented to this. ***"no" means that the collection of this material is mandatory for the study and patients are not given the choice in the ICF. If patients do not agree with sample collection, they cannot participate in the study

§ Not applicable to patients from the SURVIVE study who tested ctDNA positive outside the screening phase of the TREAT ctDNA trial.

¹ Maximum expected number of samples, without taking into account participants who tested ctDNA positive outside the screening phase of the TREAT ctDNA trial.

9.3.2 Project summary table

| Project # | Tissue(s) | Biological methods | Estimated number of samples* | Statistical analysis |
|------------------|--------------------------------------|---------------------------|-------------------------------------|-----------------------------|
| TR1 | Blood (leftovers and unused samples) | To be defined | 22990 blood tubes for plasma | To be defined in the future |
| TR2 | Blood | To be defined | 5280 blood tubes for plasma | To be defined in the future |

Table 7: Project summary table

* Maximum of expected samples

10 Statistical considerations

10.1 Estimands

| Objectives | Endpoints | Estimands | | |
|---|---|------------|--|---|
| | | Population | Handling of intercurrent events | Population-level summary |
| Primary objective | Primary endpoint | | | |
| To evaluate whether Elacestrant can delay occurrence of distant metastasis or death when compared to standard endocrine therapy in ER+/HER2- breast cancer patients with ctDNA-relapse. | Distant metastasis free survival (DMFS) defined as the time from randomisation until first distant metastatic recurrence or death from any cause, whichever occurs first. Date of first distant metastatic recurrence will be taken into account regardless of the method of assessment. DMFS will be based on the disease assessment and date of death provided by the local investigator. | ITT | <p>A number of intercurrent events may occur between the randomisation and the first DMFS event, including:</p> <ul style="list-style-type: none"> • Interruption or discontinuation of protocol treatment • Start of new therapy prior to DMFS event • Occurrence and treatment of a locoregional recurrence • Occurrence and treatment of an invasive second cancer (breast and non-breast origins) <p>The treatment policy strategy will be applied for all intercurrent events, i.e., they will be ignored in the main analysis, consistent with the intention-to-treat principle.</p> | DMFS will be compared between the two treatment arms using a 2-sided stratified log-rank test. Hazard ratio for DMFS and the corresponding confidence interval based on the stratified Cox proportional hazards model Kaplan-Meier estimates of event-free probabilities at specified time points |
| Secondary objectives | Secondary endpoints | | | |
| To evaluate invasive disease-free survival (iDFS) between the 2 treatment arms | IDFS is defined as per the STEEP criteria and will be computed as the time between the date of randomisation and the date of the first occurrence of one of the following events: <ul style="list-style-type: none"> • loco-regional disease recurrence • distant metastasis • invasive contralateral breast cancer • invasive non-breast second cancer • date of death from any cause | ITT | <p>A number of intercurrent events may occur between the randomisation and the first iDFS event, including:</p> <ul style="list-style-type: none"> • Interruption or discontinuation of protocol treatment • Start of new therapy prior to iDFS event <p>The treatment policy strategy will be applied for all intercurrent events, i.e., they will be ignored in the main analysis, consistent with the intention-to-treat principle.</p> | Hazard ratio for iDFS and the corresponding confidence interval based on the stratified Cox proportional hazards model Kaplan-Meier estimates of event-free probabilities at specified time points |

| Objectives | Endpoints | Estimands | | |
|---|--|-----------|---|---|
| | <p>Date of first disease recurrence or second cancer will be taken into account regardless of the method of assessment.</p> <p>iDFS will be based on the disease assessment and date of death provided by the local investigator.</p> | | | |
| <p>To evaluate relapse-free survival (RFS) between the 2 treatment arms</p> | <p>RFS is defined as per the STEEP criteria and will be computed as the time between the date of randomisation and the date of the first occurrence of one of the following events:</p> <ul style="list-style-type: none"> • loco-regional disease recurrence • distant metastasis • date of death from any cause <p>Date of first disease recurrence will be taken into account regardless of the method of assessment.</p> <p>RFS will be based on the disease assessment and date of death provided by the local investigator.</p> | ITT | <p>A number of intercurrent events may occur between the randomisation and the first RFS event, including:</p> <ul style="list-style-type: none"> • Interruption or discontinuation of protocol treatment • Start of new therapy prior to RFS event • Occurrence and treatment of an invasive second cancer (breast and non-breast origins) <p>The treatment policy strategy will be applied for all intercurrent events, i.e., they will be ignored in the main analysis, consistent with the intention-to-treat principle.</p> | <p>Hazard ratio for RFS and the corresponding confidence interval based on the stratified Cox proportional hazards model</p> <p>Kaplan-Meier estimates of event-free probabilities at specified time points</p> |
| <p>To evaluate overall survival (OS) between the 2 treatment arms</p> | <p>OS is defined as the time between the date of randomisation and the date of death</p> | ITT | <p>A number of intercurrent events may occur between the randomisation and death, including:</p> <ul style="list-style-type: none"> • Interruption or discontinuation of protocol treatment • Start of new therapy prior to OS event • Occurrence and treatment of a disease recurrence (loco-regional or distant metastatic recurrence) • Occurrence and treatment of an invasive second cancer (breast and non-breast origins) <p>The treatment policy strategy will be applied for all intercurrent events, i.e., they will be ignored in the main analysis,</p> | <p>Hazard ratio for OS and the corresponding confidence interval based on the stratified Cox proportional hazards model</p> <p>Kaplan-Meier estimates of event-free probabilities at specified time points</p> |

| Objectives | Endpoints | Estimands | | |
|---|--|-------------------|---|---------------------------------|
| | | | consistent with the intention-to-treat principle. | |
| To characterize the safety and tolerability | Severity of adverse events and SAEs on-study graded according to NCI CTCAE Version 5.0 | Safety population | See Section 10.3.4 for details about the analysis of safety data | |
| To establish the patient-reported tolerability profile of both treatment arms | Worst scores reported on the treatment burden and selected symptom scales from the QLQ-C30, QLQ-BR42 and IL 46 questionnaires | Safety population | See Section 10.3.5.2.2 for details about the analysis of HRQoL data | |
| To compare the patient reported benefit between the two treatment arms | Change from baseline in the Global health status/QoL and physical functioning scale scores assessed over time with the EORTC QLQ-C30 | ITT | See Section 10.3.5.2.2 for details about the analysis of HRQoL data | |
| Exploratory objectives | Exploratory endpoints | Population | Handling of intercurrent events | Population-level summary |
| To assess ctDNA elimination rate | Proportion of patients who switched from a positive to a negative ctDNA status | Not applicable | | |
| To correlate ctDNA (ctDNA as categorical and continuous variable) kinetics with DMFS, iDFS, RFS and OS according to treatment arm | ctDNA kinetics: ctDNA as categorical (negative versus positive) and continuous variable at different time points during the 3-year period post randomisation | Not applicable | | |
| To identify primary tumour and plasma circulating biomarkers associated with benefit from elacestrant | Primary tumour and plasma circulating biomarkers | Not applicable | | |

10.2 Statistical design

10.2.1 Sample size determination

For the primary endpoint of DMFS, a total of 146 events will be needed to reject the null hypothesis using a stratified log-rank test at the two-sided level of 5% and 90% power under the assumptions of an HR of 0.58. Assuming proportional hazards under an exponential model and based on an anticipated median DMFS time of 12 months in the standard adjuvant endocrine therapy arm, this is expected to correspond to a median DMFS of 20.7 months in the elacestrant arm.

Based on an annual dropout rate of 5%, a total of 220 patients are expected to be randomised in a 1:1 ratio into the elacestrant and the standard adjuvant endocrine therapy arms. The number of events/sample size calculation accounts for two interim analyses at 50% of the planned total number of events (non-binding futility analysis and early efficacy) and at 70% of the planned total number of events (interim analysis for early efficacy) (See section 10.4).

Assuming that 11.5% of screened patients will be ctDNA positive during the screening phase, approximately 1960 patients should be successfully screened.

This sample size is derived from the following assumptions:

- The median lead time from ctDNA detection to occurrence of distant metastasis is approximately 11 months without treatment following ctDNA detection [54].
- The recent results from the EMERALD study showed an observed HR of 0.70 (95%CI: 0.55;0.88) for the endpoint of PFS in the overall population of patients in second or third-line metastatic BC comparing elacestrant to standard of care as per physician's choice [28].
- In the metastatic setting, the PADA-1 trial has already shown that for patients treated with a CDK4/6 inhibitor in combination with an AI, switching to fulvestrant upon detection of an ESR1 mutation in the ctDNA, is associated with an improvement in PFS versus continuing the same treatment (median 11.9 vs. 5.7 months, HR 0.61, p=0.005) [30].
- In the present study and based on the fact that patients in the control arm will continue the same endocrine treatment they were taking at the time of ctDNA detection, a large treatment effect (hazard ratio = 0.58) is considered for the power calculation.

The EORTC QLQ-C30 global health/qol and physical functioning scales will be secondary endpoints in this study. A difference of 10 points on the 100-point QLQ-C30 scale between the two arms will be considered as clinically relevant [55]. The standard deviation of this scale is approximately 20 points. With the 2-sided alpha set at 5% and a power of 80% to detect a difference of 10 points (effect size of 0.5), a minimum of 128 patients (64 per treatment arm) is required. Therefore, this study is sufficiently powered to detect clinically relevant differences in HRQoL.

10.2.2 Measures taken to minimise bias

10.2.2.1 Randomisation and stratifications

Patients will be centrally randomised through the RTSM module from Medidata randomisation system (for practical details, see chapter on patient registration and randomisation procedure). A minimization technique will be used for random treatment allocation between the standard arm and the experimental arm in an 1:1 allocation ratio and stratifying by the following factors:

- country
- duration of ET at the time of ctDNA detection (≤ 5 years vs. >5 years)
- stage (II vs. III)
- prior use of CDK4/6-inhibitor (yes vs. no)
- prior (neo)adjuvant chemotherapy (yes vs. no)
- ctDNA assay (Signatera from Natera versus others)

10.2.2.2 Other measures

The eligibility to the randomisation will be based on the Signatera assay which will be centralized therefore this would prevent from differential diagnosis bias.

The primary endpoint has been chosen to be distant metastasis free survival as this is a clinically relevant endpoint in this setting that would lead to treatment modification in any case and which could be objectively assessed.

Evaluation biases will be minimized by a schedule of assessments balanced between the treatment arms as defined in Section 7.3.

During the study, completion rates of the HRQoL questionnaires will be investigated at each time point. These completion rates will be reviewed twice a year together with other trial operating characteristics such as recruitment rates. HRQoL data collection, which depends on the voluntary participation of the patient, will be limited until year 2 due to the expected attrition and assessment fatigue within the population over time which hampers the feasibility of long-term evaluation of the treatment benefit. HRQoL administration will be limited to a few select time points linked to clinical visits to avoid undue patient burden and maximize compliance.

10.3 Statistical analysis plan

The study endpoints are listed in Section 3.2. The definition of the estimands (population-level summary of treatment effect) and the methods used to evaluate them are detailed in Section 10.1.

The statistical analysis will be performed by the EORTC using SAS® software, according to the Statistical Analysis Plan (SAP). The initial version of the SAP will be developed by the statistician before the randomisation of the first patient. This plan will include a more technical and detailed description of the statistical analysis described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. The SAP may modify what is outlined in the protocol when appropriate; however, any major modifications related to the primary endpoint definition or analysis will be described in a protocol amendment.

10.3.1 Accrual, study duration and timing of statistical analyses

10.3.1.1 Accrual duration

Under the assumption of an accrual rate of 40 patients screened/month in 120 sites once all sites are open and considering a stepwise accrual rate during the first year of accrual to take into account the opening of the sites, it is expected that the accrual duration for the screening period will be approximately 4.7 years and will be approximately 5.7 years for the randomised part to allow a

minimum of 1-year screening period for all patients (corresponding to a minimum of 3 screening blood draws during the screening period).

10.3.1.2 Study duration

All randomised patients will be followed up until 3 years after the last patient is randomised. At that time, some patients might still be on study treatment to complete at least 7 years of endocrine therapy as described in Sections 5.2 and 6.2.4. For these patients, data will be collected until their end of treatment as per the schedule of assessment as described in Section 7.4.5. Therefore, the maximal study duration can be greater than 8.7 years. The actual end of study is therefore defined as either 3 years after the last patient is randomised or the date of end of study treatment of the last patient still on treatment, whichever occurs last, and might last up to 11.7 years.

10.3.1.3 Timing of analyses

Three analyses are planned for this study:

- An interim analysis (non-binding futility and early efficacy) of the primary endpoint DMFS will be performed when 50% of the total required number of events will be observed (73 events). Under the alternative hypothesis, it is expected to take place approximately at 4 years after the start of accrual), when approximately 140 (64%) patients would have been randomised. Accrual in the study will not be interrupted during the conduct of this interim analysis. The results of this interim analysis will be made available before the end of accrual, this would allow not to expose patients to an ineffective drug in case of evidence of futility.
- An interim analysis for early efficacy of the primary endpoint DMFS will be performed when 70% of the total required number of events will be observed (102 events). Under the alternative hypothesis, it is expected to take place approximately at 4.9 years after the start of accrual, when approximately 176 (80%) patients would have been randomised.
- The final analysis of the primary endpoint DMFS will be performed when the required number of events are observed (146 events). The required total number of events is expected to be observed maximum 7 months after the end of accrual of the randomised part, corresponding to approximately 6.25 years after the first patient randomised. The actual accumulation of events will be monitored throughout the study depending on the actual accrual rate, actual randomisation rate and event rate.
- A follow-up analysis will be performed when the follow-up will be completed, i.e., when the last patient randomised has been followed up for 3 years after randomisation (corresponding to 8.7 years after the first patient randomised). In the follow-up analysis, all endpoints will be updated (including efficacy endpoints, safety and HrQoL).
- The last analysis will be performed at the time of end of study if some patients are still on study treatment at 3 years after the last patient is randomised, i.e., if the date of end of study would correspond to the date of end of treatment of the last patient still on treatment as defined in the above Section 10.3.1.2.

10.3.2 Analysis populations

- Intent-to-treat population: All randomised patients according to the arm they were allocated to.
- Per protocol population: All randomised patients who meet the important eligibility criteria as prespecified in the medical review plan and have started their allocated treatment (i.e., received at least one dose of the protocol treatment)

- Safety population: All randomised patients who have started protocol treatment (i.e., received at least one dose of the protocol treatment). Patients will be analysed according to the treatment actually started, regardless of the treatment assigned.

Potential eligibility problems and whether patients do meet all important eligibility criteria as prespecified in the medical review plan will be assessed by the Medical Representative at time of medical review.

10.3.3 Patient disposition, data recoding and display

Patients' demographics, baseline characteristics, prior and concomitant medications, treatment exposure, protocol compliance and study withdrawals will be summarized by treatment arm in the intent-to-treat population.

For categorical variables, frequency tables (with %) will be presented with descriptive listings of details specified in text fields, when appropriate. Continuous variables will be reported using median, range and interquartile range.

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomisation – date of past event + 1) and presented using the median and range. For example, on the randomisation checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomisation – last administration/diagnosis +1). Other delays (e.g., re-treatment delays) are presented as continuous variables using the median and range.

HRQoL data from EORTC questionnaires will be scored according to the algorithm described in EORTC scoring manual [40]. All scales and single items are scored on categorical scales and linearly converted to 0-100 scales.

A CONSORT diagram will be used to document the flow of patients through the various stages of the study.

The number of patients included in the various analysis populations will be presented in a table and reasons for exclusions will be detailed in listings.

10.3.4 Safety

Safety analyses will be performed on the Safety population.

10.3.4.1 Periods

Adverse events will be analysed in 3 categories defined as follows.

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period, defined as the period between the date of randomisation and the date of the first administration of the study treatment. For patients who never started treatment, the pre-treatment period is assumed to end on the day of randomisation.
- Treatment-emergent AEs (TEAEs): AEs that developed, worsened or became serious during the on-treatment period, defined as the period from the first administration of the study treatment to and including 30 days after the day of last protocol treatment administration.

- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period from the end of the on-treatment period and until the end of follow-up period. For patients who never started treatment, the follow-up period is assumed to start on the day of randomisation.

10.3.4.2 Safety analyses

10.3.4.2.1 Adverse events

Adverse event incidence tables will report:

- all AEs irrespective of their relationship to treatment
- the AEs related to the treatment (excluding those declared not reasonably possibly related to the treatment, but including those with relationship not assessable)
- the AEs leading to permanent treatment discontinuation

The worst grade of the AEs per patient and per CTCAE term over each period will be tabulated by treatment arm. Adverse events will be graded according to the CTCAE version 5.0. Summaries will be provided for all grades combined and for Grade ≥ 3 (including Grade 5). Missing grades, if any, will be included in the “all grades” category.

The percentage of patients on each treatment arm presenting severe treatment-related AE (grade ≥ 3), of patients reported to have died of toxicity and that of patients who stopped treatment due to toxicity will also be calculated and the 95% confidence interval will be presented.

10.3.4.2.2 Serious adverse events

For the reporting of SAEs:

- the study safety overview table will list the number of reported SAE terms, SAR terms and SUSAR terms per treatment arm and the number of reported death and toxic death cases;
- line listings of SAEs and of SARs will be provided;
- the number of SAEs and SARs per System Organ Class and Preferred Term will be tabulated per treatment arm and overall.

10.3.4.2.3 Laboratory variables

For laboratory variables (haematology, biochemistry parameters) will be graded according to CTCAE version 5.0:

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the on-treatment period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

10.3.5 Study endpoints

10.3.5.1 Primary endpoint: Distant Metastasis-Free Survival

The definition of the primary endpoint DMFS is detailed in Section [8.1.2.2](#) and the corresponding primary estimand associated with the primary endpoint is provided in Section [10.1](#).

Primary efficacy analysis will consist of DMFS comparison between the elacestrant arm and the standard adjuvant endocrine therapy arm through a logrank test stratified by the stratification factors as entered at the time of randomisation. Based on the actual distribution of number of events within strata, some stratification factors might not be included in the stratified test to minimize the risk of power loss and will be described in the SAP. An overall two-sided Type I error rate of 5% will be used for statistical testing and will be split between the interim analyses for early efficacy and the final analysis as detailed in Section 10.4.

The HR estimates and corresponding confidence intervals will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the logrank test described above.

The time to event quantiles and probabilities of being event-free at different time points (calculated using the Kaplan-Meier methods) as well as corresponding 95% CIs will be presented by treatment arm (elacestrant arm and the standard adjuvant endocrine therapy arm). The Kaplan-Meier curves will also be provided.

Sensitivity and supportive analyses of DMFS will be performed as specified in the SAP.

10.3.5.2 Secondary endpoints

10.3.5.2.1 Efficacy endpoints

The definition of the secondary efficacy endpoints are detailed in Section 8.1.2.3 for invasive disease-free survival (IDFS), in Section 8.1.2.4 for relapse-free survival (RFS) and in Section 8.1.2.5 for overall survival (OS). The corresponding secondary estimands associated with the secondary endpoints are provided in Section 10.1.

The same statistical methods as described for the primary endpoint will be used except that no statistical testing will be performed as follows:

- The HR estimates and corresponding confidence intervals will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the primary endpoint.
- The time to event quantiles and probabilities of being event-free at different time points (calculated using the Kaplan-Meier methods) as well as corresponding 95% CIs will be presented by treatment arm. The Kaplan-Meier curves will also be provided.

10.3.5.2.2 HRQoL

Prior to analysing the HRQoL outcomes, the completion rates will be evaluated and if needed the time windows adapted. Questionnaires that cannot be assigned to a HRQoL assessment time point will be considered invalid for the analysis.

Missing data is a potential major source of bias in HRQoL assessment. Therefore, the missingness mechanism will be investigated prior to initiating the HRQoL analysis. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building might be used in order to investigate whether the missingness mechanism is linked to selected prognostic variables.

Evaluation of the patient reported tolerability profile of both arms will be performed via descriptive non-comparative statistics in each treatment arm. The worst score reported for each selected scale per patient from first dose until 30 days after last dose of protocol treatment or week 80 (whichever comes first) will be presented in the safety population. Multiple imputation will be used to correct for missing data. Selected scales of interest are all symptom scales from the QLQ-C30, QLQ-BR42 and IL46.

Evaluation of patient reported benefit will be done via modelling selected functional scales: global health/QoL (QLQ-C30) and physical functioning (QLQ-C30). Other functional scales will only be analysed descriptively. Changes in HRQoL scores over time will be evaluated with a repeated measurement modelling using a mixed effect procedure (MMRM). A linear mixed model with treatment, a time effect, a time-treatment interaction and possibly other baseline covariates as fixed effects and a patient specific random effect will be fitted. Prior to reducing the model, the most suitable covariance structure should be determined on the basis of Akaike's Information Criterion (AIC), starting from an unstructured covariance matrix. Covariates other than the treatment and the time indicator may be dropped from the model based on a 5% significance level for the Type III fixed effect test. The main test will be obtained by contrasting the scores in the two treatment arms over all post-baseline time points (F-test). Minimal important differences (MID) will be used to assess the clinical meaningfulness of the observed changes. The repeated measures analysis will be supplemented by a cross-sectional analysis. Graphs will display the mean score by treatment group with their 99% confidence intervals.

Once the main analysis is completed, sensitivity analyses may be undertaken to verify the robustness of the results vis-à-vis the missing data.

10.3.5.2.3 Translational Research

Detailed statistical considerations will be provided in specific TR project description and analysis plans when the available leftovers will be known.

For the pre-defined translational research project aiming at evaluating the correlation between circulating biomarkers with the clinical outcomes, their analyses will be exploratory only as the distribution of presence of the prespecified in the future molecular aberrations are expected to only in a % in the patient sample. All analyses will be performed at 5% significance level.

10.3.5.3 Exploratory endpoints

10.3.5.3.1 ctDNA kinetics

ctDNA kinetics will be analysed in the ITT population. At each time point, descriptive statistics will be displayed by treatment group. ctDNA kinetics will be considered as a categorical variable (negative versus positive).

10.3.5.3.2 Primary tumour and plasma circulating biomarkers

Analysis of exploratory endpoints will be described in the SAP.

10.3.5.3.3 ctDNA elimination rate

Corresponding 95% confidence interval based on the binomial distribution will be provided. ctDNA elimination rate will be analysed at month 1 and at month 4 after randomisation as per the endpoint defined in Section 9.2.2.1.

10.3.6 Pre-planned subgroup analyses

Subgroup analyses will be conducted to assess the consistency of the results for the primary endpoint and secondary endpoints across the following prespecified key subgroups:

- country
- duration of ET at the time of ctDNA detection (≤ 5 years vs. > 5 years)
- stage (II vs. III)
- prior (neo)adjuvant chemotherapy (yes vs. no)
- setting of prior chemotherapy treatment (neo-adjuvant vs. adjuvant)
- prior use of CDK4/6-inhibitor (yes vs. no)
- tumour grade (1 vs. 2 vs. 3)

These subgroup analyses will be exploratory. The presence of treatment heterogeneity will be examined by testing the presence of an interaction in a Cox model with the key variable of interest, treatment indicator and the interaction term as covariates and stratifying for the other stratification factors (as used in the other stratified analyses described above). In case at least one stratum for a stratification factor has fewer than 10 events, the stratification factor that contains the level with the smallest size will be dropped from the stratified analysis. The hazard ratio and associated confidence interval for the treatment effect will be calculated within the subgroups of interest from the model. The same level of confidence as for the overall population will be used for the confidence intervals in the subgroups. Furthermore, the estimated hazard ratios in all subgroups and the p-value for interaction will be displayed on a forest plot.

In addition, possible heterogeneity of the results between women and men and between patients below and above 70 years old will be similarly investigated.

The results of these subgroup analyses should be interpreted with caution. No type I error adjustment will be made for multiple testing.

10.4 Interim analyses / Decision rules

Two interim analyses are planned during the course of the study.

- One interim analysis is planned to assess the futility (non-binding) and the early efficacy of the experimental arm when 50% of the total number of events required have been observed (73 events) for the primary endpoint DMFS. This interim analysis is expected to take place approximately at 4 years after the start of accrual, when approximately 140 (64%) patients would have been randomised. The results of this interim analysis being made available before the end of accrual, this would allow not to expose patients to an ineffective drug in case of evidence of futility.

To assess futility of the experimental arm, the stopping boundaries are derived based on the O'Brien and Fleming β -spending function depending on the actual number of events observed. For the experimental treatment group, the corresponding HR boundary for futility is 0.956 at 73 events. Therefore, if the observed HR is > 0.954 , the experimental arm will be

declared futile. In this scenario, there is a 55.4% probability to stop the study in case of futility of the experimental arm.

To assess the early efficacy of the experimental arm, the stopping boundaries are derived based on the O'Brien and Fleming α -spending function. For the experimental treatment group, the HR boundary is 0.5, corresponding to a 2-sided p-value ≤ 0.0035 . Under the alternative hypothesis, there is 26.3% probability to declare early efficacy of the experimental arm.

- One interim analysis planned to assess the early efficacy of the experimental arm when 70% of the total number of events required have been observed (102 events) for the primary endpoint DMFS. This interim analysis is expected to take place approximately at 4.9 years after the start of accrual, when approximately 176 (80%) patients would have been randomised. The stopping boundaries are derived based on the O'Brien and Fleming α -spending function depending on the actual number of events observed. For the experimental treatment group, the corresponding HR boundary for early efficacy is 0.614 at 102 events (2-sided p-value ≤ 0.0137). Under the alternative hypothesis, there is a cumulative 61.7% probability to declare early efficacy of the experimental arm.

Four additional events were needed to perform the two interim analyses.

Table 8: Summary of analyses

| Analysis | Years after FPI (approx., under DMFS HR = 0.58) | Planned accrual | Number of events (under DMFS HR = 0.58) | Cumulative Probability to stop for futility of experimental arm under DMFS HR=0.58 (false negative rate) | Cumulative Power (under DMFS HR=0.58) | Futility boundary | Efficacy boundary |
|---|---|-----------------|---|--|---------------------------------------|--------------------------------|--|
| DMFS IA 1 (non-binding futility + early efficacy) | 4 years | 140 | 73 | 1.1% | 26% | HR > 0.954 | HR $\leq 0.5^*$ p-value ≤ 0.0035 |
| DMFS IA 2 (early efficacy) | 4.9 years | 176 | 102 | N/A | 62% | N/A | HR $\leq 0.614^*$ p-value ≤ 0.0137 |
| Final analysis | 6.25 years | 220 | 146 | 10% | 90% | HR > 0.718* p-value >0.0456 | HR $\leq 0.718^*$ p-value ≤ 0.0453 |

*HR is provided only for information purposes. The interim and final decisions will be based on p-values.
 FPI: First patient in; IA: interim analysis; HR: Hazard ratio; DMFS: Distant Metastasis Free-Survival
 Note: numbers have been rounded. Calculations were made using East 6.5 software.

This trial will be monitored by the EORTC IDMC to review the results of the interim analysis for futility and early efficacy as described above. In addition, this study carries some operational and feasibility risks regarding the screening phase implementation. Therefore, a regular monitoring of the accrual rate, the randomisation rate (including ctDNA detection rate, rate of negative imaging among those ctDNA positive, rate of other reasons not to be randomised) and the event rate will be done to anticipate any major issues and allow the study team to take appropriate corrective actions if necessary. The IDMC may be consulted to make recommendations with regards to the conduct of the study based on this information.

Appendix A: Lay language protocol summary

EU trial number: 2022-501453-36-00:

An international, multicenter, randomised, superiority phase III, open label, 2-arm study to investigate distant metastasis free survival with elacestrant compared with standard endocrine therapy patients with ctDNA+ ER+/HER2- early breast cancer.

This study is about patients with a type of breast cancer called Estrogen Receptor (ER)-positive and Human Epidermal Factor-2 (HER2)-negative. These particular patients have been treated with surgery and chemotherapy and have received endocrine treatment for approximately the last 1 year to 7 years and half. Endocrine treatment stops the effect of estrogens on breast tumours that grow in its presence via the estrogen receptor. Among these patients, some have a higher risk of relapse (meaning that the cancer may come back and spread to other parts of the body). We aim to identify these patients and treat them before the cancer spreads to other parts of the body - this is called metastasis.

There have been studies conducted on several types of cancer which have shown that patients with circulating tumour DNA (ctDNA: small pieces of a tumour's genetic material released by tumour cells in the blood and detected via a simple blood draw) may have a cancer relapse and develop metastasis within one year, compared to patients with undetectable ctDNA.

The aim of this study is to identify patients at high risk of relapse by the presence of ctDNA in their blood and to prevent the development of metastasis by treating these patients with a new oral drug called elacestrant.

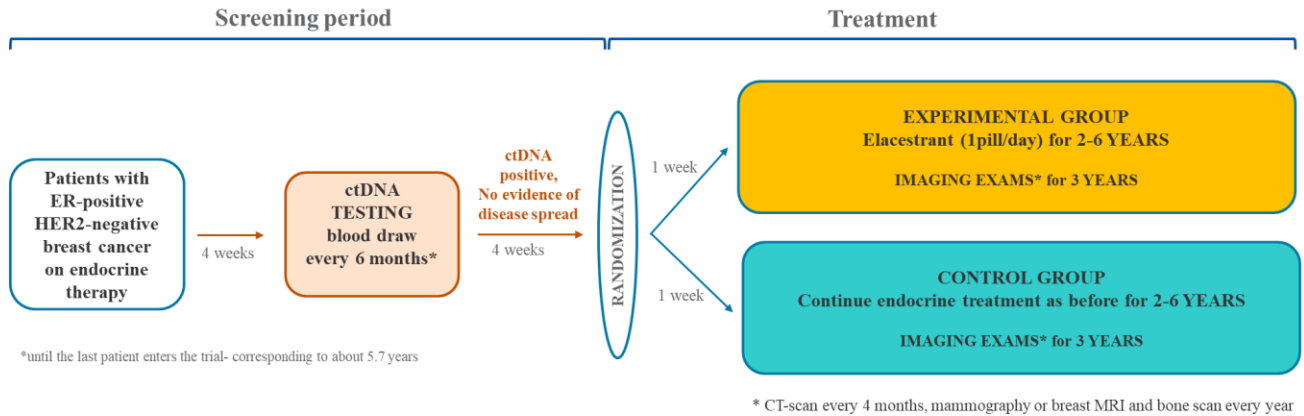
Elacestrant is a kind of anti-estrogen hormone therapy formulated in pill-form to be taken orally every day. It has already proven to be effective in patients whose breast cancer has spread to other parts of the body.

This study will be carried out in adult patients (of both genders) with ER-positive HER2-negative breast cancer who have undergone surgery and chemotherapy and have been treated with endocrine therapy. They must have been diagnosed with breast cancer since 1 year to 7 years and half ago to be candidates entering the study.

The main goal of the study is to show that treatment with Elacestrant, given when ctDNA is found in the blood, is better at preventing cancer relapse compared to continuing standard endocrine treatment.

This study also aims to study if ctDNA becomes undetectable in the blood after treatment with elacestrant, how long this takes, and if this means that the risk of the cancer coming back is reduced. The study will also look at the side effects of elacestrant and will compare the general wellbeing of patients treated with elacestrant and that of patients who continue the standard endocrine treatment.

Each patient will participate to the study as follows:



To find out if the activity observed with elacestrant is not caused by chance alone, we need to collect data from 110 who receive this treatment and 110 who receive the standard treatment. The data from these two groups of patients will be compared to see which treatment is better.

During the first part of the study, patients will be tested every 6 months for the presence of ctDNA in the blood, while continuing their normal treatment with endocrine treatment and their follow-up visits. If no ctDNA can be detected in the blood during the duration of the study, which represents a minimum of 1 year and a maximum of 5.7 years, patients will stop participating in the study.

However, if ctDNA is detected in the blood, patients will undergo imaging scans of the breast, chest, abdomen, pelvis and bones, to test if the breast cancer has not come back. If these tests do not show any sign of cancer, patients will enter the second part of the study. They will be assigned randomly to one of two groups: the first group will continue the same endocrine treatment they were receiving before, and the second group will receive elacestrant. Neither the researchers, the doctor, nor the patient will be able to choose the study group, allowing the comparison to be more objective.

The duration of the treatment will last 2 years for the patients who were on endocrine therapy for 5 years to 7 years and half, and 2 to 6 years for the patients who were on endocrine therapy for 1 to 5 years. During the first 3 years, patients will attend study visits and do imaging and blood examinations. Blood for ctDNA will be collected once during the first month of treatment and every 4 months thereafter. Imaging scans of the chest, abdomen and pelvis will be done during the first month of treatment and every 8 months thereafter. Breast and bone imaging will be organized once a year. Patients who continue treatment after 3 years will attend study visits and do blood examinations.

In practice, patients will undergo blood draws every 6 months during the ctDNA testing part of the study to detect the presence of ctDNA and qualify for the second "randomised" part of the study. After they enter the second part, independent of whether they are in the elacestrant group or control group, they will still undergo blood draws every 4 months to see if ctDNA is still present during/after treatment.

During the randomised part of the study, patients will be also asked to complete questionnaires on their general wellbeing. The questionnaires have been selected specifically for this study and are shown to be reliable and helpful to assess the patient's wellbeing. The patient responses will inform

researchers on the perceived benefit of the treatments as well as on the patient experience of side effects and symptoms during treatment.

In addition to the study treatment, and in order to answer several research questions patients will be asked provide samples of their tumour and blood.

This study will take place in several countries across Europe and on a global level. It is estimated that the recruitment of all patients will take 4.7 years. From the first patient enrolled to the visit of the last patient, the study will last: 8.7 years.

Studies in patients with breast cancer that has spread to other parts of the body showed that elacestrant prevents further spread of the tumour and reduces the size of the cancer already present. However, this may not be true in patients without evidence of disease spread. Therefore, patients participating in this study may not benefit from elacestrant and only suffer from its side effects. The most frequent side effects of elacestrant are nausea, vomiting and tiredness. To reduce these risks, patients will undergo visits to the hospital frequently in order to identify and treat early any side effects that may appear. Moreover, we will regularly check new information related to the activity of elacestrant, without waiting the end of the study. For this reason, we planned an evaluation of data related to the activity of elacestrant before the end of the study. If elacestrant seems not to benefit patients the sponsor will stop the study early.

It is believed that patients who tested positive for ctDNA in their blood but have normal imaging scans, may have breast cancer cells spreading to other parts of the body. Treatment with elacestrant should delay or kill any breast cancer cells that are in the process of spreading to other parts of the body better than endocrine therapy. In conclusion, we are confident that the benefits of participating in this study and taking elacestrant are greater than the risks.

Appendix B: Trial Governance and Data Monitoring

1 Study committees

1.1 Study Management Group (SMG)

The Study Management Group is set up for this study. It consists of the EORTC Headquarters team in charge of running the study (clinical research physician, statistician, clinical scientist, project manager and data managers) and the principal study coordinator.

The EORTC Headquarter team is responsible for the day -to-day conduct of the trial. The Study Coordinator will assist the team in case of problems with patient evaluation (eligibility, treatment compliance, safety).

The Study management Group also performs the medical review as indicated below.

1.2 Study Steering committee (SSC)

The Study Steering Committee for this study is composed of the study coordinators, a representative of each collaborative academic group, and the EORTC Headquarters team (Medical Representative, and Statistician).

This committee provides the general oversight of the study and has the executive power. The SSC monitors study progress and conduct and advises on its scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the independent data monitoring committee.

1.3 Study Steering committee for the Translational Research (TR-SSC)

The Study Steering Committee for the Translational Research for this study is composed of the study coordinators, the chair of the TR-SSC, external scientists based on their expertise and at least one representative of the EORTC Headquarters (TR scientist)

This committee provides the general oversight and has the executive power over the translational research of the project. The TR-SSC will define the translational research of this project (defined or undefined as per chapter 9).

1.4 Independent data monitoring committee (IDMC)

The independent data monitoring committee for EORTC studies (IDMC) is in charge of the independent oversight of this study, according to the EORTC Policy "Independent Data Monitoring Committees" and its functioning is ruled by the charter annexed to the Policy.

The study-specific experts on the IDMC performing this review will be selected for their relevant expertise with the disease and/or treatments assessed in the study.

The IDMC reports its recommendations in writing to the Study Management Group through the project manager to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups...).

2 Data Monitoring

2.1 Monitoring during medical review meetings

The medical review will be performed on a regular basis by the Medical Representative and the Medical Advisor assisted as needed by the study management group. The main study coordinator will, in particular, support the Medical Representative and the Medical Advisor during the medical review process and will assist the team in case of problems with patient evaluation (safety, eligibility, treatment compliance). The main study coordinator is also responsible for the review and approval of the medical review plan and medical review reports.

If at any time during the course of the study, the medical review identifies safety signals or other elements that could affect the potential risks and benefits to the study participants. These will be reported to the Study Steering Committee and may trigger a review by the EORTC Independent Data Monitoring Committee (IDMC).

2.2 Monitoring by the IDMC

The study may be subject to periodic review for feasibility, data quality and evidence of treatment harm as per EORTC Policy "Independent Data Monitoring Committees". The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up. These periodic reviews are to stop at primary study analysis but can be extended beyond that point in time by decision of the IDMC.

The IDMC will review the trial whenever safety problems or other elements are identified during the medical review or by the SMG and/or SSC that could affect the potential risks and benefits for study participants. Such emergency IDMC review may be created upon request of the study team and upon decision of the IDMC chair.

The IDMC will also review the intermediate reports of accumulating data according to the study interim monitoring plan described in the statistical section of this protocol. If a decision is made to continue without change, the IDMC may advise on the frequency of future reviews of the data on the basis of accrual and event rates.

While the trial is ongoing the accumulating data will generally remain confidential, unless the SSC and IDMC agree that the data should be made public.

Appendix C: Study suspension or study termination

EORTC reserves the right to terminate this study prematurely or discontinue parts of this study at any time for ethical/safety or unexpected operational/logistical reasons.

Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

All the investigators will be immediately informed of the suspension or termination of the study using expedited means (e.g., e-mail, investigator letters, Ethics Committee information).

The patients should be contacted by the investigators to be informed of the suspension or the termination of the study and to inform them of the actions that need to be taken.

Appendix D: First act of recruitment

The start of the study is the first act of recruitment. This is the date of signature of the informed consent by the first patient in the study.

Appendix E: Regulatory and ethical considerations

1 Regulatory considerations

The study is submitted by the principal investigator or the national coordinator or the sponsor, in accordance with local regulations, for review and approval by an appropriate Independent Ethical Review Committee (IEC)/ Institutional Review Board (IRB) and a National Competent Authority if required by the national laws of the countries where the study is conducted. Other national approvals may also be required from the regulatory bodies within the member state.

The study cannot start at a participating site until written approval by the relevant Ethics Committee(s) has been obtained and the local regulatory requirements have been complied with.

The sponsor will provide a copy of the final protocol, protocol amendments, subject information sheets, consent forms, investigator brochure and all other applicable study documentation for locally required submissions.

The investigator and sponsor ensure that the study is conducted in full conformance with the principles of the Declaration of Helsinki, as revised from time to time (available on the World Medical Association web site (<http://www.wma.net>)) and with the laws and regulations of the country in which the research is conducted, whichever provides the greatest protection of the patient.

The sponsor and investigator ensure that the study is conducted in compliance with the protocol, the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP E6 (R2)), the Regulation EU No 536/2014, the Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR), and with the EU General Data Protection Regulation (GDPR) or other national laws and regulations as applicable.

2 Patient involvement in study design

EORTC encourages our patient partners to participate in the review of protocol synopsis and patient information sheet and informed consent.

To ensure the relevance and high quality of the research, protocol synopsis is reviewed by the EORTC Protocol Review Committee. It is composed of independent external oncology experts, methodologists, and patient experts whose contribution aims to add a unique patient's perspective to the study. Reviews of patient information sheet and informed consent are made by the EORTC Group of Patient Experts helping us to strike the balance between completeness of the information, document length and relevance of the research objectives for the patients.

Both groups are multinational, diverse, focus on different types of cancer and involve people with different personal experiences.

Furthermore, EORTC has an advisory patient panel whose main objective is to provide an independent voice of "lived experience" of cancer to EORTC and advise on different aspects of patient involvement, including the strategy. The patient panel is composed of independent patient advocates, former patients and caregivers of different age, gender and with different personal

experiences of a range of cancers. Built in the spirit of co-creation, patient panel is supported in its work by one medical doctor and a Headquarters staff member.

3 Statement of compliance with EU General Data Protection Regulation (GDPR)

EORTC, in its role of Sponsor and Data Controller of the clinical study ensures that the processing activities on the personal data in scope of this study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR EU 2016/679), its subsequent amendments and any additional national laws, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organisational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and processed personal data, EORTC, in its role of Data Controller, declares that:

- It sufficiently involved and consulted the data protection officer with regards to all the aspects relevant to the compliance of data processing activities performed in the scope of study, it performed a data protection impact assessment and implemented the eventual mitigation actions prior start of the study.
- All clinical trial information is recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.
- Ensured that appropriate technical and organisational measures are implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network, such as but not limited to:
 - restriction of physical access to the offices and information processing facilities to employees, personnel and visitors;
 - monitoring of the reception areas for offices and information processing facilities by a receptionist or security guard; controlling out of hours access;
 - provision of access cards and keys to data centres, server to authorized persons only; performing regular reviews of access rights;
 - allowing authorized access to personal data, as applicable and justified;
 - ensuring sustainable identification and authentication in virtual environment; centrally logging user access in virtual environment;
 - implementing the pseudonymisation and/or encryption of personal information, where applicable or required;
 - implementing network, application, database security by means of firewalls and antivirus/anti-malware;
 - ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures; and response to such attacks;
 - the ability to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
 - logging of security events/incidents in information systems; implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents;
 - ensuring that information systems, computers and software involved in the performance of the services provided in the Study are backed up;

- a process for regularly testing, assessing and evaluating the effectiveness of technical and organisational measures for ensuring the security of the processing;
- implementing procedures for reporting and handling personal data breaches;
- implementing procedures and practices for secure destruction of paper documents containing personal data;
- implementing business continuity procedures ensuring that Sponsor can continue to provide services through operational interruption; all locations, personnel and information systems that are used to perform services for the study will be covered.

Ensured that staff involved in conducting the clinical study is suitably qualified by education, training and experience to perform their tasks, including but not limited to data protection and data privacy rules applicable to their tasks.

EORTC as Data Controller will ensure technical and organizational security measures described above are regularly reviewed and updated in accordance with evolving technology.

EORTC may apply additional statutory requirements, where applicable in the national laws, and implement necessary security measures.

Besides, EORTC as Data Controller in the study:

- ensures that data subject rights are informed about their rights and that the requests are addressed in a timely manner.
- processes personal data in a lawful, fair, and transparent manner;
- collects personal data only for purpose to conduct the study;
- ensures appropriate security of personal data and maintain its integrity and confidentiality; ensure that data collected and processed in scope of the study are accurate and up-to-date;
- ensures restricted access of its employees, processors, authorities, and subcontractors to personal data;
- maintain all records of processing activities necessary to demonstrate that personal data was only collected, processed and disclosed in compliance with the GDPR or other applicable data protection laws.

Before starting any new collaboration, EORTC performs processor and partner assessments, including the GDPR compliance assessment. Only qualified vendors will process data collected in scope of the study, as per contractual agreement between them and EORTC.

In the event of an actual or reasonably suspected personal data breach, breach of any data protection agreements in scope of the Study, or breach of applicable law, such as but not limited to GDPR, EORTC imposes to the processors and partners to:

- notify EORTC without undue delay (and in any event, within 24 business hours of Vendor/Supplier official confirmation of the actual or suspected personal data breach);
- at Vendors or Partners' sole cost and expense, undertake an appropriate investigation and all remediation efforts necessary to rectify and prevent a recurrence of the personal data breach or breach of applicable data protection laws;
- in the case of an actual or suspected personal data breach, as part of the remediation efforts, to collaborate with the Data Controller in the process of notification to all individuals whose

personal information may have been affected, with content required under GDPR and satisfactory to the Data Controller.

For any questions regarding data protection in context of this study, please contact dpo@eortc.org.

4 Protection of patient's identity

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient. In order to avoid identification errors, the patient's code (maximum of 4 alphanumeric) and year of birth will also be reported on the case report forms.

EORTC monitors or delegates of EORTC have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under the clinical trial framework, including the guidelines applying to the clinical research field, such as but not limited ICH- GCP obligations in scope of the study conduct. Staff involved in the performance of this task is sufficiently trained on personal data protection rules and is abided by additional stricter confidentiality clauses as compared with other staff members.

5 Informed consent form and procedure for obtaining patient's consent

5.1 Informed consent form

The Patient Information Sheet and Informed Consent Form (PISIC) describes the following items:

- the investigator and sponsor contact details
- the aims, description and course of the study (tests and procedures, treatment and mechanism of treatment allocation)
- the possible adverse events and potential hazards to which the patient will be exposed including risks related to a pregnancy
- benefits and interest in participating in the study
- costs related to study participation
- alternative treatment
- withdrawal from the study
- treatment after stopping or at the end of the study
- publication of study results
- translational research
- protection, privacy and confidentiality of any patient data
- insurance and liability
- notification of new information
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

At time of site authorization, the sponsor will provide a copy of the approved version of the PISIC to be used. The investigators are not allowed to make any changes to the approved version of the PISIC unless these changes are non-substantial for the sponsor, such as but not limited to adding the hospital logo and completing contact person's details.

The PISIC to be provided to patients shall be revised whenever important new information becomes available that may be relevant to the patient's consent. Any substantial amendment to the PISIC shall receive the IRB/IEC's approval/favourable opinion in advance of use.

5.2 Recruitment and informed consent procedure

The provisions described below are subject to variations depending on the country and its national laws, but also on the hospitals where the patients will be recruited.

A description of this clinical study will be available on public registries ([Appendix O](#)). The sponsor, some participating sites and networks of investigators may also publish information about the trial on their own websites.

The informed consent process can only start once the study has been given a favourable opinion by the IRB/IEC's and has been approved by the National Competent Authorities as required by the national laws of the participating country(-ies). Also, the Investigator authorization procedure must have been completed by the Sponsor or its authorized representative(s) ([Appendix F](#)).

Patients should be identified as potentially eligible by a healthcare professional who is responsible for the patient. This is to ensure that medical confidentiality is adhered to. Patients will be assessed for their potential eligibility by a healthcare professional that is authorised to recruit to the study.

Once a patient has been identified and assessed as potentially eligible for the study, the patient should be approached and informed about the study.

The person informing the subject on the study must be familiar with all aspects of the study as described in the latest IEC/IRB approved version of the protocol.

The investigator, or another member of the clinical team, should discuss the study with the patient and provide the patients with the opportunity to understand the objectives, risks and inconveniences of the study and the conditions under which it is to be conducted. The information should be provided to subjects in both oral and written forms. The language used to inform the subject, both oral and written, should be concise, should use layman's terms and should be understandable to the patient and an impartial witness/interpreter, when applicable. The person obtaining the informed consent must have the patient's medical notes and the current IEC/IRB approved versions of the PISIC available during the discussion. Other study documents may also be used during the interview (e.g., subject diaries, study schedule sheets).

All patients should receive the appropriate version of the written information and will be asked to read and review it.

Usually, if the patient is considering participating in a clinical study, he/she may take the PISIC home to discuss with family and friends.

All patients must have the cognitive ability to provide a legally effective informed consent for study participation. Therefore, for patients not qualified to give or incapable of giving consent, written consent cannot be obtained from the patient's legal representative.

In the case where the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. An impartial witness is a person, who is independent of the study and cannot be unfairly influenced by people involved in the study, who attends the informed consent process if the patient cannot read the PISIC. After the patient has/have orally consented to participation in the study, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood.

Neither the investigator nor any member of the study team shall coerce or unduly influence a subject to participate or to continue to participate in a study. The investigator or designee must explain to the subject that the participation to the study is voluntary and that the subject is free to refuse to enter the study or to withdraw from it at any time, for any reason without any impact on the patient's subsequent care.

It is the responsibility of the investigator or a person designated by the investigator (if acceptable by national regulations) to obtain a signed, written informed consent from each potential subject prior to any study-related procedure being carried out. The informed consent is applicable throughout the subject's participation to the study. It is commonly accepted that subject should have a minimum of 24 hours between the date the PISIC is provided to the patient and the actual date when the patient signs the PISIC. The date and time the study was discussed and the date the PISIC was given to the subject must be documented in the patient's medical records.

In addition, the person obtaining the patient's consent should inform relevant team members of the treatment decision for the patient.

The written PISIC must be dated and personally signed by the investigator or authorised sub-investigator and the patient giving consent.

An original copy of the signed PISIC will be retained in the Investigator's Study File (ISF) and must be made available for monitoring, audit or inspection. Another copy of the signed PISIC is given to the patient.

EORTC Headquarters does not collect any data about patients before the patient consented to participate to the study. To confirm patients' eligibility to the study, the investigator or a person designated by the investigator transmits their personal data to the EORTC Headquarters in a coded (pseudonymised) form.

In case of new information that might affect the patient's willingness to continue participating in the study or results in significant changes in the risk/benefit assessment, the PISIC will be reviewed and updated if necessary by the sponsor. All patients, including those already being treated, should be informed of the new information, given a copy of the revised PISIC or PISIC addendum (as applicable per national regulations), and give their consent to continue in the study.

Appendix F: Investigator authorization procedure

Instructions for Non-EORTC investigators can be found in their group specific appendix (GSA) (if applicable).

Prior to authorization, EORTC Principal Investigators (PI) will need to provide the following documents to EORTC Headquarters:

- A recent curriculum vitae (CV) in English signed by the PI with proof of GCP training. At the time of site authorization, the CV should not be older than 2 years.
- The Confirmation Of Participation (COP) form signed by the PI. Through this document the PI confirms the site participation to the study, provides the estimated recruitment number, provides site contact details and, if applicable, informs EORTC study team on any potential service facility.
- The Confidentiality agreement and Interest Disclosure Form signed by the PI. Through this document the PI declares any interest that could potentially conflict with activities performed in scope of the study. It aims to point to the existence of eventual conflict of interest and clarifies its nature in order to decide on adequate actions (if any).
- The protocol signature page of the applicable protocol version signed by the PI.
- The signed site-specific study agreement between EORTC and PI's institution.
- For countries outside the EU: A copy of the favourable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- In case protocol-related activities take place at another institution (service facility), i.e., outside the authorized institution, details on this institution and approval of an ethics committee (if applicable) should be in place prior to activation. Please keep in mind that all communication is done ONLY between the primary institution and EORTC Headquarters.
- The Study Tools Access Log listing the site personnel that require accesses to the study tools. Note: It is the responsibility of the PI to maintain at site a Delegation of Responsibilities Log listing all qualified and trained personnel to whom the PI has delegated significant trial-related duties. In case trial-related duties are delegated to personnel at another institution (service facility), these persons should also be listed on the Delegation of Responsibilities Log.
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.
- The completed study drug delivery address form.
- Receipt of the study drug should be confirmed prior to randomisation of the first patient.
- The completed sample(s) (HBM) collection kit delivery address form. Receipt of the sample collection kit(s) should be confirmed prior to authorization.
- The Acknowledgement of Investigator Brochure (IB) signed by the PI.
- Any other study-specific document, if applicable.

The institution specific list of all documents as required by this protocol, your group and/or the applicable national law will be included in the trial start-up package.

With exception of the institution agreement, all originally signed documents should be stored at the institution in the Investigator Study File (ISF) and a copy is provided to EORTC Headquarters.

PI will be authorized to register patients in this trial as soon as:

- All the site-specific documents as listed above and indicated in the trial start-up package have been completed and returned to EORTC Headquarters.
- The site-specific study agreement has been fully executed.
- All applicable national legal and regulatory requirements for the authorization of the site are in place.
- A confirmation of training of the PI is available at EORTC Headquarters.
- The site has received and confirmed the initial supply of the sample collection kit(s) (for any study where sample collection kit(s) are provided prior to authorization).

Appendix G: Patient registration & enrolment procedure

1 Registration

Patient registration will only be accepted from authorized investigators (see chapter on “investigator authorization procedure”).

All patients that have signed informed consent should be registered directly on the Medidata Rave EDC system, accessible 24 hours a day, 7 days a week (please consult guidelines for completion of Case Report Forms for further information). To access Medidata Rave EDC system, the investigator needs to accept a study invitation e-mail, which will be triggered by the EORTC. This allows the investigator to create an iMedidata account. If the investigator already has an iMedidata account, the invitation can also be accepted after logging in to <https://www.iMedidata.com>.

In case of problems, investigators can contact the EORTC study team using the study email address (2129@eortc.org).

A unique Subject ID is allocated to the patient upon submission of the registration form. This number allows the identification of the patients in Medidata Rave EDC.

2 Screening and eligibility check

A patient can only be enrolled after verification of eligibility and stratification factors. Both the eligibility check and randomisation must be done before the start of the protocol treatment.

2.1 Eligibility check

After all eligibility-related data have been completed on the appropriate CRFs in the Screening folder and the subject meets all eligibility criteria as defined in the protocol, the subject can be enrolled.

For detailed description on data needed for the eligibility check, please refer to the guidelines for completion of Case Report Forms.

2.2 Randomisation

The Randomisation form will appear automatically when all eligibility criteria are fulfilled. The subject is ready to be randomised when all information reported on the form is correct.

3 Enrolment

Once eligibility has been verified and the subject is randomised, the subject is enrolled and a treatment arm is allocated to the patient.

Appendix H: Forms and procedures for collecting data

Patient information will be reported on the electronic and paper CRFs specifically designed by the EORTC Headquarters for this study. Clinical data should be entered into the database or data collection tool directly from the source documents.

Data should be sent electronically to the EORTC Headquarters through the Medidata Rave EDC system (<https://www.iMedidata.com>), including the HRQoL questionnaires. These are paper forms that are completed by the patients and then have to be encoded electronically by the site staff. A copy of these questionnaires should be sent to EORTC Headquarters by one of the following means:

- By scanning and e-mailing the forms to 2129@eortc.org
- By fax, to the attention of Study 2129 Clinical Data Manager (see CRF completion guidelines)
- By post to the EORTC Headquarters:

(Study 2129 Clinical Data Manager)
EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

The original source documents should be kept on site.

The paper CRF(s) will be made available to the institution at the time the institution is authorized and shall be handled according to the "guidelines for completion of case report forms".

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see appendix on Reporting of Serious Adverse Events and Pregnancies).

The electronic CRFs to be completed for a patient and their submission schedule are available on the Medidata Rave EDC website immediately after the registration and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

All data must be electronically submitted and signed by the responsible (sub-)investigator.

All data that is generated at site will be available to the investigator at all times during and after the trial for a duration defined by country specific regulation or until 25 years after the end of study, whichever comes first. This also includes data from external sources, such as central laboratory data, centrally read imaging data and ePRO data.

The list of staff members authorized to enter data must be identified on the Study Tools Access Log and sent to the EORTC Headquarters by the responsible investigator before the start of the study.

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as the requested information is available with the shortest delay, that the electronic forms are filled out completely and correctly and signed regularly.

The EORTC Headquarters will perform extensive consistency checks on the received data. Queries will be issued in order to resolve inconsistent data. The queries for the electronic forms will appear in the Medidata Rave EDC system and must be answered there directly.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study-related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should edit the concerned data point in the Medidata Rave EDC system. The data should then be signed again.

For more information, please refer to the study-specific guidelines.

Appendix I: Reporting of Serious Adverse Events and Pregnancies

ICH GCP and the EU Regulation 536/2014 require that both investigators and sponsors follow specific procedures when notifying and reporting serious adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An Adverse Event is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavourable and unintended signs (including an abnormal laboratory finding), symptoms or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An Adverse reaction of an investigational medicinal product is defined as “all noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events assessed by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means that causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

UAR: An Unexpected Adverse Reaction is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

The expectedness of an adverse reaction is determined by the sponsor in the reference safety information (‘RSI’). The RSI is contained in the Summary of product characteristics (‘SmPC’) or the IB.

When the outcome, specificity and/or severity of the adverse reaction is not consistent with the applicable RSI (reference safety information), this adverse reaction should be considered as unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious ADR, represent unexpected events.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of

relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A Serious Adverse Event is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e., an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Inpatient hospitalization: An inpatient admission, regardless of length of stay. Inpatient hospitalization signifies that the participant has been admitted to the hospital for inpatient care, either to the inpatient ward or to the emergency room for observation and/or treatment.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting by the sponsor to the appropriate Regulatory Authorities in accordance with Regulation 536/2014 and with respective national regulations.

OSE: Other Safety Event: Unexpected SAEs related to study required procedure (e.g.: blood collection). This abbreviation is an EORTC convention.

OSEs occurring in clinical investigations qualify for expedited reporting by the sponsor to the appropriate Regulatory Authorities in accordance with respective national requirements and regulations.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, a hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines, Social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention primary cancer progression (disease progression) and clinical events related to primary cancer progression are not to be reported as SAE, even if it meets the definition of SAE report seriousness criteria, **unless** the event is more severe than expected and therefore the investigator considers that the clinical significance deserves reporting.

3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded by the investigator using CTCAE v5.0 <https://www.eortc.be/services/doc/ctc/>

4 Causality assessment

The investigator is obliged to assess the relationship between the protocol treatment and the occurrence of each SAE following the definitions in this table:

| Relationship to the protocol treatment | Description |
|--|---|
| Reasonable possibility | There is a reasonable possibility that the protocol treatment caused the event |
| No reasonable possibility | There is no reasonable possibility that the protocol treatment caused the event |

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The causality assessment will be recorded on the SAE (e) form. If necessary, the reason for the causality assessment will be recorded.

5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following RSI (reference safety information):

- For Elacestrant: the RSI is the IB section entitled “Reference Safety Information”
- For Tamoxifen: the RSI is section 4.8 in the SmPC
- For Letrozole: the RSI is section 4.8 in the SmPC
- For Anastrozole: the RSI is section 4.8 in the SmPC

- For Exemestane: the RSI is section 4.8 in the SmPC

6 Reporting procedure for investigators

This procedure applies to all events as described in the table below.

| | |
|---|---|
| Registration until Randomisation (screening period for randomised trial only) | SAEs which cause the subject to be excluded from the trial or if they are a result of a protocol-specific intervention, including death due to any cause. |
| Randomisation till 30 days after last protocol treatment administration | All SAEs |
| From day 30+1 after last protocol treatment administration | Only SAEs considered to have a reasonable possibility to be related to the protocol treatment or study participation. |

Any secondary malignancy should also be reported in expedited way as a SAE with the appropriate seriousness criteria.

The investigator is encouraged to report additionally to the local marketing authorization holder or to the national Health Authority (as defined in the appropriate regulations): Adverse reactions related (e.g., adverse events where the causality to the administered medication cannot be excluded) to the authorized auxiliary medicinal products (goserelin, leuprorelin, triptorelin). However, if there is a Serious adverse reaction for the authorized AxMP where there is a suspicion of interaction with the IMP (elacestrant), the Pharmacovigilance Department will evaluate and, submit (if required) the report to EVCTM.]

All reporting must be done by the principal investigator or authorized staff member (i.e., staff on the access log) to confirm the accuracy of the report.

All SAE data must be reported electronically using the Medidata Rave system: www.imedidata.com

Investigators participating through non-EORTC groups should follow this EORTC protocol appendix instructions for the reporting of SAEs, pregnancies and special situations.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or site staff became aware of the event.

All SAE related information must be provided in English.

The relevant information must be summarized on the SAE (e)form. Local unstructured documents such as but not limited to hospitalization reports, autopsy reports, imaging, pathology reports and lab sheets, shall be provided in anonymous format only when explicitly requested by EORTC.

If the Medidata Rave system is out of service, contact the EORTC Pharmacovigilance team for further instructions to report - SAE /Pregnancy, unless otherwise specified in the Group Specific Appendix.

EORTC Pharmacovigilance:Email: pharmacovigilance@eortc.org

Tel No. +32 2 774 1676

Fax No. +32 2 772 8027

To enable EORTC to comply with regulatory reporting requirements, all initial SAE reports should always include the following mandatory minimal information:

- Protocol number
- Identifiable patient (SeqID)
- All study treatment details
- Identifiable reporting source
- SAE medical term of the –adverse event and seriousness criteria
- Causality assessment by the investigator

Follow-up information of SAE must be completed within 7 calendar days of the initial report.

SAE-Queries sent out by the EORTC Pharmacovigilance need to be answered within 7 calendar days. Urgent SAE-Queries should be answered within the requested timeline.

All forms must be signed by the principal investigator or any authorized staff member (i.e., on the access log). Note: paper SAE form must be dated.

7 Pregnancy reporting

Pregnancy occurring during a female patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance within the same timelines as an SAE (within 24 hours). The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported.

Any pregnancy in a female subject diagnosed during the treatment period or within 1 month (if treated with elacestrant or aromatase inhibitor or 9 months (if treated with tamoxifen) after last protocol treatment administration must be reported within 24 hours of first becoming aware of the event to the Medidata Rave system (www.imedidata.com) on an electronic pregnancy form, as described in the CRF guidelines.

If an SAE occurs in conjunction with the pregnancy, please also report the SAE as explained in the SAE reporting section.

8 Special situations reporting

List of special situations requiring reporting:

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** the study treatment is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Use outside of what is foreseen in the protocol:** this relates to situations where the study treatment is intentionally used for a medical purpose not in accordance with the protocol.

- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labelling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use. As a general principle, unintentional misuse, unintentional off-label use, and unintentional overdose are medication errors. However, whether a scenario is an error or not may depend on the reason or cause.

Reporting procedure for investigator for above events **must be reported in Rave as described in the CRF guidelines to the Sponsor regardless of whether or not an AE or SAE has occurred.** If any of these events are associated with an SAE, an SAE report must be provided to the Sponsor within 24 hours of awareness.

9 Reporting responsibilities for EORTC

As the Sponsor EORTC will be responsible for the reporting of SUSARs/unexpected SARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM), cooperating groups, and all participating investigators as applicable.

EORTC will also be responsible for the reporting of Annual Safety Report/Development Safety Update Report (ASR/DSUR) to the Competent Authorities, Ethics committees, CTIS portal and cooperating groups as applicable.

EORTC is not the marketing authorization holder for the Investigational Medicinal Product (IMP) and hence is a non-commercial sponsor. A single ASR/DSUR per trial will be prepared instead of per drug. The rationale is that the IMP is used amongst different EORTC trials which implies that there is no synchronous Development International Birth Date (DIBD) for the concerned IMP. As such EORTC has chosen to prepare for each EORTC trial a separate DSUR. This holds true for trials involving multiple drugs also.

The EORTC Pharmacovigilance will be compliant with the European Regulation 536/2014 and national legislation of the participating countries.

The EORTC Pharmacovigilance will forward all SAE reports to the appropriate EORTC Headquarters staff and to the appropriate parties recorded in the pharmacovigilance agreement when appropriate.

Appendix J: Quality assurance

1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using Medidata Rave EDC. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be marked as reviewed by the Clinical Data Manager. Inconsistent forms will be kept "in progress" until resolution of the inconsistencies.

2 Site monitoring

The EORTC Headquarters and/or delegate will perform on-site and remote monitoring visits as needed, according to the approved study-monitoring plan.

The first on-site visit in a participating site will be performed within 6 to 12 months after the first patient's enrolment at this site, providing that the CRFs are completed. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the previous visit.

The aim of the on-site monitoring visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the patient's source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to assist the site in resolving any outstanding queries
- to control the drug accountability process

3 Audits and Inspection

The EORTC is responsible for the performance of the EORTC investigators.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g., a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g., CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g., pharmacy, laboratory, archives ...). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters Compliance and Audits immediately (contact at: Complianceandaudits@eortc.org).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

Appendix K: Reporting of Serious Breach

A ‘serious breach’ means any deviation to the approved protocol version or the clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The principal investigator should have a process in place to ensure that site staff can identify and notify the occurrence of a (suspected) serious breach. This may be a formal standard operating procedure or a guidance.

All (suspected) serious breaches should be immediately reported to EORTC (2129@eortc.org, quality@eortc.org, +32 2 774 16 11)]. The investigator and site staff should provide appropriate support during investigation performed by EORTC. EORTC will assess if the breach qualifies as serious breach. EORTC is responsible for the notification of serious breaches via the EU Portal.

All (suspected) serious breaches occurring within, or outside EU/EEA would need to be reported to EORTC.

Appendix L: Administrative responsibilities

1 The study coordinator

The EORTC Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for reviewing and discussing all the amendments to the protocol with the coordinating group.

At the time of publication, the EORTC study coordinator's responsibility is to assure, along with the EORTC Headquarters Team, that the results are used and analysed following the EORTC policy and quality.

Study coordinator:

Michail Ignatiadis
Institut Jules Bordet
90, rue Meylemeersch
1070 Anderlecht
Belgium
Phone: +32 25417281
Email: michail.ignatiadis@hubruxelles.be

2 The EORTC Headquarters

The EORTC Headquarters is responsible for handling investigator authorization procedure, for registration and randomisation of patients and will act as a "mailbox" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the EORTC Headquarters that will address them to the person competent for this trial.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 772 35 45

3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.org.

EORTC Breast Cancer Group

Chairman:

Michail Ignatiadis
Institut Jules Bordet
90; rue Meylemeersch
1070 Anderlecht
Belgium
Phone: +32 25417281
Email: michail.ignatiadis@hubruxelles.be

Secretary:

Frederieke Van Duijnhoven
Plesmanlaan 121
1066 CX Amsterdam
Netherlands
Phone: +31 020-5129111
e-mail: f.v.duijnhoven@nki.nl

Appendix M: Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 772 35 45
E-mail: eortc@eortc.org

Appendix N: Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centres authorized by the EORTC Headquarters. For details, please refer to the chapter on investigator authorization.

Appendix O: Results dissemination policy

1 Study disclosure

1.1 Trial Registration

This trial will be registered in a public database (<https://www.clinicaltrialsregister.eu> and <https://www.clinicaltrials.gov>). As the clinical trial (CT) regulation 536/2014 of the European Union (EU) becomes applicable, more information about this trial will be uploaded in this public database in compliance with European requirements on transparency. Information posted, among others, will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

In accordance with applicable EU regulations, a summary of the trial results, including intermediate analyses if available (i.e., not pertaining to confidential interim analyses reports), will be made publicly available within one year of the end of study declaration / intermediate data analysis data.

EORTC as Sponsor of this trial will submit the summary of the results based on the relevant analysis report in compliance with the regulations.

1.2 Final Analysis Report

A Final Analysis Report that reports summary statistics of all the data collected for the study and presents an interpretation of the study results will be issued by EORTC Headquarters. It will form the basis for the manuscript intended for publication. The Final Analysis Report or a summary thereof will be distributed to all participating groups, the supporting companies and ethics committees and the results will be posted in relevant public databases as per contractual agreements / legal obligations.

2 Publication policy

All publications must comply with the terms specified in EORTC Policy J-03-POL-01 “Publication Policy” version 1.0 dated 01.03.2023.

In accordance with the PolicyJ-03-POL-01, results of the present study will be made public once the study data are mature for the final analysis of the primary study endpoint (as described in the section “statistics” of the present protocol), irrespective of the findings (positive or negative). Deviations from the results disclosure rules specified in the Policy require authorization by the Independent Data Monitoring Committee (IDMC).

The primary trial publication will be written on the basis of the final analysis report. The principal study coordinator is responsible for drafting the manuscript.

All publications (papers, abstracts, presentations...) must be reviewed and approved by at least one EORTC Headquarters staff prior to submission to journal or congress or presentation. Approval and review by third parties involved in the study comply with all contractual agreement in place.

The authorship rules conform to the recommendations of the International Committee of Medical Journal Editors defining the roles of authors and contributors

(<http://icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>) and will be attributed for each publication in line with EORTC Policy referred above. All contributors who do not meet sufficient criteria for authorship will be acknowledged in the publication.

In the present study protocol, the following will qualify as co-authors: the study (co)-coordinators, at least one representative of each collaborating academic group, EORTC Headquarters Representatives, and the investigators from at least the 15 best recruiting clinical centres.

Investigators will not independently publish site-specific results about the study endpoints until results of the whole study are published (or after one year following database lock if there is no publication). Deviations from this rule are authorized by the study IDMC.

In the present study the publication of individual case reports is allowed after the publication of the primary endpoint.

Sources of funding or support to the study will be disclosed and acknowledged in the publication. The name “EORTC” must be visible in the publications title or authors list.

3 Data sharing

EORTC is committed to ensuring that the data generated from its studies be put to good use by the cancer research community and, whenever possible, are translated to deliver patient benefit.

It is therefore EORTC's policy to consider for sharing upon request from qualified scientific and medical researchers all data generated from its research whilst safeguarding intellectual property, the privacy of patients and confidentiality.

Considering that ongoing research contributing to the completion of datasets must not be compromised by premature or opportunistic sharing and analysis of data, EORTC will not release the data of its study until the primary study results have been published, unless authorization for release has been granted according to the terms of EORTC Policy J-03-POL-01.

Requests for accessing the data of published trials should be filed through the data-sharing tab on EORTC website (www.eortc.org).

Appendix P: ECOG performance status scale

| Grade | Performance scale |
|-------|--|
| 0 | Able to carry out all normal activity without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out light work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair |

Appendix Q: MDRD formula

$$\text{GFR [mLmin 1.73m}^2\text{]} = k \times 186 \times (\text{SCR})^{-1.154} \times (\text{age})^{-0.203}$$

k 1 (male) or 0.742 (female)

GFR glomerular filtration rate

SCR serum creatinine (mg/dL).

Appendix R: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

The EORTC Headquarters web site <https://www.eortc.be/services/doc/ctc/> provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix S: Child-Pugh assessment of hepatic function

| Parameter | Points Scored for Observed Findings | | |
|--|-------------------------------------|---------------------|---------------------|
| | 1 | 2 | 3 |
| Hepatic encefalopathy grade ^a | 0 | 1 or 2 ^b | 3 or 4 ^b |
| Ascites ^c | Absent | Slight | Moderate |
| Serum bilirubin (mg/dL) | <2 | ≥2 to ≤3 | >3 |
| Serum albumin (g/dL) | >3.5 | ≥2.8 to ≤3.5 | <2.8 |
| International normalized ratio | <1.7 | ≥1.7 to ≤2.3 | >2.3 |

^a Grade 0: normal consciousness, personality, neurological examination, or electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves.

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves.

Grade 4: unarousable coma, no personality/behaviour, decerebrate, or slow 2 to 3 cps delta activity.

^b A subject with hepatic encephalopathy of Grade 2 or above would not be admitted into the study.

^c Absent: No ascites is detectable by manual examination or by ultrasound investigation, if ultrasound investigation is performed.

Slight: Ascites palpation doubtful, but ascites measurable by ultrasound investigation, if performed.

Moderate: Ascites detectable by palpation and by ultrasound investigation, if performed.

Severe: Necessity of paracentesis; does not respond to medication treatment.

| | Class A | Class B | Class C |
|--------------|---------|---------|---------|
| Total points | 5-6 | 7-9 | 10-15 |

Appendix T: Contraception recommendations

WOCBP must agree to use highly effective birth control measures during the protocol treatment period and for at least:

- 4 months after the last dose of elacestrant
- 1 month after the last dose of aromatase inhibitors
- 9 months after the last dose of tamoxifen.

A highly effective method of birth control is defined as a method which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. These methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

Note: Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

- Sexual abstinence*

Men with pregnant female partners or female partners of childbearing potential must remain abstinent* or use a condom during the treatment period and for at least:

- 4 months after the last dose of elacestrant
- 1 month after the last dose of an aromatase inhibitors
- 5.5 months after the last dose of tamoxifen

Men must refrain from donating sperm during this same period.

Female partners of male patients must also use a highly effective form of contraception if they are of childbearing potential.

* Note: the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix U: EORTC Health-related Quality of Life evaluation: guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires

The instructions given below are intended to provide some general guidelines for collecting health-related quality of life (HRQoL) data in EORTC studies.

1. What is the purpose of collecting HRQoL data?

The purpose of collecting HRQoL data in this EORTC study is to assess patients' experience of their functioning, disease symptoms, side effects, and overall well-being. These HRQoL data provide the patient perspective which will complement clinical data for decision-making. Specific objectives for the study can be found in the protocol.

2. Who is the responsible person (RP) for HRQoL data collection?

In each institution, the principal investigator is responsible for the local organization of HRQoL data collection. This can be delegated to other staff such as a physician, data manager, (research) nurse or a psychologist. This person should have the full protocol at their disposal as well as the questionnaire(s). This person should acquaint themselves with the questionnaire(s) and assessment schedule so patients receive the correct questionnaire(s) at the correct visit.

3. Who should fill out the questionnaire(s)?

The patient must complete the HRQoL questionnaire(s) and preferably without help from others. If the patient is unable to fill out the questionnaire(s) by themselves, another person may read the questions in a neutral way without making any suggestions and report the answers on the questionnaire(s). Proxy assessment (whereby someone else fills in the questionnaire(s) as if they were the patient) is not allowed) unless specifically described in the protocol.

4. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the study objective, including the importance of completing the HRQoL questionnaire(s). The patient should be informed that collecting HRQoL data is important, and that the information provided is confidential.

The following issues should be explained to the patient

- Objective of HRQoL data collection
- The importance of HRQoL data collection at baseline and during follow-up
- The schedule of assessments.
- The questionnaire(s) is a self-administered and should be completed by the patient themselves. The patient can ask for help in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to their situation.
- There is no right or wrong answer to any of these questions. The answers will not influence their participation in the study. If the patient feels that there is a specific question that raises an issue, they are encouraged to discuss this with their physician.

- All questions should be answered.
- The patient will be given a questionnaire(s) in the default language(s) of the hospital. If desired, the patient may request another language. The RP should contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions and fills out the questionnaire(s) in the correct order. At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire(s) from the RP or from other appropriate staff if the RP is unavailable.

5. Where should the patient complete the questionnaire(s)?

The patient should ideally complete the questionnaire(s) at the clinic. Estimated time to complete the questionnaire(s) is provided in the protocol and patients should be given the time they need to answer all questions.

6. When should they complete the questionnaire(s)?

The timing of the planned HRQoL assessments is detailed in the protocol. The RP should have printed copies of the questionnaire(s) in advance of an HRQoL assessment and check that the “Hospital Staff” specific data box aligns with the correct study. The questionnaire(s) should preferably be given to the patient before the meeting with the physician, to ensure that the patient has enough time to complete the questionnaire (s) and provide opportunity for the patient to discuss relevant HRQoL issues with their physician. If the patient is to receive treatment, the questionnaire(s) should be filled out before or at the start of administration of the treatment (unless indicated otherwise in the protocol).

7. Review of the completed questionnaire(s)

After the patient has completed the questionnaire(s), the person handling the questionnaire(s) should:

- Complete the “Hospital Staff” specific data box.
- Check that the completion date is correctly filled in by the patient. If not, provide the correct date.
- If the patient added text that would identify them (e.g., name), this needs to be made unreadable.
- Screen the questionnaire(s) for unanswered questions (i.e., omissions).

In case of omissions:

Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. Additional explanation may be provided, but the questions should not be rephrased. The patient should not be forced to provide an answer if they do not wish to do so.

8. Missing questionnaire(s)

It is important to follow the assessment schedule outlined in the protocol to avoid missing questionnaires. Missing information can negatively affect the quality of the data.

If, for some reason, the patient is unable or does not wish to complete the HRQoL questionnaire(s), please collect the main reason for non-completion.

The reason and the date of visit should be documented on the corresponding CRF (case report form).

9. Data transfer to EORTC Headquarters

The completed HRQoL questionnaire(s) should be encoded electronically according to the protocol guideline on “Forms and procedures for collecting data”.

A copy/scan of the questionnaire(s) should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site.

As it is impossible to retrospectively collect missing HRQoL data, please make sure that the patient completes the questionnaire(s) at the intended time-point.

Thank you very much for your cooperation.

Appendix V: G8 geriatric screening tool (Version 1.0 - December 2010)

To be completed by: Clinician, nurse or trained coder.

Notes: This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient.

Score: Total score by adding up coded answers.

| G8 Screening tool | | | |
|--------------------------|--|---|--------------|
| | Items | Possible answers | Score |
| A | Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties? | 0: severe reduction in food intake 1: moderate reduction in food intake 2: normal food intake | |
| B | Weight loss during the last 3 months? | 0: weight loss >3kg 1: does not know 2: weight loss between 1 and 3 kg 3: no weight loss | |
| C | Mobility | 0: bed or chair bound 1: able to get out of bed/chair but does not go out 2: goes out | |
| E | Neuropsychological problems | 0: severe dementia or depression 1: mild dementia or depression 2: no psychological problems | |
| F | Body Mass Index (weight in kg/height in m ²) | 0: BMI less than 19 1: BMI 19 to less than 21 2: BMI 21 to less than 23 3: BMI 23 or greater | |
| H | Takes more than 3 medications per day | 0: yes 1: no | |
| P | In comparison with other people of the same age, how does the patient consider his/her health status? | 0: not as good 0,5: does not know 1: as good 2: better | |
| | Age | 0: >85 1: 80-85 2: <80 | |
| | Total score (0-17) | | |

Appendix W: Medications and foods that are moderate or strong inducers or inhibitors of CYP3A4/5

A clinical PK DDI was observed between elacestrant and itraconazole (a strong inhibitor of CYP3A), with a large increase in elacestrant exposure (AUC increased more than 5-fold), potentially leading to safety concerns. Therefore, it is recommended to avoid co-administration of elacestrant with strong CYP3A4 inhibitors.

A clinical PK DDI was also observed between elacestrant and rifampin (a strong inducer of CYP3A), with a large decrease in elacestrant exposure (80% decrease in AUC) potentially leading to efficacy concerns. Therefore, it is recommended to avoid co-administration of elacestrant with strong CYP3A4 inducers.

If a strong CYP3A4 inhibitor must be used, elacestrant dose should be reduced to 100 mg once daily with careful monitoring of tolerability.

If a moderate CYP3A4 inhibitor must be used, the elacestrant dose should be reduced to 200 mg once daily with careful monitoring of the tolerability. Subsequent dose reduction to 100 mg once daily may be considered with moderate CYP3A4 inhibitors based on tolerability.

| CYP3A4/5 Moderate or Strong Inducers | CYP3A4/5 Moderate or Strong inhibitors |
|---|---|
| Apalutamide | Aprepitant |
| Bosentan | Boceprevir |
| Carbamazepine | Ciprofloxacin |
| Enzalutamide | Cobicistat |
| Etravirine | Conivaptan |
| Mitotane | Crizotinib |
| Phenobarbital | Cyclosporine |
| Phenytoin | Diltiazim |
| Primidone | Dronedarone |
| Rifampin | Erithromycin |
| St. John's Wort | Fluconazole |
| | Fluvoxamine |
| | Grapefruit |
| | Imatinib |
| | Itraconazole |
| | Ketoconazole |
| | Pomelo |
| | Posaconazole |
| | Ritonavir (alone or with danoprevir, dasabuvir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitsavir, saquinavir, tipranavir) |
| | Seville Orangea |
| | Star Fruita |
| | Telaprevir |

| CYP3A4/5 Moderate or Strong Inducers | CYP3A4/5 Moderate or Strong inhibitors |
|---|---|
| | Telithromycin Tofisopam Troleandomycin Verapamil Voriconazole |

Appendix X: Health-Related Quality of Life questionnaires



EORTC QLQ-C30 (version 3)

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

Today's date (Day, Month, Year): 77

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

During the past week:

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

Please go on to the next page

During the past week:

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

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

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

1 2 3 4 5 6 7

Very poor

Excellent

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

1 2 3 4 5 6 7

Very poor

Excellent

Please go on to the next page

**EORTC QLQ-BR42**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week: | | Not at All | A Little | Quite a Bit | Very Much | |
|---|---|-----------------------|---------------------|------------------------|----------------------|---------------------------|
| 31. | Have you had a dry mouth? | 1 | 2 | 3 | 4 | |
| 32. | Have food and drink tasted different than usual? | 1 | 2 | 3 | 4 | |
| 33. | Have your eyes been painful, irritated or watery? | 1 | 2 | 3 | 4 | |
| 34. | Have you lost any hair? | 1 | 2 | 3 | 4 | |
| 35. | Answer this question only if you have lost any hair: Have you been upset by the loss of your hair? | 1 | 2 | 3 | 4 | |
| 36. | Have you felt ill or unwell? | 1 | 2 | 3 | 4 | |
| 37. | Have you had hot flushes? | 1 | 2 | 3 | 4 | |
| 38. | Have you had headaches? | 1 | 2 | 3 | 4 | |
| 39. | Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 | |
| 40. | Have you felt less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 | |
| 41. | Have you had problems looking at yourself naked? | 1 | 2 | 3 | 4 | |
| 42. | Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 | |
| 43. | Have you worried about your health in the future? | 1 | 2 | 3 | 4 | |
| During the past <u>four</u> weeks: | | Not at All | A Little | Quite a Bit | Very Much | Not Applicable |
| 44. | Have you been interested in sex? | 1 | 2 | 3 | 4 | |
| 45. | Have you been sexually active (with or without intercourse)? | 1 | 2 | 3 | 4 | |
| 46. | Has sex been enjoyable for you? | 1 | 2 | 3 | 4 | N/A |

Please go on to the next page

ENGLISH

| During the past week: | | Not at All | A Little | Quite a Bit | Very Much |
|------------------------------|---|-----------------------|---------------------|------------------------|----------------------|
| 47. | Have you had any pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| 48. | Have you had a swollen arm or hand? | 1 | 2 | 3 | 4 |
| 49. | Have you had problems raising your arm or moving it sideways? | 1 | 2 | 3 | 4 |
| 50. | Have you had any pain in the area of your affected breast? | 1 | 2 | 3 | 4 |
| 51. | Has the area of your affected breast been swollen? | 1 | 2 | 3 | 4 |
| 52. | Has the area of your affected breast been oversensitive? | 1 | 2 | 3 | 4 |
| 53. | Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)? | 1 | 2 | 3 | 4 |
| 54. | Have you sweated excessively? | 1 | 2 | 3 | 4 |
| 55. | Have you had mood swings? | 1 | 2 | 3 | 4 |
| 56. | Have you been dizzy? | 1 | 2 | 3 | 4 |
| 57. | Have you had soreness in your mouth? | 1 | 2 | 3 | 4 |
| 58. | Have you had any redness in your mouth? | 1 | 2 | 3 | 4 |
| 59. | Have you had pain in your hands or feet? | 1 | 2 | 3 | 4 |
| 60. | Have you had any redness on your hands or feet? | 1 | 2 | 3 | 4 |
| 61. | Have you had tingling in your fingers or toes? | 1 | 2 | 3 | 4 |
| 62. | Have you had numbness in your fingers or toes? | 1 | 2 | 3 | 4 |
| 63. | Have you had problems with your joints? | 1 | 2 | 3 | 4 |
| 64. | Have you had stiffness in your joints? | 1 | 2 | 3 | 4 |
| 65. | Have you had pain in your joints? | 1 | 2 | 3 | 4 |
| 66. | Have you had aches or pains in your bones? | 1 | 2 | 3 | 4 |
| 67. | Have you gained weight? | 1 | 2 | 3 | 4 |

Please go on to the next page

During the past four weeks:

| | Not at All | A Little | Quite a Bit | Very Much |
|---|-----------------------|---------------------|------------------------|----------------------|
| 68. Have you had discomfort in your vagina? | 1 | 2 | 3 | 4 |

Please answer the following two questions only if you have been sexually active:

| | Not at All | A Little | Quite a Bit | Very Much |
|---|-----------------------|---------------------|------------------------|----------------------|
| 69. Have you had pain in your vagina during sexual activity? | 1 | 2 | 3 | 4 |
| 70. Have you experienced a dry vagina during sexual activity? | 1 | 2 | 3 | 4 |

During the past week:

| | Not at All | A Little | Quite a Bit | Very Much | Not Applicable |
|--|-----------------------|---------------------|------------------------|----------------------|---------------------------|
| 71. Have you been satisfied with the cosmetic result of the surgery? | 1 | 2 | 3 | 4 | N/A |
| 72. Have you been satisfied with the appearance of the skin of your affected breast (thoracic area)? | 1 | 2 | 3 | 4 | N/A |

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EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

| | Not at All | A Little | Quite a Bit | Very Much |
|--|-----------------------|---------------------|------------------------|----------------------|
| 73. To what extent have you been troubled with side-effects from your treatment? | 1 | 2 | 3 | 4 |

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Appendix Y: Abbreviations

| | |
|---------|---|
| ADME | Absorption, distribution, metabolism, and excretion |
| ADR | Adverse drug reaction |
| AI | Aromatase inhibitor |
| AMP | Auxiliary medical product |
| BBB | Blood-brain barrier |
| BCRP | Breast cancer resistance protein |
| CA 15-3 | Cancer antigen 15-3 |
| CBR | Clinical benefit rate |
| CDK 4/6 | Cyclin dependent kinase 4/6 |
| CHIP | Clonal haematopoiesis of indeterminate potential |
| CI | Confidence interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| CR | Complete response |
| CRF | Case report form |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| CtDNA | Circulating tumour deoxyribonucleic acid |
| CYP3A4 | Cytochrome P450 3A4 |
| DFS | Disease free survival |
| DMFS | Distant metastasis free survival |
| DoR | Duration of response |
| E2 | Oestradiol |
| ER | Oestrogen receptor |
| ESR1 | Oestrogen receptor 1 |
| ET | Endocrine treatment |
| FDA | Food and Drug Administration |
| FFPE | Formalin fixed paraffin embedded |
| FSH | Follicle stimulating hormone |
| GnRH | Gonadotropin releasing hormone |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HER2 | Human epidermal growth factor receptor 2 |
| HIV | Human Immunodeficiency Virus |
| HRQoL | Health Related Quality of Life |
| iDFS | Invasive disease-free survival |
| IL | Item Library |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IVD | In-vitro diagnostics |
| LHRH | Luteinising hormone releasing hormone |
| mBC | Metastatic breast cancer |
| MDRD | Modification of Diet in Renal Disease |
| MTD | Maximum Tolerated Dose |

| | |
|---------|--|
| mTOR | Mammalian target of rapamycin |
| NGS | Next Generation Sequencing |
| OATP2B1 | Organic-anion-transporting polypeptide 2B1 |
| OFS | Ovarian function suppression |
| ORR | Overall response rate |
| OS | Overall survival |
| PARP-I | Poly (ADP-ribose) polymerase inhibitor |
| PCR | Polymerase chain reaction |
| PET | Positron emission tomography |
| PFS | Progression free survival |
| PGP | P-glycoprotein |
| PgR | Progesterone receptor |
| PK | Pharmacokinetics |
| PR | Partial response |
| QD | Once daily |
| RaDaR | Residual Disease and Recurrence |
| RFS | Relapse free survival |
| RP2D | Recommended Phase II Dose |
| SAE | Serious adverse event |
| SERD | Oestrogen receptor degrader |
| SERM | Oestrogen receptor modulator |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SmPC | Summary of Product Characteristics |
| SNVs | Single nucleotide variants |
| SOC | Standard of care |
| TEAE | Treatment emergent adverse event |
| ULN | Upper limit of normal |
| US | Ultrasound |
| VAF | Variant allele/allelic fraction/frequency |
| WES | Whole Exome Sequencing |
| WOCBP | Women of childbearing potential |

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