Statistical Analysis Plan

Client Study Code:	
Study Title:	Survival and axillary recurrence following sentinel node- positive breast cancer without completion axillary lymph node dissection – the SENOMAC trial. A randomized study of patients with sentinel node macrometastasis
SDS Project Code:	KI4233_SENOMAC

Document Control

Control

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Signatures

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History

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0.1	Robert Szulkin, SDS LS	2023-08-25	First draft
1.0	Robert Szulkin, SDS Jana de Boniface, PI	2023-09-07	Final version

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Abbreviations

Abbreviation	Term
ALND	Axillary lymph node dissection
BCSS	Breast cancer-specific survival
CSP	Clinical study protocol
EMA	European Medicines Agency
HR	Hazard ratio
ITT	Intention-to-treat
Max	Maximum
Min	Minimum
N	Number of observations
PP	Per-protocol
OS	Overall survival
RFS	Recurrence-free survival
SAP	Statistical analysis plan
SOC	Standard of care
SN	Sentinel node
SNB	Sentinel node biopsy

1. Introduction

This Statistical Analysis Plan (SAP) provides a detailed and technical description of the planned statistical evaluation of the study Survival and axillary recurrence following sentinel node- positive breast cancer without completion axillary lymph node dissection– the SENOMAC trial "*A randomized study of patients with sentinel node macrometastasis*".

This SAP describes the analysis of the primary outcome, overall survival (OS) and the secondary outcomes, breast cancer-specific survival (BCSS) and recurrence-free survival (RFS) of the SENOMAC trial. The study was designed to investigate non-inferiority in patients treated without completion of axillary lymph node dissection (ALND), in all these outcomes. The analysis of the other outcomes specified in the Clinical Study Protocol (CSP) will be described in separate SAPs.
Full description of investigational plan, selection criteria, assessments, etc. are given in the CSP "NCT 02240472 version 8.2".

In case this SAP deviates from the statistical analysis described in the study protocol, the reason for the deviation and/or alternative or additional statistical analyses will be documented in amendments to the study protocol or in this SAP.

2. Study Objectives

2.1 Primary Objective

Assess if refraining from axillary lymph node dissection (ALND) among patients with 1-2 sentinel node (SN) macrometastases will not worsen overall survival by more than a maximum of 2.5% after 5 years.

2.2 Secondary Objectives

Assess if refraining from axillary lymph node dissection among patients with 1-2 sentinel node macrometastases will not worsen:

1. Breast-cancer specific survival (BCSS) by more than a maximum of 2.5% after 5 years.
2. Recurrence-free survival (RFS) by more than a maximum of 4.1% after 5 years, evaluated after 1, 2, 3, 4, 5, 10 and 15 years.

3. Study Details

3.1 Study Design

This study is a multi-country (Sweden, Denmark, Germany, Italy, and Greece), prospective, randomized trial of breast cancer patients diagnosed with 1-2 SN macrometastases.

3.2 Study population

Breast cancer patients with macrometastases in at most two sentinel nodes are included in this study. The following inclusion and exclusion criteria (copied from study protocol) apply to the study cohort.

Inclusion criteria:

- Patients with primary invasive breast cancer T1-T3
- No palpable lymph node metastases prior to sentinel node biopsy (SNB)
- Macrometastasis in not more than 2 sentinel lymph nodes (further lymph nodes with micrometastasis or ITC do not result in exclusion)
- Oral and written consent
- Age ≥ 18 years
- Preoperative ultrasound of axilla performed

Exclusion criteria:

- Regional or distant metastases outside of the ipsilateral axilla
- Prior history of invasive breast cancer
- Pregnancy
- Bilateral invasive breast cancer, if one side meets exclusion criteria. Patients with bilateral cancers where both sides fulfill all inclusion criteria and no exclusion criteria may, however, not be included for either side.
- Medical contraindication for radiotherapy
- Medical contraindication for systemic treatment
- Inability to absorb or understand the meaning of the study information; for example, through disability, inadequate language skills or dementia.

Furthermore, all types of breast surgery are eligible in this trial and patients with planned neoadjuvant systemic treatment.

3.3 Randomisation

Patients are randomized to undergo
1) standard of care (SOC) - completion of axillary lymph node dissection (ALND) *or*
2) intervention - not to have any further axillary surgery, i.e. sentinel node biopsy (SNB) only.

All randomisations are stratified by country, and treatment arms are allocated with a 1:1 ratio.

3.4 Number of Patients

The safety interim analysis of the SENOMAC Trial in May 2020 estimated a 5-year OS of 94%. Clinical non-inferiority is in this study defined as a 5-year OS not worsened by more than 2.5% when refraining from ALND. To show that the OS at five years is not worsened by more than 2.5% (5-year OS of 91.5% in the intervention group compared to 94% in the standard of care group) using a one-sided α of 10% and with a power of 80%, a total of 190 all-cause deaths needs to be observed in the study. This corresponds to showing that the upper one-sided 90% confidence interval for the hazard ratio (HR: Intervention/Standard of care) falls below 1.44. The sample size calculation was reproduced by Robert Szulkin (2023-08-25) with the following R-code:

```
> library(powerSurvEpi)

> ssizeCT.default(power = 0.8, k = 1, pE = 0.085, pC = 0.06, RR = 1.44, alp
ha = 0.1)
  nE   nC
1312 1312
> # 1312 patients needed in each group (2624 in total)

> ### Number of needed events (deaths)
> round(as.numeric(0.085*1312+0.06*1312))
[1] 190
```

2767 patients have been recruited to the study, and recruitment was finalized in year 2021.

4. Study populations

4.1 Modified intention-to-treat (ITT) analysis set

The modified ITT cohort is defined as all study participants who were randomized to a treatment and did not withdraw their consent within 21 days from randomization (before potential date of reoperation with ALND).

4.2 Per-protocol (PP) Analysis Set

The PP population is a subset of the modified ITT population and consists of patients who have sufficiently complied with the protocol. Patients with the following protocol deviations will be excluded:

1. Did not meet all inclusion criteria or met exclusion criteria, even if discovered after randomisation (**`EOS_why`** = "Does not meet inclusion/exclusion criteria any more")
2. Early drop-outs, i.e. patient dropped out of study within 21 days (**`EOS_why`** = "Early drop out (physician's decision)" or "Other").
3. Patients who did not comply with assigned treatment, i.e. underwent ALND despite being assigned SNB only, and participants who received SNB only despite being assigned to ALND, and patients with missing ALND information.

5. Data

5.1 Demographic and Baseline Characteristics

The following demographic and baseline data will be presented in a descriptive table:

- Age – continuous + categories (<40, 40-49, 50-64, 65-74, 75+)
- Year of randomisation – categories 2015-2016, 2017-2018, 2019-2020, 2021-2022
- T stage – T1 (1-20 mm), T2 (21-50 mm), T3 (>50 mm)
- Histopathological tumor size – T1mi (<=1 mm), T1a (>1 to 5 mm), T1b (>5 to 10 mm), T1c (>10 to 20 mm), T2 (21-50 mm), T3 (>50 mm). Only defined for patients without neoadjuvant treatment (patients with neoadjuvant treatment coded as "neoadjuvant treatment").
- Suspicious lymph nodes on ultrasound – Yes/No
- Confirmed preoperative lymph node metastasis – Yes/No

- Number of sentinel nodes removed – continuous + categories (1-2, 3-4, >4)
- Number of SN macrometastases (**SN_macro**) – categories (1 or 2).
- Number of SN with micrometastases (**SN_micro**) - categories (0, 1 or 2).
- Total number of SN metastases – sum of SN macro- and micrometastases. Continuous and categories (0, 1, 2, 3, 4).
- Extracapsular extension SN – Yes/No
- Total number of lymph nodes removed – calculated as number of SN (**SN_number**) + number of removed lymph nodes (**ALND_number**) + additional lymph nodes (**add_LN_number**). Continuous.
- Number of metastases (**mets_total**) – ALND macrometastases (**ALND_macro**)+ ALND micrometastases (**ALND_micro**) + SN macrometastases (**SN_macro**) + SN micrometastases (**SN_micro**) + additional lymph node macrometastases (**add_LN_macro**) + additional lymph node micrometastases (**add_LN_micro**)
- Nodal stage (pN) – categories: pN0 (**mets_total**=0), pN1 (**mets_total**=1 to 3), pN2 (**mets_total**=4 to 9), pN3 (**mets_total**>=10). Only calculated for patients without neoadjuvant chemotherapy (patients with neoadjuvant chemo treatment are coded as "neoadjuvant treatment").
- Primary treatment – Categories: Neoadjuvant systemic treatment or Surgery. Systemic treatment was defined if chemotherapy with or without taxanes was given *or* AntiHer2 target therapy *or* Aromatase inhib *or* any other therapy (if any of the variables **NACT_tax**, **NACT_no_tax**, **NACT_HER2**, **NACT_AI** or **NACT_other** was coded as "yes") was given. Else surgery is defined as primary treatment.
- Breast surgery performed – Categories (breast conserving or mastectomy)
- Tumor type – Categories (Ductal, Lobular, Other)
- Histological grade – Categories (Grade 1, Grade 2 or Grade 3)
- HER2 status – Categories (HER2- , HER2-). HER2- is defined as HER2_IHC=0 or 1+ *or* HER2_ISH="not amplified". HER2+ is defined as HER2_IHC=3+ *or* both HER2_IHC=2+ and HER2_ISH="amplified".
- ER status – categories: Positive (10 % or more), Negative (less than 10%), Not done
- PR status - categories: Positive (10 % or more), Negative (less than 10%), Not done
- Subtype – categories: HR+HER2- (ER positive and HER2-), HR+HER2+ (ER positive and HER2+), HR-HER2+, (ER negative and HER2 positive), HR+HER2+ (ER positive and HER2+)
- Lymphovascular invasion – Yes/No
- Adjuvant chemotherapy – Yes/No/Drop-out prior to FU1. The latter refers to patients without registered treatment and end of study date (**EOS_date**) before first follow-up visit (**visit1_date**) or **EOS_date** within 365 days after randomisation.
- Adjuvant endocrine treatment – Yes/No/Drop-out prior to FU1, which refers to patients without registered treatment and end of study date (**EOS_date**) before first follow-up visit (**visit1_date**) or **EOS_date** within 365 days after randomisation.
- Adjuvant HER2-targeted treatment – Yes/No/Drop-out prior to FU1, which refers to patients without registered treatment and end of study date (**EOS_date**) before first follow-up visit (**visit1_date**) or **EOS_date** within 365 days after randomisation.
- Adjuvant radiotherapy – categories: None (**RT_any**=No, **RT_local**=No, **RT_nodal**=No), Breast or chest wall only (**RT_any**=Yes, **RT_local**=Yes, **RT_nodal**=No), Nodal fields only (**RT_any**=Yes, **RT_local**=No, **RT_nodal**=Yes), Breast and nodal fields (**RT_any**=Yes, **RT_local**=Yes, **RT_nodal**=Yes). NOTE: a missing value in **RT_local** or **RT_nodal** are considered as a "No".
- Country – Sweden, Denmark, Germany, Italy, Greece

5.1.1 Medical History

NA

5.1.2 Prior Medications

NA

5.2 Efficacy Variables

5.2.1 Primary outcome

Overall survival

Overall survival is measured from the date of randomization (variable **rando_date**) until the date of death (variable **death_date**) by any cause. Alive participants are censored at the time of last follow-up.

Patients are defined as dead during follow-up if:

- A death date (**death_date**) is registered.
- If patient was registered as dead in any planned follow-up visit (**alive_FU1, alive_FU2, alive_FU3, alive_FU4, alive_FU5, alive_FU10**)
- If any of the death variables indicate death (**EOS_why** = Dead or **alive_YN** = No)

Censoring date among alive patients is defined as the latest available date of the following:

- Last registered follow-up visit (**FU_date_FU1, alive_date_FU1, FU_date_FU2, alive_date_FU2, FU_date_FU3, alive_date_FU3, FU_date_FU4, alive_date_FU4, FU_date_FU5, alive_date_FU5, FU_date_FU10, alive_date_FU10**).
- End of study date (**EOS_date**).

For the primary outcome (OS at five years) patients will be censored after 5 years.

5.2.2 Secondary outcomes

Recurrence-free survival (RFS)

Recurrence-free survival is measured from the date of randomization (variable **rando_date**) until the date of any first recurrence (variable **rec_date**) or death. Contralateral breast cancer is not considered a RFS event. Recurrence-free and alive participants are censored at the time of last follow-up.

Death and time of censoring are defined as for overall survival above.

Breast cancer-specific survival (BCSS)

Breast cancer-specific survival is measured from the date of randomization until the date of death by breast cancer (**death_why**=breast cancer). Participants without a breast cancer death will be censored at the date of death by other causes or the date of last follow-up if still alive.

5.3 Exposure variables

Treatment arm, ALND (standard of care) or SNB only (intervention) will be the exposure variable in this study.

6. Analysis Methods

All statistical analyses will be performed at SDS Life Science using R version 4.1.2.

6.1 General Principles for Presenting baseline characteristics (Table 1)

Continuous data will be summarized using descriptive statistics where the following parameters will be reported:

- Number of missing observations (n),
- Mean,
- Median,
- Standard deviation (SD),
- Range (Min,Max)

Categorical data will be presented as the number and percentage of patients.

All summary tables will be structured with a column for each treatment in the order (SOC = ALND, Intervention = SN biopsy only) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2 Statistical/Analytical issues

6.2.1 Missing Data and Handling of Dropouts

Only complete cases will be analysed. Extremely few or no missing is expected.

6.2.2 Outliers

No expected outliers.

6.2.3 Non-inferiority analysis

This study is a non-inferiority study, investigating non-inferiority of the primary (OS) and secondary (RFS and BCSS) outcomes.

OS

Clinical non-inferiority in this study is defined as a 5-year OS not worsened by more than 2.5% (5-year OS of 91.5% in the intervention group compared to 94% in the standard of care group) when

refraining from ALND. This non-inferiority margin (Δ) corresponds to a hazard ratio (HR) of 1.44, which is obtained as follows.

The relation between the hazard(λ) and probability of event(p) at time t assuming a constant hazard is given by λ=log(1-p)/t.

In the intervention group (patients refraining from ALND) the probability of death after t=5 years is expected to be 0.085 (91.5% OS).

In the Standard of care (SOC) group (patients who undergo ALND) the probability of death after t=5 years is 0.06 (94% OS).

Hence, $HR = \frac{\lambda_{intervention}}{\lambda_{SOC}} = \frac{log(1-0.085)/5}{log(1-0.06)/5} \approx 1.44$

BCSS

For BCSS the same non-inferiority margin of 2.5% (5-year BCSS of 94.5% in the intervention group compared to 97% in the standard of care group) corresponds to a HR of 1.86.

$$HR = \frac{\lambda_{intervention}}{\lambda_{SOC}} = \frac{log(1-0.055)/5}{log(1-0.03)/5} \approx 1.86$$

RFS

For RFS, the same HR as for OS will be used for non-inferiority margin (1.44). This corresponds to a 4.1% non-inferiority margin (5-year RFS of 85.9% in the intervention group compared to 90% in the standard of care group).

$$HR = \frac{\lambda_{intervention}}{\lambda_{SOC}} = \frac{log(1-0.1)/5}{log(1-0.141)/5} \approx 1.44$$

6.3 Efficacy Analyses

Descriptive summaries for continuous data and for categorical data will be provided in accordance with Section 6.1.

6.3.1 Primary Non-inferiority Analysis

Since the objectives in this SAP are to show non-inferiority for the time-to-event outcomes OS, BCSS and RFS, the PP analysis dataset will be used for the main analysis. For non-inferiority trials the PP population is in general considered as more conservative, see for example the ICH E9 guideline[1] and its addendum on estimands by the European Medicines Agency (EMA)[2]. The effect of the intervention on these outcomes will be assessed using a Cox proportional hazards model. Both unadjusted analyses and analyses adjusting for country (randomization was stratified by country) will be performed. Results will be presented as HRs (the hazard of the intervention group that refrained from ALND divided by the standard of care group) together with confidence intervals (CI). For the primary outcome, a two-sided 80% confidence interval will be used to correspond to a one-sided statistical test at 10% level of significance (which was used for the power calculations). For a more

conservative analysis, a 90% and 95% confidence interval will also be assessed. For the BCSS and RFS outcomes, 95% confidence intervals will be used.

A one-sided statistical non-inferiority test will be performed where the following null hypothesis (H_0) will be tested against an alternative hypothesis (H_A):

H_0: The 5-year event hazard ratio between the intervention group and the standard of care group is below or equal to the non-inferiority margin HR_Δ ($\frac{\lambda_i}{\lambda_{soc}} \leq \mathrm{HR}_\Delta$) *vs*
H_A: The 5-year event hazard ratio is greater than the non-inferiority margin HR_Δ ($\frac{\lambda_i}{\lambda_{soc}} > \mathrm{HR}_\Delta$).

HR_Δ = 1.44 will be used as a non-inferiority margin for the OS and RFS outcomes, and HR_Δ = 1.86 for BCSS as mentioned in section 6.2.3. In the statistical tests, the confidence level used to assess statistical significance will be corresponding to the confidence intervals, i.e. for OS 10% significance level will be used (5% and 2.5% in the more conservative analysis) and 2.5% significance level for BCSS and RFS.

Results from the OS, BCSS and RFS analysis for which non-inferiority was hypothesized will also be presented as a figure showing CIs for the hazard ratio, the non-inferiority margin and non-inferiority p-value.

As a descriptive analysis, non-parametric Kaplan-Meier curves for the OS, BCSS and RFS outcomes will be calculated, stratified on treatment arm. For the BCSS outcome, the cause-specific cumulative incidence - taking competing risks (death from other causes than breast cancer) into account - will be estimated using non-parametric Aalen-Johansen plug-in estimator.

6.3.2 Subgroup Analyses

No sub-groups to analyse.

6.3.3 Sensitivity Analyses

The modified ITT population will be used for sensitivity analysis. The same analysis as described above in section 6.3.1 will be performed.

6.4 Changes to Planned Analysis

This section should identify changes made in the statistical plans compared to the plans made in the study protocol. Analyses are usually faithful to those specified in the protocol, but occasionally different, or supplemental, analyses are needed. Explain the reason for such changes.
This does not include specifications of methods, where only more details are given, if these are not explicit changes from the plans in the study protocol.
Other important, non-statistical changes to the protocol should also be noted in this section, for example the introduction of an additional treatment group.

In the study protocol it is stated that 80% confidence intervals of the OS hazard ratio from the Cox regression model will be calculated. This SAP has been modified to also include 90% (required in FDA guidelines of non-inferiority studies) and 95% confidence intervals (required by EMA guidelines), which is a more conservative analysis. We anticipate that this will be required by scientific journals.

It was initially anticipated that the study will be able to recruit up to 3000 patients by the end of 2021. The final number of recruited study participants is 2767 patients.

7. References

1. European Medicines Agency. ICH Topic E 9 Statistical Principles for Clinical Trials. CPMP/ICH/363/96. September 1998.
2. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017. 17 February 2020.