

## Statistical Analysis Plan

Drug substances: Anastrozol  
Study code: D539L00016; 1033AU/003; ABCSG 16

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**S.A.L.S.A. (Secondary Adjuvant Longterm Study with Arimidex®):  
A Prospective, randomized, open, multicentre phase III-study to  
assess the efficacy of secondary adjuvant endocrine anastrozole  
therapy for 2 further years vs. 5 further years in patients with  
hormone receptor positive breast cancer after a 5-year primary  
adjuvant endocrine therapy.**

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**Austrian Breast and Colorectal Cancer Study Group  
ABCSG Protocol number 16**

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## Table of contents

1.	Introduction .....	4
2.	Study details .....	4
2.1.	Study design .....	4
2.1.1.	Study duration.....	5
2.2.	Study objectives .....	5
2.2.1.	Primary objective.....	5
2.2.2.	Secondary objectives .....	5
2.3.	Randomization and stratification criteria .....	6
2.4.	Number of subjects - sample size estimation .....	7
3.	Statistical methods .....	7
3.1.	Data handling conventions .....	7
3.1.1.	Data entry errors and potential outliers .....	7
3.1.2.	Missing data.....	7
3.1.3.	Stratification errors .....	9
3.1.4.	Original eCRF pages and amended eCRF pages.....	9
3.2.	Types and time points of analyses.....	9
3.2.1.	Interim analysis.....	9
3.2.2.	Advanced analysis .....	9
3.2.3.	Final analysis .....	9
3.3.	Definition of populations for analyses .....	9
3.3.1.	Per-protocol (PP) population .....	9
3.3.2.	Intention to Treat (ITT) population .....	10
3.3.3.	Safety (SAF) population.....	10
3.4.	Description of study population .....	10
3.4.1.	Disposition of patients .....	10
3.4.2.	Important Protocol Deviations (IPDs).....	10
3.4.3.	Baseline demographic and disease characteristics .....	10
3.5.	Primary endpoint evaluation .....	11
3.5.1.	Primary endpoint .....	11
3.5.2.	Efficacy analysis for primary endpoint .....	11
3.6.	Secondary endpoint evaluation .....	12
3.6.1.	Overall survival (OS).....	12
3.6.2.	Time to new contralateral breast cancer .....	12
3.6.3.	Time to secondary carcinoma.....	12
3.6.4.	Time to first clinical fracture .....	13
3.7.	Safety evaluation .....	13
3.8.	Exploratory analyses .....	13
3.8.1.	Subgroup analyses .....	13
3.8.2.	Multivariable analyses .....	13
3.9.	Software.....	14
4.	Changes of analysis compared to study protocol.....	14
4.1.	Interim analysis .....	14
4.2.	Advanced analysis.....	14
4.2.1.	Data set for advanced analysis.....	14
4.2.2.	Primary and secondary endpoints in advanced analysis.....	14
4.2.3.	Exploratory objectives in advanced analysis.....	15

Glossary of abbreviations

ABCSCG	Austrian Breast and Colorectal Cancer Study Group
AE	Adverse event
AI	Aromatase Inhibitor
CA 15-3	Cancer Antigen 15-3
CEA	Carcino-embryonal Antigen
DFS	Disease free survival
eCRF	Electronic case report form
EOS	End of study
ER	Estrogen receptor
IPD	Important protocol deviation
ITT	Intention to treat
OS	Overall survival
PgR	Progesterone receptor
PP	Per-Protocol
pT-Stadium	Pathologic classification of the tumor stage
pN-Stadium	Pathologic classification of the lymph node status
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse event
SAF	Safety
SAP	Statistical Analysis Plan

## 1. Introduction

The Austrian Breast & Colorectal Cancer Study Group (ABCSCG) is a cooperative institution that was set up to conduct controlled clinical trials in breast and colorectal cancer and to facilitate communication and the dissemination of knowledge among scientists and others dedicated to the cancer problem. Since its establishment in 1984, more than 15,000 patients have been enrolled in ABCSCG investigations. In certain patient risk groups, ABCSCG is currently recruiting up to 40 per cent of all Austrian breast cancer patients to their clinical trials. The ultimate goal of the ABCSCG is to enhance the standard of cancer treatment in this country and abroad by developing innovative approaches and testing increasingly more effective therapeutic strategies.

Prospectively randomized clinical investigations have come to be seen as the only instrument to generate valid and reliable clinical data, to gain insights into significant prognostic and predictive factors, and thus to enhance all aspects of evidence-based medicine. As a target of oncological research and practice, the ABCSCG has selected two of the most common malignancies affecting women and men in the present-day western world: carcinoma of the breast and bowel.

As a whole, the ABCSCG collaborates toward the common goal of controlling, effectively treating, and ultimately curing cancer by means of large, multicenter cancer trials in the (neo-) adjuvant setting. Research results are provided to the medical community through scientific publications and professional meetings.

This Statistical Analysis Plan (SAP) is based on the Amended Clinical Study Protocol for ABCSCG study 16 (1033AU/0003) and gives a detailed description of all statistical analyses planned to be conducted within this trial at predefined time points.

## 2. Study details

ABCSCG-16 is a prospective, randomized, open-label, multicenter Phase III study in endocrine-responsive postmenopausal women with early breast cancer who have already received their standard 5 years of adjuvant endocrine treatment

Patients aged  $\leq 80$  years, who are recurrence-free 60 months after the operation and who have completed a primary 5-year endocrine treatment, are being randomized to receive a further 2 (arm A) or 5 (arm B) years of treatment with anastrozole.

### 2.1. Study design

All patients free of recurrence 60 ( $\pm 12$ ) months after operation are randomized following a primary 5-year endocrine therapy with therapy intervals of maximal 12 months (e.g. from studies 8 and 9) as follows:

- Arm A: 2-year anastrozole therapy (Arimidex<sup>®</sup>)
- Arm B: 5-year anastrozole therapy (Arimidex<sup>®</sup>)

### 2.1.1. Study duration

The duration of therapy is 2 or 5 years respectively. The follow-up period will last 8 years for arm A and 5 years for arm B.

Scheduled study start: December 2003

Scheduled end of recruitment: original protocol: December 2008  
protocol amendment 3: June 2010

#### 2.1.1.1. *End of treatment*

Scheduled end of max. treatment phase: original protocol: December 2013  
protocol amendment 3: December 2015

#### 2.1.1.2. *End of study*

Scheduled end of follow-up: original protocol: December 2018  
protocol amendment 3: December 2020

## 2.2. **Study objectives**

### 2.2.1. Primary objective

The primary objective is the assessment of the effect of 2 further years of anastrozole treatment vs. further 5 years of anastrozole treatment on disease-free survival (DFS), following a five-year adjuvant endocrine therapy.

### 2.2.2. Secondary objectives

- Assessment of the effect of further 2 years of anastrozole treatment vs. 5 further years of anastrozole treatment on the overall survival (OS) following five years of adjuvant endocrine therapy.
- Comparison of the respective rates of fracture occurrence in the two groups
- Comparison of the occurrence of secondary carcinoma in the two groups
  - Comparison of the occurrence of contra-lateral breast cancer in the two groups, respectively
  - Comparison of the occurrence of secondary carcinoma except the contra-lateral mammary carcinoma in the two groups respectively

## 2.3. Randomization and stratification criteria

Stratification criteria:

The following stratification criteria are applied:

- 1) pT-Stadium:
  - i) - pT1( $\leq 2$  cm)
  - ii) - pT2 ( $> 2 - 5$  cm)
  - iii) - pT3( $> 5 - 10$  cm)
  
- 2) pN-Stadium:
  - i) no lymph node metastasis
  - ii) 1 - 3 lymph node metastasis
  - iii) 4 - 9 lymph node metastasis
  - iv)  $\geq 10$  lymph node metastasis
  
- 3) Adjuvant primary hormone therapy :
  - i) 5 years of anti-estrogen
  - ii) 2 years of anti-estrogen + 3 years anastrozole
  - iii) Another, comparable endocrine therapy
  
- 4) Adjuvant chemotherapy :-
  - i) Chemotherapy containing anthracycline
  - ii) Chemotherapy containing taxane
  - iii) Other chemotherapy
  - iv) No chemotherapy
  
- 5) Participation in a clinical study:
  - i) Study 8 (ABCSCG)
  - ii) Study 9 (ABCSCG)
  - iii) None
  
- 6) Receptor status:
  - i) ER+PgR+
  - ii) ER+PgR-
  - iii) ER-PgR+
  
- 7) Federal states:
  - (I) Vienna
  - (II) Lower Austria
  - (III) Burgenland
  - (IV) Styria
  - (V) Carinthia
  - (VI) Upper Austria
  - (VII) Salzburg
  - (VIII) Tyrol
  - (IX) Vorarlberg

## 2.4. Number of subjects - sample size estimation

As of randomization, all patients receive the same therapy for 2 years. After that, one group will continue the therapy for 3 further years. Therefore, differences between the groups are only to be expected 2 years after randomization. Therefore, the most relevant point in time regarding evaluation of the data will be 2 years after randomization (i.e. change of therapy) for each patient.

It is to be expected that 700 patients can be recruited per year. Considering that 5% of patients will drop out of the study within the first 2 years due to recurrence, an effective rate of recruitment of 665 remains.

A difference between the therapy group and the control group of 0.916 and 0.937 3 years after change of therapy at exponential survival (corresponding to a hazard quotient of 1.35) can be uncovered with 85% power at a two-sided level of significance of 5%, if 433 events are observed. This is feasible, if 665 patients are recruited annually for 5 years and followed up for another 2.7 years, amounting to a case number of 3,500, and of these 3325 evaluable patients. The expected total duration of the study is 9.7 years.

With an exponential drop-out rate of 7%, the power would be reduced to 80%.

## 3. Statistical methods

### 3.1. Data handling conventions

#### 3.1.1. Data entry errors and potential outliers

Patients may have potential outliers for particular observations. Observations will be checked for correctness by the study team before data freeze and at the time point of data freeze all data should be correct. Remaining potential outliers based on correct values will be included in analysis. Values found to be incorrect due to data entry error after data freeze will be excluded from all analyses as missing values.

#### 3.1.2. Missing data

Subjects may have missing specific data points for a variety of causes. In general, data may be missing due to a missed visit, non-evaluability of a specific clinical measurement at its planned clinical visit or a subject's early withdrawal from study. The general procedures outlined below describe what will be done when a data point is missing.

##### 3.1.2.1. *Imputations of missing data*

Generally, only evaluable measurements are considered for the analyses. No values are imputed for missed or non-evaluable visits. In case of primary and secondary efficacy endpoints possible specific requirements are stated in the according analysis sections.

### 3.1.2.2. Partial dates

Partially incomplete dates (day or day/month missing) will be imputed for dates of progression as well as for therapy begin and/or end dates. Completely missing dates and missing years will not be imputed.

#### Imputation Rules for Partial Progression Dates

	Missing	Impute	Exception
Oncological Event Date	Day	01	Default to the Randomization date if the imputed date is before the Randomization date.
	Day /Month	01JAN	
Death Date	Day	01	Default to the Randomization date if the imputed date is before the Randomization date.
	Day /Month	01JAN	
Fracture Date	Day	01	Default to the Randomization date if the imputed date is before the Randomization date.
	Day /Month	01JAN	

#### Imputation Rules for Partial Therapy Dates

	Missing	Impute	Exception
Therapy Examination* Date	Day	15	Default to the Randomization date if the imputed date is before the Randomization date. Default to the EOS date if the imputed date is after the EOS date
	Day /Month	Visit due date or 1 <sup>st</sup> July	
Primary Surgery Date	Day	15	
	Day /Month	1 <sup>st</sup> July	
AI Start Date	Day	1	Default to the Randomization date if the imputed date is before the Randomization date.
	Day /Month	01JAN	
AI End Date	Day	Last day of the month	Default to the Randomization date if the imputed date is before the Randomization date. Default to the EOS date if the imputed date is after the EOS date
	Day/Month	31DEZ	

#### Imputation Rules for Follow Up and End of Study Dates

	Missing	Impute	Exception
Follow Up Examination Date	Day	15	Default to the EOS date if the imputed therapy stop date is after the EOS date
	Day /Month	Follow up visit due date window lower bound	Default to the EOS date if the imputed therapy stop date is after the EOS date
End of Study Date	Day	15	10,5 Years after Randomization Date if the imputed date is after the EOS date
	Day /Month	10,5 Years after Randomization Date	

### 3.1.3. Stratification errors

Stratification errors defined as different values in the stratification factors compared between the randomization system and actual patient values from the electronic case report forms (eCRF) will be tabulated.

### 3.1.4. Original eCRF pages and amended eCRF pages

If different data were entered on the same data field on the original eCRF page and on the amended eCRF page, the data of the amended eCRF will be chosen and the data on the original eCRF will be discarded.

## 3.2. Types and time points of analyses

According to the protocol, the final analysis of the study should take place after a follow-up of 10 years for each patient. End of 2016 similar studies with prolonged endocrine therapy were presented to the scientific community. At this time, the required number of events was long since been reached. Therefore, the ABCSCG presidium decided in January 2017 to submit an abstract for the presentation at the San Antonio Breast Cancer Symposium (SABCS) in December 2017 based on an advanced analysis. The final analysis should take place approximately after 1 additional year. AstraZeneca agreed to these changes in April 2017.

### 3.2.1. Interim analysis

After recruitment of two thirds of the required number of patients an interim analysis will take place. A significance level of 0.001 will be used, according to the guidelines of Geller and Pocock (1987). If an unexpectedly high effect of the therapy should occur, the study can be terminated early.

### 3.2.2. Advanced analysis

The advanced analysis for the presentation at SABCS 2017 will be based on the cleaned data with cutoff date June 30<sup>th</sup>, 2016.

### 3.2.3. Final analysis

The final analysis will be performed after the last visit of each patient occurring until June 30<sup>th</sup>, 2017 and subsequent data cleaning.

## 3.3. Definition of populations for analyses

### 3.3.1. Per-protocol (PP) population

Primary endpoint analysis will be based on the PP; that is, all patients who were randomized, signed the Informed Consent, comply with inclusion and exclusion criteria and have had at least one follow-up examination after randomization and who survived without recurrence for two years. All subjects will be analyzed according to the therapy arm to which they have been

randomized. Subjects who terminate the study before their scheduled final study visits will be censored.

### 3.3.2. Intention to Treat (ITT) population

Secondary endpoint analyses and all sensitivity analyses (including sensitivity analyses for the primary endpoint) will be based on the ITT population; that is, all patients who were randomized and signed the Informed Consent. All subjects will be analyzed according to the therapy arm to which they have been randomized. Subjects who terminate the study before their scheduled final study visits will be censored.

### 3.3.3. Safety (SAF) population

Safety analyses will be based on the SAF population and include all enrolled and treated patients. Hence, all patients who were randomized and received at least one dose of study treatment.

## 3.4. **Description of study population**

The description of the study population is based on the ITT population.

### 3.4.1. Disposition of patients

Recruitment, discontinuation from study including reasons for discontinuation, as well as patient disposition and discontinuation from treatment including reasons for discontinuation will be summarized overall and by treatment arm.

### 3.4.2. Important Protocol Deviations (IPDs)

IPDs include inclusion and exclusion criteria, as well as selected variables related to additional relevant screening assessments, study treatment administration/dispensation, concomitant medication, primary endpoint, study treatment/randomization, study procedures/assessments, withdrawal/termination criteria and safety reporting. The IPDs are defined in a separate document listing all IPDs, their classification and additional details. IPDs will be summarized in total and by treatment arm.

### 3.4.3. Baseline demographic and disease characteristics

Demographic and tumour characteristics data at baseline will be summarized descriptively per treatment arm and in total. Demographic and anamnestic data at baseline include age, tumour stage, nodal status, tumour grade, hormone receptor status (estrogen and progesterone), type of surgery, prior radiotherapy, prior chemotherapy and type of prior endocrine therapy.

## 3.5. Primary endpoint evaluation

### 3.5.1. Primary endpoint

Disease-free survival (DFS) is defined as the time from randomization or from two years after randomization (depending on the type of analysis, see below) to the earliest occurrence of loco-regional recurrence, distant recurrence, contralateral new breast cancer, second cancer or death, from any cause. Patients who have not had a disease recurrence or died will be right-censored at the date of their last assessment of their DFS status.

### 3.5.2. Efficacy analysis for primary endpoint

For the primary endpoint, a 2-sided log-rank test (unstratified) will be used to test for differences between 2 additional years anastrozole versus 5 additional years anastrozole at an overall alpha level of 0.05.

#### *Types of analyses for the primary endpoint*

##### Main analysis:

Start time for DFS: 2 year after randomization

Population: PP

##### Sensitivity analysis 1:

Start time for DFS: 2 year after randomization

Population: ITT

##### Sensitivity analysis 2:

Start time for DFS: randomization

Population: ITT

#### *Evaluation of censoring date for DFS analysis*

In case of no events and no early study termination, patients will be censored after 10.5 years. The last DFS event free day is evaluated as the maximum of the last treatment visit date and last follow up visit date including only visits with cancer status evaluation. In case of follow-up visits with documented cancer status but without a documented visit date, the lower bound of the due visit date window will be used. Follow-up visits with information whether patient is alive but without cancer status evaluation will not be used.

#### *Additional specifications*

It was possible to document the location of successive events after the first events within the event categories ‘distant metastases’ (‘Fernmetastasen’) and ‘secondary carcinoma’ (‘Zweitkarzinome’) in the eCRF. In these cases, the text “[Folge-Event]” in notes related to the location data entry fields indicate that the affected location does not belong to the first event within the respected event category. These locations will be excluded from listings of affected locations for the first events within the respective event category.

### 3.6. Secondary endpoint evaluation

All secondary endpoint analyses will be based on the ITT population. For all secondary endpoints, 2-sided log-rank tests (unstratified) will be used to test for differences between 2 additional years anastrozole versus 5 additional years anastrozole at an overall alpha level of 0.05. No multiplicity adjustment will be applied for the secondary endpoints.

#### 3.6.1. Overall survival (OS)

This is defined as the time from randomization or from two years after randomization to death due to any cause. Patients who have not died will be right-censored at the last date when they were known to be alive (date of their last assessment).

##### Main analysis

Start time for OS: 2 year after randomization

##### Sensitivity analyses

Start time for OS: randomization

#### 3.6.2. Time to new contralateral breast cancer

This is defined as the time from randomization or from two years after randomization to first occurrence of new contralateral breast cancer. Subjects without contralateral breast cancer event would be censored at last date when they were known to be contralateral breast cancer free.

##### Main analysis

Start time for time until new contralateral breast cancer: 2 year after randomization

##### Sensitivity analyses

Start time for time until new contralateral breast cancer: randomization

#### 3.6.3. Time to secondary carcinoma

This is defined as the time from randomization or from two years after randomization to first occurrence of new secondary cancer without new breast cancer (local or contralateral). Subjects without secondary cancer event would be censored at last date when they were known to be secondary cancer free.

##### Main analysis

Start time for time until new second cancer: 2 year after randomization

##### Sensitivity analyses

Start time for time until new second cancer: randomization

### 3.6.4. Time to first clinical fracture

This is defined as the time from two years after randomization to first clinical fracture. Patients without clinical fractures were censored at their last therapy visit (maximum approximately 5 years after randomization).

## 3.7. Safety evaluation

Analyses of the safety data are based on the SAF population. Only serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation of the therapy are collected in this trial. Frequencies of serious adverse events will be summarized descriptively per treatment arm and in total. Patient listings of SAEs and of AEs leading to discontinuation of the therapy will be given. Change in tumor markers CEA and CA 15-3 will be descriptively summarized (e.g., means, median, standard deviations, ranges).

## 3.8. Exploratory analyses

Exploratory analyses will be based on the ITT population.

### 3.8.1. Subgroup analyses

DFS will be analyzed using Cox proportional hazard models within each of following subgroups:

- Age group: age  $\leq$  60, age  $>$  60
- Tumor stage: T1, T2 and T3
- Histological grade: Grade I, Grade II, Grade IIIs
- Hormone receptor status: ER+/PgR+, any negative
- Previous hormone therapy: Tamoxifen, Tamoxifen+AI, AI
- Previous chemotherapy: any chemotherapy, no chemotherapy

### 3.8.2. Multivariable analyses

To adjust for the possible effect of demographic or prognostic factors on the primary and the secondary endpoints, multivariable analyses will be performed. To avoid multi-collinearity between the covariates, prior correlation analyses will be performed. Depending on the statistical results and the clinical relevance, highly correlated covariates may be excluded from multivariable analyses.

The following stratification factors will be used as covariates to explore the relationship to the primary and secondary endpoints (the stratification factor 'Federal states' will not be included):

- pT-stage
- pN-stage
- Histologic grade
- Hormone Receptor status
- Previous hormone therapy
- Previous chemotherapy
- Previous radiotherapy
- Participation in a clinical study

In addition, age will be included in the multivariable analysis.

### 3.9. Software

All analyses will be done using SAS version 9.3 or higher.

## 4. Changes of analysis compared to study protocol

### 4.1. Interim analysis

According to the protocol, an interim analysis was planned to take place after the recruitment of two thirds of the required number of patients. Because the number of events was too low (67 DFS events) at the time when 2333 patients had been recruited, no interim analysis was performed.

### 4.2. Advanced analysis

The advanced analysis for the presentation at SABCS 2017 will be based on the cleaned data with cutoff date June 30<sup>th</sup>, 2016.

#### 4.2.1. Data set for advanced analysis

According to the protocol, the final analysis will follow the principle of intent-to-treat of all randomized patients who comply with inclusion and exclusion criteria and have had at least one follow-up examination after randomization and who survived without recurrence for two years. This population will be used for the final analysis for consistency with the protocol. As this definition of an ITT population is outdated, the up-to-date definition of ITT as described in section 3.3.2. will be used for the advanced analysis.

#### 4.2.2. Primary and secondary endpoints in advanced analysis

##### 4.2.2.1. *Two years after randomization as start time for time to event calculation*

According to the protocol, two years after randomization will be used as starting point for the calculation of the time until the occurrence of an event.

#### 4.2.2.2. *Randomization as start time for time to event calculation*

In addition to analyses according to protocol (starting two years after randomization) time-to-event analyses will be conducted with the starting point being the date of randomization.

#### 4.2.3. Exploratory objectives in advanced analysis

Additional exploratory objectives were added for the advanced analyses:

- Influence of adherence to prescribed therapy on DFS
- The effect of the proportion of the treatment duration with anastrozole compared to the total duration of endocrine treatment in previous therapy on disease-free survival

##### 4.2.3.1. *Adherence to prescribed therapy*

Adherence is defined as the consistency of taking protocol treatment. Treatment duration will be calculated on the basis of documented start and end of therapy. Early/Late end of therapy is defined as departure from prescribed duration of arm therapy for more than or less than 6 months.

Patient is adherent if duration of therapy is not shorter than 6 month and not longer than 6 month then prescribed therapy for therapy group or has an early end of therapy with reason recurrence or death.

Patient with an early/late end of therapy with reason for end of therapy different from recurrence/death are defined as non-adherent. Patients who died during treatment period and do not have reported treatment discontinuation before their death are considered adherent. Patients who never started therapy treatment are consider non-adherent.

The adherent population consists of all patients from the ITT population who are adherent to prescribed treatment. Analyses for the primary and for all secondary endpoints will be repeated based on the adherent population with time at randomization as start point.

##### 4.2.3.2. *The effect of previous endocrine therapy*

The effect of the proportion of the treatment duration with anastrozole compared to the total duration of endocrine treatment in previous therapy on disease-free survival will be analyzed using Cox proportional hazard models with therapy group, type of previous endocrine therapy and their interactions as covariates.