ABCSG Protocol 16

S.A.L.S.A (Secondary Adjuvant Long-term Study with Arimidex®)

A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

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Sponsor: AstraZeneca Österreich

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SIGNATURE PAGE

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Study number: ABCSG 16 (1033AU/0003)

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Site number: << >>

I agree to conduct the clinical study named above according to this protocol and will assure that it is conducted in accordance with the Declaration of Helsinki, the Austrian Medicinal Products Act (AMG) and GCP.

Investigator: _____
(Name, title in block letters)

_____ _____
Signature Date

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Abbreviations

ABCSG	Austrian Breast and Colorectal Cancer Study Group
AI	Aromatase inhibitor
AMG	Arzneimittelgesetz (Medicinal Products Act)
AP	Alkaline phosphatase
BUMI	Bundesministerium für Frauen und Gesundheit (Federal Ministry for Women and Health)
CT	Computed tomography
CA 15-3	Cancer antigen 15-3
CEA	Carcinoembryonic antigen
CI	Confidence interval
CR	Complete remission
CRF	Case Report Form(s)
CRS	Creative Research Solutions GmbH
DFS	Disease-free survival
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EC	Executive Committee
ECOG	Eastern Cooperative Oncology Group
ER	Oestrogen receptor
GOT	Glutamate oxalacetate transaminase
GPT	Glutamate pyruvate transaminase
Hb	Haemoglobin
HR	Hormone receptor
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IF	Investigator file
ITT	Intention to treat

i.v.	Intravenous
LFP	Liver function parameters
Mb	Morbus (disease)
n.a.	not available
n.d.	not done
RFP	Renal function parameters
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall survival
PgR	Progesterone receptor
PT stage	Pathological classification of tumour stage
PN stage	Pathological classification of lymph node status
RR	Relative risk
SAE	Serious adverse event
SLN	Sentinel lymph node(s)
SDV	Source data verification
SOP	Standard operating procedure(s)
SPAM	Study Procedures and Administrative Manual
STS	Study site
TGF-β	Transforming growth factor-beta
TNM	Tumour node metastasis; classification of anatomical distribution
AE	Adverse event
ULN	Upper limit of normal
WHO	World Health Organisation
ZMA	Zentralmeldeamt (Central Registration Office)

1. GENERAL INFORMATION

1.1. Study summary

Title: S.A.L.S.A (Secondary adjuvant, long-term study with Arimidex®):
A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Objective of the study:

Primary:
1. Assess the effect in terms of disease-free survival (DFS) of a further 2 years of anastrozole vs. a further 5 years of anastrozole after 5 years of adjuvant endocrine therapy

Secondary:
1. Assess the effect in terms of overall survival (OS) of a further 2 years of anastrozole vs. a further 5 years of anastrozole after 5 years of adjuvant endocrine therapy
2. Compare the fracture rate between the two treatment groups
3. Compare the occurrence of
a) secondary cancers with the exception of the contralateral breast cancer
b) contralateral breast cancer between the two treatment groups

Design: Prospective, randomised, open-label, multicentre phase III study in breast cancer patients in the adjuvant setting
Stratification by:
- PT stage
- PN stage
- Adjuvant primary hormone therapy
- Adjuvant chemotherapy
- Receptor status
- Previous participation in an ABCSG study
- Participating federal state

Therapy: Arm A: Anastrozole (Arimidex®) 1 mg per day orally for 2 years
Arm B: Anastrozole (Arimidex®) 1 mg per day orally for 5 years

Sample size: 3500 randomised patients

Patient selection:

Inclusion criteria:

1. Postmenopausal patients with histologically verified invasive or minimally invasive breast cancer that has been radically treated locally with or without previous chemotherapy and/or radiotherapy
2. Age ≤ 80 years
3. No distant metastasis at randomisation
4. No recurrence at randomisation
5. TNM-classification at the time of diagnosis: T1-3, N0-1, M0
6. Oestrogen and/or progesterone receptor-positive before the start of primary endocrine therapy
7. Endocrine therapy for 5 years (maximum deviation ± 12 months)
8. Therapy break (from the preliminary therapy) maximum 12 months
9. At the time of randomisation, the results of the following tests must be available:
   a) Medical history and clinical examination (within one month prior to randomisation)
   b) Gynaecological examination (within one month prior to randomisation)
   c) Chest x-ray or CT scan (within one year prior to randomisation)
   d) Bilateral mammogram (within one year prior to randomisation) – exception are women with mastectomy (unilateral)
   f) Ultrasound of the abdomen or abdominal CT (within one year prior to randomisation)
   e) Laboratory parameters (within 3 months prior to randomisation)
      - Adequate liver function (GOT or GPT ≤ 2.5 x ULN; total bilirubin < 2 x ULN, AP < 2 x ULN)
      - Serum creatinine ≤ 1.5 x ULN
10. Informed consent prior to randomisation

Exclusion criteria:

1. Premenopausal patients or patients with non-determinable menopausal status at randomisation
2. Manifest secondary malignancy or status post secondary malignancy between the time of initial diagnosis and randomisation
3. General contraindications and/or hypersensitivity to anastrozole
4. Carcinoma in situ of any size with or without Paget's disease of the nipple or T4 tumours at the time of initial diagnosis
5. Receptor determination unknown or negative at the time of diagnosis or at the start of the primary endocrine therapy
6. Age > 80 years
7. Performance index > 3 as per WHO
8. Regular use of hormone products and hormone replacement therapy (HRT) for more than 6 months since the primary breast cancer surgery
9. Serious concomitant disease preventing implementation of adjuvant therapy in line with the protocol and/or controlled follow-up
10. Lack of patient cooperation
11. Legal incapacity and/or other circumstances preventing the patient from understanding the nature, significance and implications of the clinical trial
12. Existing psychiatric disease as per ICD at study enrolment (especially alcohol dependency)

Efficacy parameters:	- Disease-free survival (DFS) - Overall survival (OS) - Fracture rate	
Schedule for study process:	Planned study start: Planned recruitment end: Planned end of the max. treatment phase: Planned end of follow-up:	December 2003 December 2008 December 2013 December 2018
Study drug:	Anastrozole (Arimidex®) 1 mg	
Sponsor:	AstraZeneca Österreich GmbH	

1.2. Flow chart

Parameter	Screening	6 months	12 months	24 months	36 months	48 months	60 months	6 years	7 years	8 years	9 years	10 years
Verification of inclusion and exclusion criteria	x											
Medical history	x											
Clinical examination	x	x	x	x	x	x	x	x	x	x	x	x
Gynaecological examination	x		x	x	x	x	x					
Ultrasound or CT of abdomen	x		x	x	x	x	x					
Chest x-ray or CT	x		x	x	x	x	x					
Bilateral or unilateral mammogram	x		x	x	x	x	x	x	x	x	x	x
Measurement of bone density (optional)	x		x	x	x****	x****	x****					
Survey of fracture rate		x	x	x	x	x	x					
LFP*	x		x	x	x	x	x					
RFP**	x		x	x	x	x	x					
TU marker*** (optional)	x		x	x	x	x	x					
SAE/AE		See point 9						See point 9				

Legend: * LFP: GOT,GPT, AP, total bilirubin
** RFP: Serum creatinine
*** TU marker: CEA, CA 15-3
**** Only for patients in Arm B (5 years of anastrazole)

2. INTRODUCTION AND RATIONALE

2.1. Breast cancer

Breast cancer is one of the most common causes of death in women. The new diagnosis rate in Austria recently exceeded 5000 cases per year. Through the multifaceted efforts of science, there have been remarkable improvements in the results of treatment in the last few years. This has also recently been reflected in the first reduction in overall mortality in Central Europe and also in Austria [1] against a continued increase in prevalence. The treatment methods are varied and, today, are conducted on an interdisciplinary and individual, risk-adapted basis.

The vast majority of patients with breast cancer are in the low-risk subgroup. These are mainly women who are over 50 years of age and have undergone the menopause. In these patients, the majority of tumours are of a limited size at the time of diagnosis and surgery, and have hormone receptors (oestrogen, progesterone) on the surface of the tumour cells. Once primary therapy is complete, this makes these patients candidates for adjuvant endocrine therapy, which has so far been administered using anti-oestrogens as standard.

2.1.1. Standard hormone therapy

Over the last 25 years, a remarkable amount of scientific evidence has been accumulated, which substantiates the benefits of adjuvant tamoxifen in patients with hormone-dependent breast cancer [2–10]. As a result, tamoxifen is currently regarded as the standard adjuvant endocrine therapy in patients with tumours that are hormone-dependent. This is reflected in the current global standard therapy recommendations [11,12]. Despite the development of various newer anti-oestrogens, none of the products has so far proved to be superior to tamoxifen in the adjuvant breast cancer setting.

2.1.2. Overall duration of treatment

Overall, a certain “chronification” of the disease of breast cancer has been observed from an epidemiological point of view, which is pleasing in itself. However, data from meta-analyses and community databases with a high evidence level are now available, which show there are a considerable number of recurrences a long time after the usual follow-up phases. Unlike the survival curves usually observed in bowel cancer, for example, the survival curves of low-risk breast cancer only flatten off marginally after 5 to 10 years.

In other words, this means that the annual recurrence and mortality rates in the 3rd five-year cycle are only marginally lower than in the first two.
The actual figures are as follows [Source: EBCTCG 2000; figures for tamoxifen therapy, in brackets: without tamoxifen)]:

	Annual recurrences (%)	Annual fatalities (%)
Year 0–5	3.30 (3.86)	1.80 (2.56)
Year 6–10	2.46 (3.25)	2.54 (3.62)
Year 11–15	2.17 (2.57)	2.16 (2.78)

This observation necessarily leads to the question of whether the current standard treatment duration with adjuvant endocrine therapy for postmenopausal breast cancer patients is not significantly too short. Is a treatment duration of 5 years, as is currently the world standard, actually sufficient when 3% disease recurrences still occur annually between the 6th and 10th year and 2% annual recurrences still occur between the 10th and 15th year?

Data from Austria (M.Gnant 2003, n>12,000, data on file) show that the recurrence rate hardly drops at all in the second and third five-year cycles, and is about 3% annually in this country.

A recently published highly regarded international multicentre study (MA-17) shows that adjuvant treatment beyond the first 5 years after surgery brings a real benefit. In this study, more than 5000 patients were randomised double-blind after 5 years of tamoxifen between no further therapy and a further 5 years of therapy with the aromatase inhibitor letrozole; after a 2.4-year average follow-up time, the difference between the two groups was so great (to the benefit of the treatment group) that the study had to be discontinued, unblinded and published [13]. This result shows the fundamental correctness of the question asked at baseline after extension of the endocrine therapy. However, as a result of the unexpected discontinuation of the study, many questions remain unanswered, particularly the question relating to the optimal duration of secondary adjuvant treatment.

This study aims to clarify precisely this question. The study will consider secondary adjuvant treatment of 2 years versus 5 years after initial primary adjuvant treatment with tamoxifen or tamoxifen followed by anastrozole or a comparable endocrine therapy.

Study 8 from the ABCSG, which has been open for randomisation since 1996, will randomise a total of 3500 evaluable patients from the risk group described. The effect of 5 years of tamoxifen will be compared to the effect of 2 years of tamoxifen followed by 3 years of anastrozole. This provides an ideal starting point for this extension protocol, as a large portion of the patients to be randomised for this Protocol 16 are already in prospective GCP-compliant recording and documentation since diagnosis and primary therapy. In addition, relapse-free patients are available from Protocol 9 of the ABCSG.

It is assumed that approximately 1500 patients from these prior protocols are available for inclusion in this protocol. In addition, some 2000 patients who were previously treated with endocrine therapy outside of these studies are therefore also being included. Patients with 5 years of standard endocrine therapy with or without initial chemotherapy are being approached. This method should make the target randomisation number of 3500 evaluable patients possible.

2.2. Tamoxifen

2.2.1. Duration of treatment with tamoxifen

Although the value of adjuvant tamoxifen therapy has been established, definitive information on the optimum duration of therapy with a high evidence level has only recently become available, while for many researchers the matter has long been the subject of scientific debate [14].

However, it is certain from today's perspective that there is clearly a period, after which point the tamoxifen loses its effect and continued therapy might be harmful to the patient. Indications of this can be found in the results of adjuvant tamoxifen studies, as well as in observations in patients with advanced breast cancer: Some women relapse during the adjuvant therapy or stop responding to the tamoxifen therapy. With regard to the optimum administration duration of tamoxifen in the adjuvant setting, most of the initial studies compared 1–2 years of tamoxifen treatment with no treatment. These studies produced reductions in tumour recurrence in women treated with tamoxifen, which occurred most frequently during the treatment period, with little or no benefit thereafter. Together with experimental evidence proving that the effect of tamoxifen in chemically induced breast tumours is cytostatic instead of cytotoxic, these observations suggest that the benefit of tamoxifen could be increased by prolonged administration.

A Swedish multicentre study [8] compared 2 years with 5 years of adjuvant tamoxifen (20–40 mg/d) in postmenopausal women with early lymph node-negative or positive invasive breast cancer. 3545 (91%) of the 3887 patients were relapse-free after 2 years, enabling key information to be collected for the 2 vs. 5 year comparison. Ten years after enrolment, the reduction in relapse and mortality rates in patients on prolonged tamoxifen therapy was significant (DFS: 73% vs. 67%, p=0.009; survival (S): 80% vs. 74%, p=0.03).

A British study, which randomised 2937 relapse-free patients after 2 years of tamoxifen to no further treatment or 3 additional years of tamoxifen therapy, came to similar conclusions [9]. After a 2-year median follow-up post-randomisation, a statistically significant benefit was observed in women who had been treated for longer (relative risk: 0.81%, 95% CI: 0.69–1.15).

Together with non-randomised comparisons between 3 and 2 years of tamoxifen administration in an NSABP study [10] and in a meta-analysis of the EBCTCG [15], these results substantiated the value of prolonged tamoxifen administration (up to 5 years).

The next obvious question was whether the administration of tamoxifen beyond 5 years would result in an additional improvement in DFS and OS. In order to answer this question, NSABP randomised patients who had taken part in the B-14 study and were relapse-free after 5 years of tamoxifen, to a further 5 years of tamoxifen or placebo [16]. Significant advantages in terms of DFS (88% vs. 80%, p=0.004) and OS (97% vs. 91%, p=0.007) were observed for the whole 6 years after re-randomisation in patients receiving placebo, in contrast to tamoxifen-treated women (NSABP data on file, 1998). This study shows that tamoxifen therapy exceeding 5 years brings no benefit for lymph node-negative patients and that extended administration may even be harmful.

These results were confirmed by a Scottish study [17], which had a similar design in terms of tamoxifen administration being continued vs. halted after 5 years. In the 342 patients assigned to a prolonged tamoxifen administration in this study, an insignificant trend towards a higher recurrence rate was observed after 6 years of median follow-up (RR: 1.27, 95% CI: 0.87–1.85).

On the other hand, a small-scale study by the ECOG, which compared 5 years of tamoxifen administration with more than 5 years in 193 lymph node-positive patients, showed an insignificant trend towards a reduced recurrence rate with extended tamoxifen administration (15 vs. 23) [18].

2.2.2. Limitations in efficacy and development of tamoxifen resistance

The experimental and clinical data indicates more than one mechanism of tamoxifen resistance. These include the development of a partial agonistic activity of tamoxifen with stimulation of tumour growth [16,17,19–21], the alteration or mutation of the ER [20,22–24], the clonal selection of an ER-negative phenotype [20,24,25], the development of a metabolic tolerance [20,24], inadequate intra-tumoural tamoxifen concentrations [20,25] and increased gene expression and growth factor production by tumour cells, which may lead to autocrine stimulation [26].

Alteration or mutation of the ER: Despite the popularity of this theory of tamoxifen resistance and a large number of previous studies, there is no compelling evidence that the ER mutation in that molecular mechanism triggers tamoxifen-stimulated growth in human breast cancer [20,22–24,27]. There is some evidence for the remodelling of ER expression in relapse, however, it remains to be determined whether there is increased sensitivity of ER-positive cells compared to hormonal stimuli [20]. In most cases, the expression of a fully functional wild-type receptor continues in the event of relapse.

Clonal selection of an ER-negative phenotype: ER-negative tumour cells clones do not seem to occur frequently, and there is little clinical evidence to support the role of ER variants or mutants [22–25].

Development of metabolic tolerance and inadequate intratumoural tamoxifen concentrations: An ineffective oestrogen blockade might arise from metabolic tolerance and inadequate intratumoural tamoxifen concentrations [20]. There are indications that the intratumoural concentration of the drug in the event of relapse is considerably reduced in some patients despite unchanged plasma levels [24,25].

Increased gene expression and growth factor production lead to autocrine stimulation: This has been considered as one of the potential mechanisms of tamoxifen resistance. The overexpression of transforming growth factor TGFβ has been reported in tamoxifen-resistant breast cancer in humans [26]. In addition, reversion of tamoxifen resistance was shown in vivo with TGFβ-neutralising antibodies. MCF-7 cell lines infected with fibroblast growth factor (FGF) responded in a reduced form to pure anti-oestrogens or aromatase inhibitors (AI), suggesting that the autocrine activity of the disrupted FGF could replace oestrogen as a mitotic stimulus of tumour growth [28]. Finally, knowledge of the molecular pathways that regulate cell growth and apoptosis in hormone-sensitive cells is increasing. Constitutive activation of these pathways could provide the cell with a mechanism with which it can bypass the requirement for oestrogen.

In relapsing patients undergoing adjuvant tamoxifen therapy, some (if not all) of the mechanisms described above could play a significant but variable role in the development of tamoxifen resistance. The predominant mechanism or mechanisms will ultimately determine whether additional clinical benefit can result from prolonged hormonal manipulation. In progressive disease, patients who develop an acquired resistance after an initial response have about a 50 percent chance of responding to another hormonal agent [25].

2.3. Anastrozole

2.3.1. Rationale for use of aromatase inhibitors after tamoxifen

Based on the above arguments and until new information indicates to the contrary, adjuvant tamoxifen is administered for a period of 5 years worldwide. As a result, the majority of low-risk patients are disease free at the end of the tamoxifen therapy.

However, some of these “seemingly” disease-free patients harbour residual or micrometastatic tumour cells even after several years of tamoxifen therapy. In a fraction of these women, these residual tumour cells may still respond to tamoxifen and proliferate on discontinuation. However, clinical data supports the idea that in some patients treated with tamoxifen, the micrometastatic tumour cells are stimulated by the medication when tamoxifen therapy is continued. So while tamoxifen discontinuation may be of benefit for the latter group, it would be harmful for the former. Since residual or micrometastatic tumour cells are hormone-sensitive in both groups, reducing the level of oestrogen stimulation at the time of tamoxifen dose setting appears to be a theoretically sound strategy.

Aromatase inhibitors (AI) systemically inhibit oestrogen synthesis in a variety of tissues. They prevent oestrogen biosynthesis by inhibiting the aromatase enzyme, which catalyses the conversion of androgens to oestrogen. For several years, there has a keen interest in the development of aromatase inhibitors as potential treatment modalities in hormone-sensitive breast cancer in postmenopausal women.

Aminoglutethimide was the first-generation inhibitor. Despite its effectiveness as an adjuvant therapy in breast cancer [29], the medication exhibited low tolerability. In Study 6, the ABCSG already tried to improve the treatment results by adding aminoglutethimide to tamoxifen therapy [30].

Efforts to develop a better tolerated second-generation aromatase inhibitor resulted in the development of formestane (4-OH-androstenedione). However, since this product suppressed plasma oestradiol to only 1/3 of baseline levels and required parenteral administration, it was of limited clinical use [31,32].

As a result, third-generation aromatase inhibitors were developed. These are split into two basic categories:

- Non-steroidal aromatase inhibitors, e.g. fadrozole, vorozole, letrozole and anastrozole, and
- Steroidal aromatase inhibitors, such as exemestane

It is not known whether additional hormonal interventions after completing 5 years of tamoxifen therapy would be beneficial in relapse-free breast cancer patients at the respective time. However, there are many indications that sequential administration of aromatase inhibitors during or at the end of the tamoxifen therapy can produce significant anti-tumour responses in a portion of those patients who relapse [31–34]. The disadvantage of a wait-and-see approach is that at the time of relapse an additional portion of tumours have become hormone-resistant, while another would only remain hormone-sensitive for a short time.

Thus, there are theoretical advantages to secondary adjuvant administration of aromatase inhibitors, which may hold the promise of further reducing the subsequent relapse risk in patients who remain relapse-free after completing adjuvant tamoxifen therapy. A significant percentage of women who are relapse-free after 5 years (the usual time for discontinuing tamoxifen), would suffer an event if left untreated over the course of a further 5 years: for example, approximately 10% of the lymph node-negative (NSABP B–14, data on file, 1998) and approximately 17–19% of the lymph node-positive patients (NSABP B-16, data on file, 1998). These figures are likely to increase with additional follow-up.

2.3.2. Anastrozole data

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal patients, oestradiol is primarily produced through conversion of androstenedione into oestrone by the aromatase enzyme complex in peripheral tissue. Oestrone is subsequently converted into oestradiol. Reducing circulating oestradiol levels in women with breast cancer has been shown to have a positive effect. In postmenopausal patients, anastrozole induced oestradiol suppression of over 80% at a daily dose of 1 mg.

Anastrozole does not have a gestagenic, androgenic or oestrogenic effect. Absorption of anastrozole is rapid and peak plasma concentrations are observed within 2 hours of application (on an empty stomach). Anastrozole is eliminated slowly with a plasma elimination half-life of 40–50 h. Around 90 to 95% of steady state plasma concentrations are reached after 7 daily doses.

Anastrozole is extensively metabolised in postmenopausal women, where <10% of the dose is excreted unchanged in the urine within 72 hours after application.

Anastrozole is only 40% bound to plasma proteins.

Anastrozole is a substance that is well tolerated overall and has been implemented in the adjuvant setting on the basis of very promising data from phase II and III trials. The adverse effects are known compared to tamoxifen from the randomised palliative and adjuvant trials,

and include hot flushes, vaginal dryness and hair thinning, caused by the pharmacological activity (reduction of oestrogen). Adverse effects are presented in Table 1 and relate to a total of 665 patients from a randomised study into advanced breast cancer in postmenopausal women. A significant reduction in thromboembolic diseases is especially noteworthy when comparing anastrozole and tamoxifen; the other adverse effects do not differ significantly.

Table 1: Adverse effects in % [35]

	Anastrozole (1 mg) (n = 336)	Tamoxifen (20 mg) (n = 329)
Depression	4.2	5.5
Thromboembolic disorders	4.8	7.3
GI disorders	23.5	28.0
Hot flushes	20.5	20.7
Vaginal dryness	2.1	1.8
Vaginal bleeding	1.2	2.4
Lethargy	1.2	2.7
Weight gain	1.8	1.8

Initial investigations from the largest ever adjuvant study conducted in patients with breast cancer, the ATAC trial involving over 9000 patients, were presented in San Antonio in 2001 [36]. The results showed that anastrozole is statistically significantly more effective in reducing early relapses than tamoxifen (p=0.013). However, it should be noted that at this point in time, the mean duration of therapy and the mean retention time of patients in the study were between 30 and 36 months and thus the duration of therapy of 5 years stated in the study was not reached by a long shot. Therefore, at this point in time tamoxifen is still to be considered the treatment of choice, although the hope is that anastrozole will also show a benefit over tamoxifen at the 5-year treatment duration point.
The adverse effect profile is shown in Table 2. This shows a significant reduction in the occurrence of endometrial cancer and vaginal bleeding as well as thromboembolic episodes, stroke and hot flushes in the anastrozole-treated group compared to the tamoxifen-treated group. However, musculoskeletal symptoms, especially joint pain, and fractures are significantly more common with anastrozole. Other significant side effects, such as fatigue, changes in emotional state, ischaemic cardiovascular disease and cataracts are not significantly different.

As interaction studies with antipyrine and cimetidine showed, it is unlikely that concomitant administration of Arimidex® with other medicines leads to clinically significant, cytochrome P450-mediated drug interactions. Furthermore, safety data from clinical studies showed no evidence of clinically significant interactions between Arimidex® and other commonly prescribed medications. Oestrogen-containing therapies should not be administered together with Arimidex®, since they could neutralise its pharmacological effect.

A dose of anastrozole of up to 10 mg does not cause any change in the secretion of cortisol or aldosterone. Interactions with bisphosphonates are yet to be established.

Table 2: Adverse effects ATAC trial in % [36]

	Anastrozole (n = 3125)	Tamoxifen (n = 3116)	Combination (n = 3125)
Hot flushes	34.3	39.7	40.2
Nausea & vomiting	10.5	10.2	11.7
Fatigue (asthenia)	15.7	15.1	14.0
Mood swings	15.5	15.2	15.6
Muscle and joint problems	27.8	21.2	22.1
Vaginal bleeding	4.5	8.1	7.7
Vaginal discharge	2.8	11.4	11.4
Endometrial cancer*	0.1	0.5	0.2
Fractures overall	5.8	3.7	4.6
Fractures of spine, hip, wrist	2.2	1.4	1.6
Ischaemic cardiovascular events	2.5	1.9	2.2
Ischaemic cerebrovascular events	1.0	2.1	1.6
Venous thromboembolic events	2.1	3.5	4.0
Deep vein thrombosis	1.0	1.7	2.0
Cataract	3.5	3.8	3.4

* Excluding patients with a hysterectomy at the time of baseline examinations

2.4. Rationale

2.4.1. Patient population

As can be seen from the overview data (Peto 2000, personal communication) as well as from recent internal statements (Gnant, 2003, unpublished data), stage I and II breast cancer patients who have had tamoxifen treatment for 5 years have a 10–12% probability of suffering a recurrence of their breast cancer in the 2nd and 3rd 5-year cycle, in a relatively lower percentage of dying from their underlying disease. It would therefore appear useful to examine the effect of two different time periods (2 vs. 5 years) of prolonged (secondary adjuvant) anti-hormonal therapy in this number of cases.

2.4.2. Justification for the primary study objective

It is possible that prolonged endocrine therapy has a positive effect on the rate of recurrence.

2.4.3. Therapy plan

In the ATAC study, anastrozole was administered in the therapy plan for 5 years, thus this duration of therapy constitutes a sensible rationale. Since a portion of the patients who are to be included in the protocol had already been treated with anastrozole for 3 years (ABCSG-8), these patients will also receive the aromatase inhibitor in the 2-year group of the present study for a total of 5 years. The difference between 2 and 5 years is clinically relevant (see the discussion of tamoxifen 2 decades ago) and mathematically realistic.

3. OBJECTIVE

3.1. Primary objective

3.1.1. Assessment of the effect in terms of disease-free survival (DFS) of a further 2 years of anastrozole vs. a further 5 years of anastrozole after 5 years of adjuvant endocrine therapy

3.2. Secondary objective

3.2.1. Assessment of the effect in terms of overall survival (OS) of a further 2 years of anastrozole vs. a further 5 years of anastrozole after 5 years of adjuvant endocrine therapy

3.2.2. Comparison of the fracture rate between the two treatment groups

3.2.3. Comparison of the occurrence of secondary cancers between the two treatment groups

3.2.3.1. Comparison of the occurrence of contralateral breast cancer between the two treatment groups

3.2.3.2. Comparison of the occurrence of secondary cancers, with the exception of a contralateral breast cancer, between the two treatment groups

4. DESIGN

This is a prospective, randomised, open-label, multicentre phase III study in HR-positive breast cancer patients in the adjuvant setting.

All patients who are relapse-free at 60 months after surgery will be randomised after 5 years of primary endocrine treatment and maximum break in therapy of 12 months (e.g. from Studies 8 and 9 of the ABCSG) to:

Arm A: 2 years of therapy with anastrozole (Arimidex®)
Arm B: 5 years of therapy with anastrozole (Arimidex®)

The treatment phase lasts for 2 or 5 years. The follow-up phase has been set at 8 years in Arm A and 5 years in Arm B.

Planned study start:	December 2003
Planned recruitment end:	December 2008
Planned end of the maximum treatment phase:	December 2013
Planned end of follow-up:	December 2018

5. STUDY POPULATION

5.1. Sample size

The aim is to recruit 3500 patients in a multicentre design.
Full details of the statistical calculation of sample size can be found under item 10.

5.2. Inclusion criteria

1. Postmenopausal patients with histologically verified invasive or minimally invasive breast cancer that has been radically treated locally with or without previous chemotherapy and/or radiotherapy
2. Age ≤ 80 years
3. No distant metastasis at randomisation
4. No recurrence at randomisation
5. TNM-classification at the time of diagnosis: T1-3, N0-1, M0
6. Oestrogen and/or progesterone receptor-positive before the start of primary endocrine therapy
7. Endocrine therapy for 5 years (maximum deviation ± 12 months)
8. Therapy break (from the preliminary therapy) maximum 12 months
9. At the time of randomisation, the results of the following tests must be available:
    a) Medical history and clinical examination (within one month prior to randomisation)
    b) Gynaecological examination (within one month prior to randomisation)
    c) Chest x-ray or CT scan (within one year prior to randomisation)
    d) Bilateral mammogram (within one year prior to randomisation) – exception are women with mastectomy (unilateral)
    f) Ultrasound of the abdomen or abdominal CT (within one year prior to randomisation)
    e) Laboratory parameters (within 3 months prior to randomisation)
        - Adequate liver function (GOT or GPT ≤ 2.5 x ULN; total bilirubin < 2 x ULN, AP < 2 x ULN)
        - Serum creatinine ≤ 1.5 x ULN
10. Informed consent prior to randomisation

5.3. Exclusion criteria

1. Premenopausal patients or patients with non-determinable menopausal status at randomisation
2. Manifest secondary malignancy or status post secondary malignancy between the time of initial diagnosis and randomisation
3. General contraindications and/or hypersensitivity to anastrozole
4. Carcinoma in situ of any size with or without Paget's disease of the nipple or T4 tumours at the time of initial diagnosis
5. Receptor determination unknown or negative at the time of diagnosis or at the start of the primary endocrine therapy
6. Age > 80 years
7. Performance index >3 as per WHO
8. Regular use of hormone products and hormone replacement therapy (HRT) for more than 6 months since the primary breast cancer surgery
9. Serious concomitant disease preventing implementation of adjuvant therapy in line with the protocol and/or controlled follow-up
10. Lack of patient cooperation

11. Legal incapacity and/or other circumstances preventing the patient from understanding the nature, significance and implications of the clinical trial
12. Existing psychiatric disease as per ICD at study enrolment (especially alcohol dependency)

5.4. Premature termination of the clinical study

5.4.1. Premature termination in an individual case

Reasons leading to study discontinuation are:

1. Withdrawal of patient consent
2. Occurrence of intolerable adverse events
3. Occurrence of relapse, secondary cancer or death of the patient
4. Lack of compliance or cooperation of the patient
5. Serious protocol violation
6. Other personal reasons for the patient (e.g. change of location); there is usually the possibility of ongoing care at another ABCSG study site
7. Patient no longer attends (lost to follow-up): the maximum time frame for this is
    - In the therapy phase: +6 months calculated from the scheduled visit date (see 6.5.)
    - In the follow-up phase: +12 months from the scheduled visit date

    The investigator must make every effort to establish contact with the patient.

Each patient has the right to withdraw their consent to take further part in the clinical trial at any time and without giving reasons. You will not be disadvantaged as a result. The investigator will attempt to ascertain the reasons for the discontinuation, but the patient's rights must not be violated. The time of the discontinuation, the results to date, and, if known, the reason for the patient's discontinuation should be documented in the patient file and the CRF. If a patient wishes to withdraw from the study, they must be asked whether or not they agree to the further use of their clinical data (in particular to disease-related events and follow-up) for study-related purposes.
The investigator may also terminate the trial if he no longer deems the patient's participation to be justified e.g. from a medical point of view. The date and reason for discontinuation, as well as all observations gathered up to the point of discontinuation are to be recorded in the medical history and CRF.

The investigator will continue to observe patients who were removed from the study due to intolerable adverse events until these have resolved or findings have normalised.

All patients, regardless of whether the treatment was discontinued prematurely or not, will receive follow-up care as per the study protocol. Data will be collected and documented in accordance with the FUP guidelines (see 7.3.).

5.4.2. Discontinuation of the entire trial

The entire clinical trial may be interrupted or terminated at any time by the Coordinating Investigator in consultation with AstraZeneca due to considerations of risk vs. benefit where criteria leading to discontinuation in an individual case occur in an intolerably frequent manner or new knowledge regarding adverse effects or interactions of the study drug render this necessary.

AstraZeneca in agreement with the Coordinating Investigator reserves the right to discontinue the trial at any time, if

1. A change in the benefit vs. risk ratio precludes the continuation of the study for medical ethical reasons
2. The results of the planned interim analysis (see 10.3.) mean that it no longer appears to makes sense to continue the study
3. There is a delay in patient recruitment (evaluation after enrolment of 2000 patients) and it can be assumed that the recruitment period will be extended by $\geq$ 25%.

5.4.3. Closure of an individual site

AstraZeneca, in agreement with the EC of the ABCSG, is entitled to close individual sites subject to the following conditions:

1. Lack of recruitment
2. Lack of cooperation of the site
3. Other reasons that speak against correct conduct of the study

6. STUDY DRUG

6.1. Information on anastrozole

Name of product:	Arimidex®
Name of the manufacturer:	AstraZeneca Pharmaceuticals
Composition:	Each film-coated tablet contains 1 mg anastrozole as the active substance
Pharmaceutical form:	Film-coated tablet
Shelf life:	5 years
Storage advice:	Store below 30°C
Pack size:	112 tablets

6.2. Labelling

The investigational product is labelled in accordance with Section 32 para. 7 of the Austrian AMG.

6.3. Provision of the study drug

Anastrozole (Arimidex®) is supplied to each patient free of charge in containers containing 112 tablets for the entire treatment period.

6.4. Dosage

1 mg film-coated tablet of anastrozole is taken once daily. The duration of therapy is 2 or 5 years.

6.5. Dose modifications and delays

There are no dose modifications for anastrozole. A temporary interruption of treatment is only permitted for a maximum of 3 months.

6.6. Handling of the study drug by the investigator and documentation of its whereabouts

AstraZeneca will supply the required quantity of the study drug for the clinical trial. The study drug must only be dispensed to patients in this protocol. The investigator will confirm correct receipt of the study drug in writing and ensure secure and appropriate storage.
Each pack comes with a tear-off, self-adhesive label. The investigator must fill in the dispensing date on the day of dispensing to the patient and stick it into the “Prescription Record Cards” in the CRF. Return of any medication must also be documented on an individual basis.
The monitor will examine full documentation of the whereabouts of the study drug during regular visits to the investigator and will resolve any discrepancies between used and dispensed study drug. The result is documented in the Monitoring Report.

A “Drug Accountability Log” is kept, in which receipt of the study drug, patient-specific study drug withdrawals and stock are recorded at monitoring visits.

6.7. Disposal of the study drug

Any trial drug that is returned by patients or unused (e.g. expired) is passed on to AstraZeneca by the Monitor to be destroyed.

7. IMPLEMENTATION

7.1. Examination parameters before study start

1. Medical history, e.g. histological findings, HR status findings, WHO status (within one month prior to randomisation)
2. Clinical examinations (within one month prior to randomisation):
    - Clinical examination
    - Gynaecological examination
3. Radiological investigations (within one year prior to randomisation):
    - Sonography of the abdomen or abdominal CT
    - Chest x-ray or CT
    - Bilateral mammogram (unilateral mammogram in the case of mastectomy)
    - Bone density measurement (optional)
4. Laboratory parameters (within 3 months prior to randomisation):
    - LFP (GOT, GPT, total bilirubin, AP)
    - RFP (serum creatinine)
    - Optional tumour markers: CEA, CA 15-3

7.2. Examination parameters during the study

7.2.1. After 6 months (Arm A and B)

1. Clinical examination
2. Survey of fracture rate
3. Adverse events leading to discontinuation of therapy
4. Severe adverse events

The time frame for these examinations is defined as +/- 6 weeks.

7.2.2. After 12 and 24 months (Arm A and B)

1. Clinical examination
2. Survey of fracture rate
3. Adverse events leading to discontinuation of therapy
4. Serious adverse events
5. Laboratory parameters:
    - LFP (GOT, GPT, total bilirubin, AP)
    - RFP (serum creatinine)
    - Optional TU marker: CEA, CA 15-3
6. Gynaecological examination
7. Radiological examinations
    - Sonography of the abdomen or abdominal CT
    - Chest x-ray or CT
    - Bilateral mammogram (unilateral mammogram in the case of mastectomy)
    - Bone density measurement (optional)

The time frame for these examinations is defined as +/- 6 months. If the patient does not attend the visit at the designated interval, this results in the patient being set to the off position.

7.2.3. After 36, 48 and 60 months (Arm B)

1. Clinical examination
2. Survey of fracture rate
3. Adverse events leading to discontinuation of therapy
4. Serious adverse events
5. Laboratory parameters:
    - LFP (GOT, GPT, total bilirubin, AP)
    - RFP (serum creatinine)
    - Optional TU marker: CEA, CA 15-3
6. Gynaecological examination
7. Radiological examinations
    - Sonography of the abdomen or abdominal CT
    - Chest x-ray or CT
    - Bilateral mammogram (unilateral mammogram in the case of mastectomy)
    - Bone density measurement (optional)

The time frame for these examinations is defined as +/- 6 months. If the patient does not attend the visit at the designated interval, this results in the patient being set to the off position.

7.3. Follow-up

After the therapy is complete, follow-up examinations are carried out at yearly intervals (+/- 6 months) for a period of 8 years in Arm A and 5 years in Arm B.

1. Clinical examinations
2. Bilateral mammogram (unilateral mammogram in the case of mastectomy)
3. Serious adverse events (see 9.1 and 9.2.4)

Written contact with the patient to obtain findings is permitted. It is also possible to check the patient's status (living or deceased) via the Central Registration Office (ZMA) or the GP. If the patient does not attend a visit for more than 2 years during the follow-up period, this results in the patient being set to the off position.

8. METHODS

8.1. Methods/parameters relating to efficacy

DFS: Time from randomisation to onset of any of the following events:

- Occurrence of a relapse (locoregional relapse, distant metastasis)
- Occurrence of a secondary cancer (except basal cell carcinoma of the skin, in-situ carcinoma of the cervix or LCIS)
- All deaths regardless of cause

Overall survival: Time from randomisation to onset of death, regardless of the cause

Locoregional relapse: Definition:
1. Relapse in the operated breast
2. Chest wall relapse on the operated side
3. Axillary lymph node recurrence

In addition to the exact date of verification of the locoregional recurrence, the type of diagnostic measure used is documented in detail.

Distant metastasis: Definition:
1. All distant lymph node metastasis (supraclavicular, internal mammary lymph nodes, contralateral axilla)
2. All organ metastasis

In addition to the exact date of the verification of the metastasis, the type of diagnostic measure used is documented in detail.

Event: Definition:
1. Locoregional recurrence
2. Contralateral breast cancer
3. Distant metastasis
4. Fatality regardless of the cause

Fracture rate: The occurrence of fractures is assessed according to the following locations:

- Hip
- Lumbar spine
- Radius
- Other

8.2. Concomitant diseases

Concomitant diseases that do not fall under the exclusion criteria referred to in 5.3., such as diabetes mellitus, hypertension etc., should be stabilised with suitable medication before inclusion in the clinical trial.

8.3. Concomitant therapy

With the exception of anastrozole, no other systemic breast cancer treatments may be used for the entire duration of the study.

The administration of substances that have an influence on the status of sex hormones (e.g. prednisolone, hormone replacement with oestrogen or progesterone) is not permitted with the exception of topical application of oestrogen and use of phytoestrogens.

For all other medications, there are no restrictions.

According to the guidelines from the American Society of Clinical Oncology [37] (Appendix B), postmenopausal women receiving aromatase inhibitors as part of their adjuvant therapy are always classified as “high risk” for developing therapy-induced osteoporosis.

For these patients, and thus for all patients within this study, the following recommendations apply:

- Ongoing monitoring of bone density (once a year)
- If T score >-1: Observance, life style recommendations, possibly calcium + vitamin D
- If T score >-2.5 and <-1: Life style recommendations, calcium + vitamin D
- If T score >-2.5: Life style recommendations, calcium + vitamin D **and** Therapy with bisphosphonates

With the exception of osteoporosis-associated therapy, concomitant medications do not need to be documented in the CRF.

9. ADVERSE EVENTS

Adverse events or serious adverse events are defined below. It is vitally important that all persons who are involved in the conduct of this clinical study are familiar with the content of this section of the Protocol. It is the job of each investigator involved in the study to ensure this happens.

9.1 Definition of "adverse event – (AE)"

An adverse event is the occurrence of a disorder or exacerbation of a pre-existing condition in the context of a clinical study and is independent of a possible causal relationship with the administration of the trial drug. Disorders may be subjective and objective symptoms of the disease, including laboratory abnormalities. Adverse events leading to discontinuation of therapy must be documented in both the medical history and in the CRF.

With the exception of AEs that lead to discontinuation of therapy and fractures, all other AEs that are non-serious are not documented in the CRF within this study. However, it is mandatory to record all adverse effects in the patient's medical file.

9.2. Definition of "serious adverse event – SAE"

A serious adverse event is an event that:

- Has a fatal outcome (for whatever reason)
- Has led to an immediate threat to life
- Has necessitated an inpatient admission or has prolonged an inpatient stay
- Has led to a lasting or significant disability/incapacity for work
- Has caused congenital malformations
- Constitutes a malignant tumour

Other serious, medically relevant events that endanger the patient or require a medical intervention in order to protect them from the above-mentioned damage, are also classified as serious adverse events.

9.3. Reporting of serious adverse events by the investigator

9.3.1. Reporting during the therapy phase

If the AE is classified as serious by the investigator, an AstraZeneca-specific SAE Reporting Form must be filled out and sent to AstraZeneca by the investigator within 24 hours of discovery.

An original copy of the Reporting Form(s) and the fax confirmation(s) should be filed in the IF for the respective study site.

In addition, AstraZeneca undertakes to submit a quarterly statement of all SAEs that occurred in the context of the study to ABCSG Regulatory Affairs.

Details can be found in the study-specific SOPs under the item "Recording, assessment and reporting of serious adverse events".

9.3.2. Reporting during follow-up or after discontinuation of therapy

The occurrence of serious adverse events in patients, in whom the study drug / study participation has been discontinued or terminated or the therapy has ended in line with the protocol only need to be reported if the adverse event occurred

- Within 30 days of discontinuing the study drug (drug incidents that are a causally linked to a follow-on therapy are not reported)
- More than 30 days after discontinuing the study drug, but the investigator cannot rule out a causal link with the previous therapy (anastrozole).

9.3.3. Reporting of protocol violations

Serious adverse events in patients who violate the protocol only need to be reported if the patient in question has already received the trial substance.

Irrespective of these exceptions, the investigator may at any time express to the sponsor that, in his opinion, an SAE should nevertheless be reported.

9.4. Reporting of serious adverse events by AstraZeneca

All SAEs reported to AstraZeneca are assessed, documented and evaluated according to the SOPs applicable to the clinical trial, and reported to the Federal Ministry for Women and Health and to AstraZeneca Drug Safety. Where applicable, SAEs are also reported to the hospitals in the Viennese Hospital Association [Wiener Krankenanstaltenverbund (KAV)].

In accordance with ICH-GCP, AstraZeneca will also inform all investigators involved of unexpected serious adverse effects of anastrozole occurring within the implementation of this clinical trial. This information will also be issued to the ABCSG.

9.5. Exceptions

The following events that occur over the course of Study 16 will not be reported as serious adverse events:

- Progression of the underlying disease or death as a result of the underlying disease
- Hospitalisation:
  - Hospitalisation already scheduled or planned before enrolment in the study.
  - Hospitalisation to undergo purely diagnostic measures in particular, patient-related situations (such as elderly patients with a long journey to the study site). Hospitalisation would not normally be required.
  - Hospitalisation for cosmetic surgical measures.

  NB: Complications that occur during these hospitalisations are regarded as serious adverse events and are subject to the obligation to report!
- Accidents with demonstrable third party responsibility only (passive involvement of the patient).

However, all of these events must be documented in the medical records (traceable for the monitor) in each case until their conclusion.

10. STATISTICAL ANALYSIS

10.1. Sample size

From randomisation, all patients receive the same therapy for 2 years, and one group for a further 3 years. Any difference between the groups is thus only to be expected after 2 years from randomisation. Therefore, 2 years after randomisation (= change of therapy) is defined as the primary time of interest for the analysis for each patient.
It is expected that 700 patients may be recruited per year. Considering that 5% of the patients drop out in the first two years due to relapses, 665 patients per year remains an effective recruitment rate.
A difference between the treatment group and the control group of 0.916 and 0.937 after 3 years from the date of change of therapy in exponential survival (which corresponds to a hazard ratio of 1.35) can be disclosed with a power of 85% and a bilateral significance level of 5% when 433 events are observed. This will be achieved when 665 patients are recruited over 5 years and followed up for a further 2.7 years. This produces a sample size of 3500 patients of which 3325 are evaluable. The expected total duration of the study is 9.7 years.
At an exponential drop-out rate of 7%, the power would reduce to 80%.

10.2. Stratification and randomisation

Patients who meet the inclusion and exclusion criteria will be randomised by telephone message in the ABCSG randomisation centre

Tel. no.: [redacted]8
or
[redacted]

Randomisation times:
Mon – Thu 8:30 am – 12:00 pm and 1:00 pm – 3:00 pm
Fri 8:30 am – 2:00 pm

using a computer program and in accordance with the adaptive Pocock and Simon (1975) randomisation method. This computer-aided randomisation procedure ensures that the marginal distribution of the characteristics of the stratification criteria is the same in both treatment groups. The randomisation date is recorded. For randomisation, the personal patient data and stratification criteria must be announced.

The patient number received from the randomisation centre consists of two elements:

- A four-digit number for sequential numbering of patients
- A letter code indicating the treatment arm:
  - A: For Arm A, 2 years of therapy with anastrozole (Arimidex®)
  - B: For Arm B, 5 years of therapy with anastrozole (Arimidex®)

Stratification criteria:

The following stratification criteria are used:

1. PT stage:	- PT1 ($\leq$ 2 cm) - PT2 (> 2–5 cm) - PT3 (> 5 cm)
2. PN stage:	- No LN metastasis - 1–3 LN metastasis - 4–9 LN metastasis - $\geq$ 10 LN metastasis
3. Adjuvant primary hormone therapy:	- 5 years anti-oestrogen - 2 years + anti-oestrogen + 3 years anastrozole - Comparable endocrine therapy
4. Adjuvant chemotherapy:	- Anthracycline-containing CT - Taxane-containing CT - Other CT - No CT
5. Study participation:	- Study 8 from ABCSG - Study 9 from ABCSG - None
6. Receptor status:	- ER+PgR+ - ER+PgR- - ER-PgR+ In principle, the result of the examination of the biochemical receptor determination should override that obtained by immunohistochemistry.
7. State:	- Vienna - Lower Austria - Burgenland - Styria - Carinthia - Upper Austria - Salzburg - Tyrol - Vorarlberg

10.3. Interim analyses

An interim analysis is carried out once 2/3 of the target recruitment is reached using a significance level of 0.001, according to the guidelines of Geller and Pocock (1987). If an unexpectedly strong therapeutic effect occurs, the study may be discontinued early.

10.4. Efficacy analysis

The final analysis is carried out according to the intent-to-treat principle of all randomised patients who meet the inclusion and exclusion criteria, have at least one follow-up examination after randomisation, and have survived for 2 years relapse free. They will be assigned to the group into which they were randomised regardless of whether they actually received the therapy or which one.
The graphical representation of the therapeutic effect on the primary and secondary target variables (DFS, overall survival and occurrence of secondary cancers, contralateral breast cancer and fractures) is based on the survival functions according to Kaplan and Meier (1958). The differences between the two study arms are tested using the log-rank test (Mantel (1966)).
In addition, the regression model according to Cox (1972) is used in an exploratory way to examine whether the consideration of additional prognostic factors modifies the results of the log-rank tests. This takes into account primarily the stratification criteria of the randomisation but also other prognostic factors. Differences in the therapy are quantified using hazard ratios (relative mortality risk during therapy compared with the control group). In addition, possible interactions of the therapy with other prognostic factors are examined. In the event of significant interactions, subgroup analyses are carried out.
All calculations are performed using the statistical software SAS® (Statistical Analysis Software; version 8) and all tests are two-tailed, where $p \leq 0.05$ is deemed statistically significant.

10.5. Safety analysis

The safety analysis is based on all randomised patients who started the therapy. All serious adverse events, adverse events leading to therapy discontinuation and fracture rates observed during or after therapeutic administration of the study drug are recorded. The worst value per patient is included in the analysis.

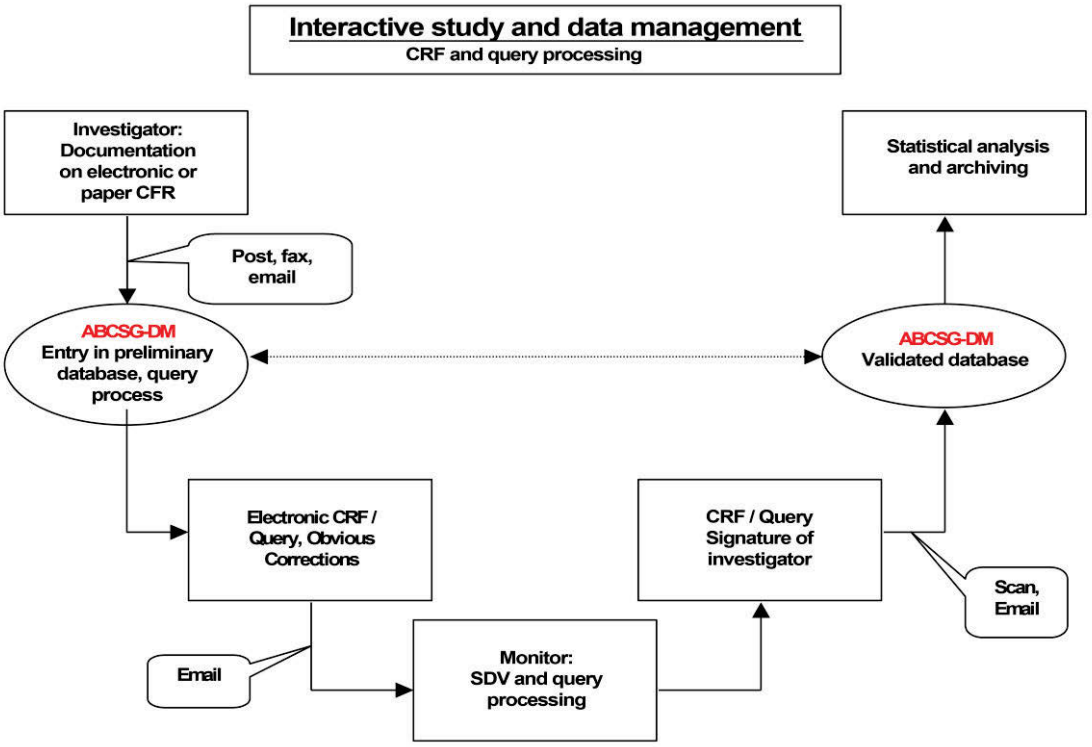
The laboratory data measured is described and maximum and minimum measurements are presented over time or by maximum deviations from the normal range. In addition, absolute and percentage changes from the baseline measurement values and maximum fluctuations over time are described.

10.6. Substitution of patients

No patient who meets the inclusion and exclusion criteria and who stops taking part in the study early for any reason will be replaced.

11. DATA MANAGEMENT

Data is managed by the ABCSG in cooperation with the contract research organisation CRS Creative Research Solutions GmbH using the IntTrial® system. IntTrial® is a modular system based on the universal PDF format for creating, evaluating and archiving study CRFs. The following diagram provides an overview of the "CRF flow" on IntTrial®:



11.1. Patient identification list

All patient-related data will be recorded in anonymous form. Each patient is assigned a patient number at randomisation that uniquely identifies them by their initials and date of birth. The investigator will keep a confidential patient list, in which the identifying data is linked to the patients' full name and optionally the insurance number.

11.2. Data collection / documentation sheets

11.2.1. Documentation

At the study sites, all data required by the study protocol as well as objective and subjective information must be entered directly into the relevant medical files/original patient documentation before documentation in the CRF.

All data collected during the study is entered into the designated documentation forms (CRFs) by the investigator or a person who has previously been authorised in writing. These provide a mirror image of the requirements according to the protocol.

If an examination has not been completed, this will be indicated with "n.d.". If information is not available, this will be documented with "n.a.".

The IntTrial® system allows the investigator to document study data electronically ("on-screen"; "e-CRF") or conventionally on a paper CRF. The study CRF is made available on CD-ROM. The CD-ROM contains all CRF pages both in the form of fillable PDF documents (e-CRF) and as a print version, which can be printed out and completed by hand.

After completion on computer, the CRF pages are sent to Data Management by email. Alternatively, the pages can also be printed out and either faxed or sent by mail. A copy of each page sent is kept at the site, either in electronic or paper form.

In the case of conventional documentation, the print template of the CRF is used. Fully completed pages are sent by post or faxed to Data Management. All entries must be made in permanent black or blue ballpoint pen to ensure the legibility of all copies.

It is important that documentation is completed soon after therapy. Documentation should therefore be completed and sent to Data Management within 7 days of a visit.

The completed CRF pages are sent to:

ABCSG Data Management
FAO [redacted]
Theresiengasse 32
1180 Vienna, Austria

Study fax: [redacted]
Study email: s[redacted]

11.2.2. Subsequent corrections to documentation

Once a CRF page has been completed on the computer and forwarded to Data Management, the page can no longer be corrected by the investigator and resubmitted to Data Management. The CRF page is entered into the preliminary database and further adjustments may only be carried out again during SDV.

If a CRF page is accidentally sent to Data Management twice, the second page will not be input, but simply archived. SDV is performed on the first version of the respective CRF page.

The same rules apply to paper CRFs. Since in this case, entries are made by hand, corrections made during documentation are made in accordance with the usual rules. An incorrect entry is crossed out, however, the deleted entry must remain recognisable. The corrected value should be written next to it. The date of the change and signature/initials of the investigator or authorised person must be added to each correction. The use of correction fluid is prohibited.

11.3. Data acquisition

Data acquisition is carried out by the person responsible for data management. Data entry takes place on an ongoing basis, in parallel with the clinical trial.

11.3.1. Data entry / obvious corrections / queries

CRFs received by Data Management are included in the preliminary study database. A system consisting of the Cardiff Teleform Reader, the Teleform Verifier and MS-SQL is used for the input process with IntTrial®. The input process is divided into automatic data acquisition, followed by a manual check by the data entry staff, with each value being checked subsequently.

A copy of each CRF page is automatically archived in electronic format as an indexed PDF. Corrections of obvious mistakes in the documentation (obvious corrections) are made immediately during input by the input staff and the changes are logged in the database. Missing, contradictory or illegible entries are also logged as queries in the database.

11.3.2. Creating an electronic copy of the CRF for source data verification (SDV)

To enable the study data to be monitored, the data from each CRF page included in the preliminary study database is exported into a blank CRF form. The obvious corrections made as well as the queries logged in the database are exported into the form.

These CRF pages are then made available to the competent monitor for source data adjustment. During SDV, queries already listed are processed and the CRF page is signed by the investigator after any corrections are made. A copy of the signed CRF remains at the site and the original is given to the monitor.

11.3.3. Data entry / database validation / database lock

The signed CRF pages are forwarded by the monitor to Data Management and then entered into the database again from there. This data is then validated by a final query process, based on checks for validity, consistency and plausibility.

Query forms to clarify any queries are passed on to the investigator for processing via the monitor. After processing, these are sent back to Data Management, and a copy is retained at the site.

After clarification of all possible queries using query forms, the database is closed. The analysis and statistical analysis is carried out using SAS® (Statistical Analysis Software) version 8.

11.4. Original data in the CRF

All data collected within this protocol must be available as original data in the respective medical history. Direct entries in the CRF are not considered to be source data.

11.5. Storage of CRFs

Once the study is completed, the documentation remains with the ABCSG. The originals of all central study documents including the documentation sheets are stored at the study site for at least 15 years after the end of the study. CRFs can also be stored on image carriers or other data storage devices.

During the study, one copy of the CRF remains with the respective investigator. The investigator also retains the administrative documents produced (correspondence with the Ethics Committee, BUMI, AstraZeneca, study site etc.), the patient identification list, signed informed consent forms, copies of documentation sheets and the general study documentation (protocol, amendments) for the period of time stated above.
Original data on study patients (medical files) must be stored in accordance with the archiving term applicable to the study sites, however, for a minimum of 15 years.

If the investigator does not stay at the study site for whatever reason (e.g. retirement, appointment elsewhere), the retention of the documents must be handed over to a successor, who consequently takes on the responsibility, and this must be documented in writing. Both AstraZeneca and the ABCSG must be informed of such a transfer in writing.

12. LEGAL AND ETHICAL PRINCIPLES

12.1. Legal basis

The study complies with

- The Declaration of Helsinki (1996 version, Appendix A)
- The currently valid Austrian AMG Section 2a and III. Sections 28 to 48
- and GCP/ICH.

12.2. Ethics Committee

Prior to commencement of the study, the vote from the competent Ethics Committee is obtained by the STS of ABCSG. This is the responsibility of the employee for Regulatory Affairs at the ABCSG.
Once the investigator receives the written vote, a copy is forwarded to AstraZeneca and the ABCSG-STS.

The Ethics Committee must also be informed by the ABCSG-STS of serious adverse events at the site, changes to the protocol (Amendments) as well as the discontinuation of the study.

12.3. Patient data and data protection

The investigator will not pass on the patient's name or other personal information. The collected patient data will be used only in anonymous form for the purposes of scientific work, and where necessary, for submission to the regulatory authorities by AstraZeneca. If it is necessary to identify the name of the patient during the course of the study for medical reasons, this will be done while maintaining the confidentiality of the persons involved in the study. The investigator keeps a separate Patient Identification List, which enables the randomisation numbers to be allocated to the names and addresses of the patients at any time. These Patient Identification Lists are stored in the IF.

Medical files can be viewed by authorised persons as part of monitoring, an audit by AstraZeneca or inspection by the authorities. The patient declared her written consent to this prior to the start of the trial.

The relevant provisions of the data protection legislation will be fulfilled.

12.4. Informed consent of the patient

Prior to inclusion in the clinical trial, each patient will receive an explanation of the nature, objectives, expected benefits and potential risks of the study and its procedure in a comprehensible form.
The explanation is given verbally during a conversation in which the patient is given sufficient time and opportunity to clarify any outstanding questions. The contents of the consent conversation are summarised in writing in the Patient Information.
The patient must have given their voluntary written consent to take part in the clinical trial prior to the randomisation process, at the latest on the day of randomisation, once the patient has had sufficient time to decide whether to take part in the study or not.
The original version of the Informed Consent Form signed and dated by the investigator and patient's own hand is filed in the IF, with a copy being given to the patient.

12.5. Liability and insurance

AstraZeneca has taken out appropriate patient insurance with Allianz Elementar Versicherungs-AG in accordance with Section 32, para.11 AMG (policy number: [redacted]) as well as third party liability for investigators (policy number: [redacted]. The patient will be informed of the provisions of this insurance by the investigator. In accordance with the Terms and Conditions of Insurance, the patient is obligated – except in emergencies – to undergo other medical treatment only in consultation with the investigator for the duration of the clinical trial, not to take part in another clinical trial and to report any injury to health that may have occurred as a result of the clinical trial to the insurer without delay.

The patient will be informed about the "General Terms and Conditions of Insurance" as part of the consent discussion. The patient may request a copy of these.

12.6. Amendments

Changes to the final protocol should be made by means of amendments and are subject to approval by AstraZeneca. Amendments must be processed in accordance with the statutory provisions.

Protocol amendments that might affect the health interests of patients require a new vote from the Ethics Committee and an updated Informed consent/Patient information, insofar as they are affected by the changes. Administrative or technical changes to the protocol do not require a new vote from the Ethics Committee. The Ethics Committee will, however, be informed of all protocol amendments.

12.7. Archiving

The investigator will ensure that the Patient Identification List and the written Informed Consent Forms are stored for at least 15 years after completion of the study, unless statutory regulations stipulate a longer retention period.

12.8. Confidentiality

The objectives and content of this study as well as its results must be treated as confidential and may not be made accessible to third parties. Employees involved in the study are also bound by this agreement.

13. QUALITY MANAGEMENT

13.1. SOPs and agreements

This clinical trial will be conducted in accordance with the SOPs of AstraZeneca and SOPs of ABCSG, as defined in a separate agreement. Deviations from this will be regulated in a special study-specific SOP.
The division of responsibilities between AstraZeneca, the investigators and ABCSG is defined in separate agreements.

13.2. Training

AstraZeneca must ensure that all monitors and other persons involved in the study, in consultation with the ABCSG, are fully cognizant of the applicable SOPs. This is achieved by means of training in the latest version of the SOPs.

At each study site, the responsible investigator must ensure that all employees involved in the implementation of the clinical trial or the care of trial subjects, are provided with all relevant information.

13.3. Site approval

Sites that are interested in taking part are assessed with regard to their suitability by the ABCSG on the basis of a study-specific checklist. The completed checklist is forwarded to AstraZeneca for site approval. AstraZeneca effects the approval by countersigning the checklist. Only then can an initiation of this site take place.

13.4. Initiation visits

Each site will be visited by employees from the monitoring unit of the ABCSG before the first patient is enrolled onto the study. The purpose of this visit is to ensure that all persons from the study site involved in the study are familiar with the contents of the protocol, that all prerequisites for implementing the study are met, and to verify that the following documents are already in place at the site:

- Signed investigator agreement
- Protocol signed by the investigator
- Positive vote from the ethics committee
- Site registration with the Federal Ministry
- Site registration with the medical director of the hospital
- Confirmation of insurance

Other requirements for starting the study include suitable supply of trial samples, the IntTrial® CD-ROM, assurance that IT facilities at the study site are sufficient and that IntTrial® is operational.

Once all of the above requirements have been met, the site is authorised to enrol the first patient onto the study.

13.5. Monitoring

Monitoring will be carried out by employees from the monitoring unit of the ABCSG. As part of quality assurance, the investigators involved in the study will therefore allow the monitor to visit each study site and the facilities involved in the study (e.g. laboratories) on a regular basis, depending on the number of patients enrolled.
These visits are used to evaluate the completeness, plausibility and evaluability of data entered in the CRF, compliance with the protocol and correct handling of the study drug.
The investigator will also allow monitors to check entries on the basis of study-related original data (source data verification = SDV) and must ensure the required findings are provided in written form. SDV is carried out in accordance with the study-specific SDV schedule.

13.6. Audits and inspections

In accordance with the AMG and GCP, AstraZeneca is entitled to arrange inspections of parts or the entire clinical trial by an independent quality assurance unit. This quality assurance is guaranteed by professionally qualified persons (auditors). The auditors are hierarchically independent of the clinical research department of AstraZeneca.
The investigator/study site may carry out audits to verify that the clinical trial and monitoring are being performed properly. Audits may take place before, during or after the end of the clinical trial. As part of this independent inspection, the auditor will check compliance of the original data with the entries in the CRFs at random as a minimum. In addition, he will check compliance with the protocol and the provisions to ensure the proper implementation of the clinical trial in accordance with the AMG and GCP. An audit report will be drawn up.

Trial sites, facilities and any type of study-specific data must be made accessible for an audit and/or an inspection at all times.

14. FINAL REPORT AND PUBLICATION

14.1. Final report

An integrated clinical biometric final report will be created by the ABCSG.

The final report will be authorised by the signature of the Coordinating Investigator and signed by AstraZeneca and the biometricians.

14.2. Publication

All data collected in association with the study will be treated confidentially by AstraZeneca and the Investigator/Coordinating Investigator up to the point of publication.

Publication of the collected study data in the form of lectures, abstracts and other publications will be issued primarily by the principal investigator or the directors of the individual trial sites following appropriate consultation within the study team. The number of co-authors will be determined based the extent of contribution by the EC or the Board of Directors of the study team.

AstraZeneca will be informed of publications and presentations prior to their publication (within thirty 30 days) prior to the planned submission for publication.

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Appendices

A Declaration of Helsinki (1996 version)
B American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer

Appendix A

DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly,
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

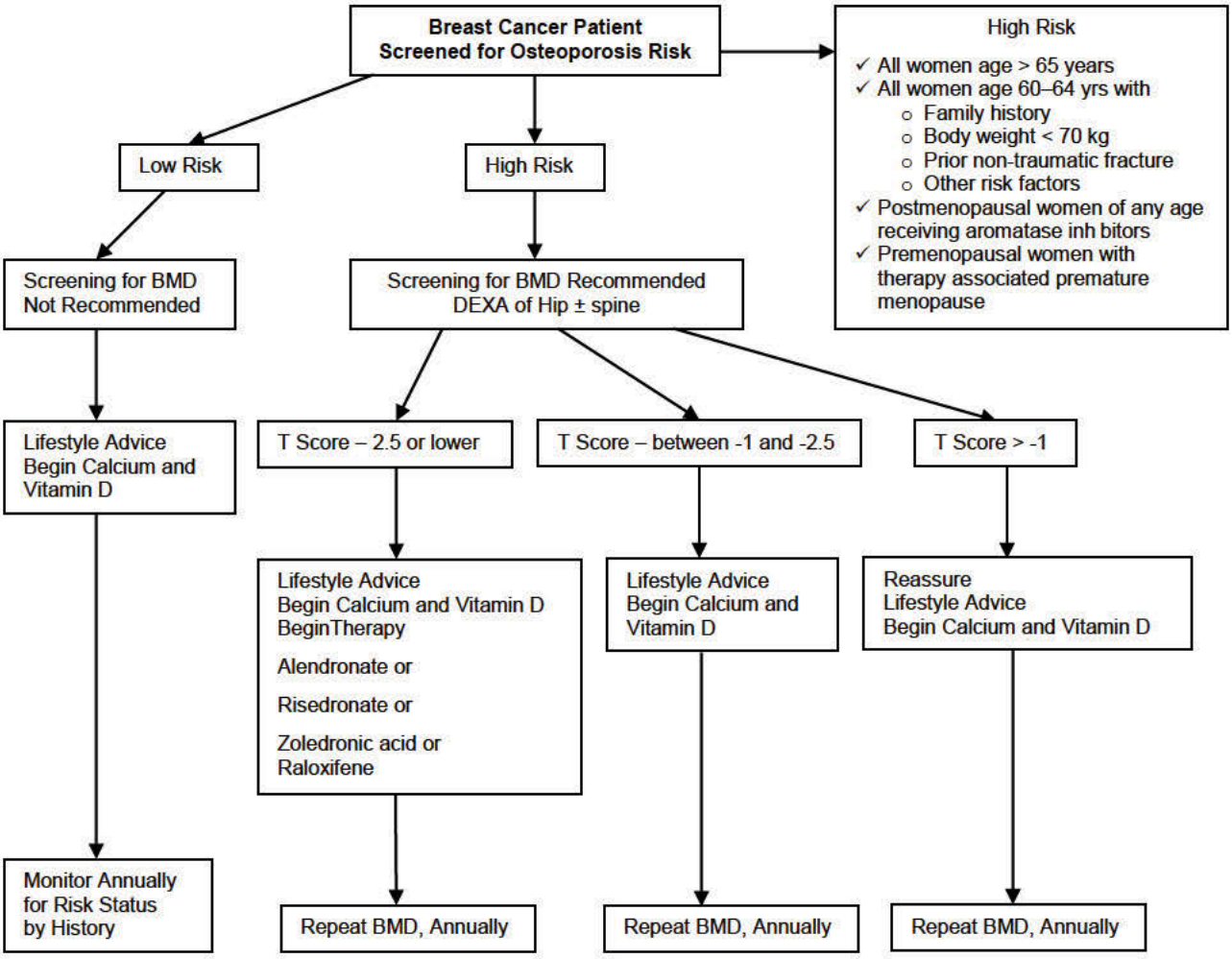
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix B

American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer

Source: Hillner B,et al: J Clin Oncol 21: 4042–4057, 2003.



BMD = bone mass density
DEXA = dual energy x-ray absorptiometry bone scan

AstraZeneca

Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	Arimidex (Anastrozole)
Study Code	1033AU/0003, ABCSG Protocol 16, S.A.L.S.A.
Date	2005-03-21

S.A.L.S.A. (Secondary adjuvant, long-term study with Arimidex®):
A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

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Sponsor:

AstraZeneca Österreich GmbH, Schwarzenbergplatz 7, A-1037 Vienna, Austria

[redacted]

Study sites affected by the amendment

The amendment applies to all participating study sites in this study.

The study protocol shall be amended as follows:

Affected protocol point:

Point 1.1. Study summary / patient selection (page 10) and
Point 5.2. and 5.3: Inclusion and exclusion criteria (page 22)

Old text:

Inclusion criteria:

1. Postmenopausal patients with histologically verified invasive or minimally invasive breast cancer that has been radically treated locally with or without previous chemotherapy and/or radiotherapy
2. Age≤ 80 years
3. No distant metastasis at randomisation
4. No recurrence at randomisation
5. TNM-classification at the time of diagnosis: T1-3, N0-1, M0
6. Oestrogen and/or progesterone receptor-positive before the start of primary endocrine therapy
7. Endocrine therapy for 5 years (maximum deviation ± 12 months)
8. Therapy break (from the preliminary therapy) maximum 12 months
9. At the time of randomisation, the results of the following tests must be available:
    a) Medical history and clinical examination (within one month prior to randomisation)
    b) Gynaecological examination (within one month prior to randomisation)
    c) Chest x-ray or CT scan (within one year prior to randomisation)
    d) Bilateral mammogram (within one year prior to randomisation) – exception are women with mastectomy (unilateral)
    f) Ultrasound of the abdomen or abdominal CT (within one year prior to randomisation)
    e) Laboratory parameters (within 3 months prior to randomisation)
        - Adequate liver function (GOT or GPT >≤ 2.5 x ULN; total bilirubin < 2 x ULN, AP < 2 x ULN)
        - Serum creatinine ≤ 1.5 x ULN
10. Informed consent prior to randomisation

Amended text:

Inclusion criteria:

1. Postmenopausal patients with histologically verified invasive or minimally invasive breast cancer that has been radically treated locally with or without previous chemotherapy and/or radiotherapy
2. Age≤ 80 years
3. No distant metastasis at randomisation 1
4. No recurrence at randomisation 1
5. TNM-classification at the time of diagnosis: T1-3, N0-1, M0
6. Oestrogen and/or progesterone receptor-positive before the start of primary endocrine therapy
7. Endocrine therapy for 5 years (maximum deviation ± 12 months)
8. Therapy break (from the preliminary therapy) maximum 12 months
9. Informed consent prior to randomisation

[1] See section 5.4

Old text:

Exclusion criteria:

1. Premenopausal patients or patients with non-determinable menopausal status at randomisation
2. Manifest secondary malignancy or status post secondary malignancy between the time of initial diagnosis and randomisation
3. General contraindications and/or hypersensitivity to anastrozole
4. Carcinoma in situ of any size with or without Paget's disease of the nipple or T4 tumours at the time of initial diagnosis
5. Receptor determination unknown or negative at the time of diagnosis or at the start of the primary endocrine therapy
6. Age > 80 years
7. Performance index > 3 as per WHO
8. Regular use of hormone products and hormone replacement therapy (HRT) for more than 6 months since the primary breast cancer surgery
9. Serious concomitant disease preventing implementation of adjuvant therapy in line with the protocol and/or controlled follow-up
10. Lack of patient cooperation
11. Legal incapacity and/or other circumstances preventing the patient from understanding the nature, significance and implications of the clinical trial
12. Existing psychiatric disease as per ICD at study enrolment (especially alcohol dependency)

Amended text:

Exclusion criteria:

1. Premenopausal patients or patients with non-determinable menopausal status at randomisation
2. Manifest secondary malignancy or status post secondary malignancy
3. General contraindications and/or hypersensitivity to anastrozole
4. Carcinoma in situ of any size with or without Paget's disease of the nipple or T4 tumours at the time of initial diagnosis
5. Receptor determination unknown or negative at the time of diagnosis or at the start of the primary endocrine therapy
6. Age > 80 years
7. Known hepatic and/or renal impairment
8. Performance index >2 as per WHO
9. Regular use of hormone products and hormone replacement therapy (HRT) for more than 6 months since the primary breast cancer surgery
10. Serious concomitant disease preventing implementation of adjuvant therapy in line with the protocol and/or controlled follow-up
11. Lack of patient cooperation
12. Legal incapacity and/or other circumstances preventing the patient from understanding the nature, significance and implications of the clinical trial
13. Existing psychiatric disease as per ICD at study enrolment (especially alcohol dependency)

Affected protocol point:

Amendment of the text under point 1 "Patient population – exclusion criteria" or addition as a separate item under point 5 "Study population": **5.4. Diagnosis**

New text:

Distant metastasis and local recurrence at the time of randomisation are ruled out in any case using the following examinations at the least, or using methods regarded as equivalent or better according the current state of scientific knowledge:

a) Medical history within one month prior to randomisation
b) Gynaecological examination including ultrasound within six months prior to randomisation (exceptions are women with a hysterectomy)
c) Chest x-ray or CT scan within one year prior to randomisation
d) Bilateral mammogram within one year prior to randomisation – exception are women with mastectomy (unilateral)
e) Ultrasound of the abdomen or abdominal CT within one year prior to randomisation

Affected protocol point:

5.4. Premature termination of the clinical study (page 23)

Old text:

5.4. Premature termination of the clinical study
5.4.1. Premature termination in an individual case

Reasons leading to study discontinuation are:

- Withdrawal of patient consent
- Occurrence of intolerable adverse events
- Occurrence of relapse, secondary cancer or death of the patient
- Lack of compliance or cooperation of the patient
- Serious protocol violation
- Other personal reasons for the patient (e.g. change of location); there is usually the possibility of ongoing care at another ABCSG study site
- Patient no longer attends (lost to follow-up): the maximum time frame for this is
    - In the therapy phase: +6 months calculated from the scheduled visit date (see 6.5.)
    - In the follow-up phase: +12 months from the scheduled visit date

  The investigator must make every effort to establish contact with the patient.

5.4.2. Discontinuation of the entire study
5.4.3. Closure of an individual site

Amended text:

5.5. Premature termination of the clinical study

5.5.1. Premature termination in an individual case

Reasons leading to study discontinuation are:

- Withdrawal of patient consent
- Occurrence of intolerable adverse events
- Occurrence of relapse, secondary cancer or death of the patient
- Lack of compliance or cooperation of the patient
- Serious protocol violation
- Other personal reasons for the patient (e.g. change of location); there is usually the possibility of ongoing care at another ABCSG study site
- Patient no longer attends (lost to follow-up): the maximum time frame for this is
    - In the therapy phase: +6 months calculated from the scheduled visit date (see 6.5.)
    - In the follow-up phase: +12 months from the scheduled visit date

  The investigator must make every effort to establish contact with the patient.
- Development of hepatic, renal insufficiency

5.5.2. Discontinuation of the entire study

5.5.3. Closure of an individual site

Affected protocol point:

7. Implementation
7.1. Examination parameters before study start (page 27)

Old text:

7.1. Examination parameters before study start

1. Medical history, e.g. histological findings, HR status findings, WHO status (within one month prior to randomisation)
2. Clinical examinations (within one month prior to randomisation):
   - Clinical examination
   - Gynaecological examination
3. Radiological investigations (within one year prior to randomisation):
   - Sonography of the abdomen or abdominal CT
   - Chest x-ray or CT
   - Bilateral mammogram (unilateral mammogram in the case of mastectomy)
   - Bone density measurement (optional)
4. Laboratory parameters (within 3 months prior to randomisation):
   - LFP (GOT, GPT, total bilirubin, AP)
   - RFP (serum creatinine)
   - Optional tumour markers: CEA, CA 15-3

Amended text:

7.1. Examination parameters before study start

1. Medical history, e.g. histological findings, HR status findings (within one month prior to randomisation)
2. Physical examinations, medical history, WHO status (within one month prior to randomisation)
3. Gynaecological examination (including ultrasound) (within 6 months prior to randomisation)
4. Radiological investigations (within one year prior to randomisation):
   - Sonography of the abdomen or abdominal CT
   - Chest x-ray or CT
   - Bilateral mammogram (unilateral mammogram in the case of mastectomy)
   - Bone density measurement (optional)
5. Query known hepatic, renal insufficiency
6. Optional tumour markers: CEA, CA 15-3

Affected protocol point:

7. Implementation
7.2. Examination parameters during the study (page 27)

Old text:

7.2.2. After 12 and 24 months (Arm A and B)

1. Clinical examination
2. Survey of fracture rate
3. Adverse events leading to discontinuation of therapy
4. Serious adverse events
5. Laboratory parameters:
    - LFP (GOT, GPT, total bilirubin, AP)
    - RFP (serum creatinine)
    - Optional TU marker: CEA, CA 15-3
6. Gynaecological examination
7. Radiological examinations
    - Sonography of the abdomen or abdominal CT
    - Chest x-ray or CT
    - Bilateral mammogram (unilateral mammogram in the case of
    - mastectomy)
6. Bone density measurement (optional)

Amended text:

7.2.2. After 12, 24, 36, 48 and 60 months

1. Physical examination
2. Survey of fracture rate
3. Adverse events leading to discontinuation of therapy
4. Serious adverse events
5. Development of hepatic, renal insufficiency
6. Optional TU marker: CEA, CA 15-3
7. Gynaecological examination
8. Radiological examinations
    - Sonography of the abdomen or abdominal CT
    - Chest x-ray or CT
    - Bilateral mammogram (unilateral mammogram in the case of
    - mastectomy)
9. Bone density measurement (optional)

Affected protocol point:

7. Implementation
7.3. Follow-up (page 28)

Old text:

7.3. Follow-up

After the therapy is complete, follow-up examinations are carried out at yearly intervals (+/- 6 months) for a period of 8 years in Arm A and 5 years in Arm B.

1. Clinical examinations
2. Bilateral mammogram (unilateral mammogram in the case of mastectomy)
3. Serious adverse events (see 9.1 and 9.2.4)

Amended text:

7.3. Follow-up

After the therapy is complete, follow-up examinations are carried out at 36, 48 and 60 months in Arm A analogously to the therapy examinations in the Arm B. After the 60th monthly visits, the standardised follow-up examinations are carried out at yearly intervals (+/- 6 months) over a period of 5 years for both arms.

1. Physical examination
2. Bilateral mammogram (unilateral mammogram in the case of mastectomy)
3. Serious adverse events (see 9.1 and 9.2.4)

Affected protocol point:

1.2. Flow chart (page 12)

Old text:

1. Separate specification for patient history and clinical examination
2. No detailed information for gynaecological examination

Amended text:

1. Change to physical examination
2. Gynaecological examination with asterisk * in screening: * Including ultrasound (exception: status post hysterectomy) or ** at the therapy visits: ** "Follow-up examination in accordance with the current state of scientific knowledge"

Justification for the amendment:

- Points 9a–9f in the inclusion criteria are handled in a separate point (i.e. Amendment in point 1 "Patient selection" or additional point 5.4 "Diagnosis") (reason: The above-mentioned examinations from point 9 are not actual inclusion criteria but rather constitute guidelines for how inclusion criteria 3 and 4 are should be ensured.)
- Change of description in the exclusion criteria: "Manifest secondary malignancy or status post secondary malignancy between the time of initial diagnosis and randomisation" to "manifest secondary malignancy or status post secondary malignancy" (reason: misleading description; there are patients who were included status post secondary cancer who had to be set to ineligible.)
- The gynaecological examination at screening has been supplemented by a mandatory ultrasound examination (reason: accurate clarification of any pathological changes which otherwise could be attributed to the study medication is possible at inclusion.)
- The time frame for the gynaecological examination is extended to 6 months (reason: it is not feasible to obtain findings in a time frame of one month prior to randomisation.)
- Clarification of hepatic and/or renal impairment at the time of inclusion or development of hepatic and/or renal insufficiency at the individual therapy visits will be queried instead of separate laboratory values (reason: absence of a consistent documentation and quality assurance from external laboratories; no change in the safety profile for patients is expected – known hepatic and/or renal impairment would still ensure exclusion of the patient.)
- Patients with WHO>2 will not be enrolled onto the study (reason: patients with WHO ≥3 require continuous care or hospitalisation and would therefore not be suitable for the study protocol.)
- Clinical examination / vital signs / WHO status: Change to physical examination (reason: vital parameters are not relevant in the course of this protocol, only recording of the WHO status – this is possible when gathering the medical history or performing a physical examination.)

Initiators of the amendment:

Coordinating Investigator: [redacted]
Biometrics: [redacted]
Sponsor: AstraZeneca Österreich GmbH, Medical Director: [redacted]

AstraZeneca

Agreement for Protocol Amendment No. 1

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final version 1.0 dated 21/03/2005

I agree with the contents of this protocol amendment.

....

Date [redacted]

[redacted]

Coordinating Investigator

University Clinic for Surgery

Währinger Gürtel 18–20

1090 Vienna, Austria

Agreement for Protocol Amendment No. 1

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final version 1.0 dated 21/03/2005

I agree with the contents of this protocol amendment.

. . . .

Date [redacted]

[redacted]

Responsible statistician

Special Facility for Medical Statistics and Information Technology

Institute of Clinical Biometrics

Medical University of Vienna

Spitalgasse 23

1090 Vienna, Austria

Agreement for Protocol Amendment No. 1

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final version 1.0 dated 21/03/2005

I agree with the contents of this protocol amendment.

....

Date [redacted]

[redacted]

Medical Director at AstraZeneca Österreich

Schwarzenbergplatz 7

1037 Vienna, Austria

AstraZeneca

Clinical Study Protocol Amendment

Amendment Number	2
Drug Substance	Arimidex (Anastrozole)
Study Code	1033AU/0003, ABCSG Protocol 16, S.A.L.S.A.
Date	2008-10-30

S.A.L.S.A. (Secondary adjuvant, long-term study with Arimidex®):
A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

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Sponsor:

AstraZeneca Österreich GmbH, Schwarzenbergplatz 7, A-1037 Vienna, Austria

[redacted]

Study sites affected by the amendment

The amendment applies to all participating study sites in this study.

The study protocol shall be amended as follows:

Affected protocol point:

Point 1.1. Study summary/patient selection (protocol, page 10; amendment 1, page 2) and point 5.2. and 5.3: Inclusion and exclusion criteria (protocol, page 22 and amendment 1, page 2)

Old text:

Inclusion criteria:

1. Postmenopausal patients with histologically verified invasive or minimally invasive breast cancer that has been radically treated locally with or without previous chemotherapy and/or radiotherapy
2. **Age≤ 80 years**
3. No distant metastasis at randomisation
4. No recurrence at randomisation
5. TNM-classification at the time of diagnosis: T1-3, **N0-1**, M0
6. Oestrogen and/or progesterone receptor-positive before the start of primary endocrine therapy
7. Endocrine therapy for 5 years (maximum deviation ± 12 months)
8. Therapy break (from the preliminary therapy) maximum 12 months
9. Informed consent prior to randomisation

Amended text:

Inclusion criteria:

1. Postmenopausal patients with histologically verified invasive or minimally invasive breast cancer that has been radically treated locally with or without previous chemotherapy and/or radiotherapy
2. No distant metastasis at randomisation
3. No recurrence at randomisation
4. TNM-classification at the time of diagnosis: T1-3, **N0 and N+**, M0
5. Oestrogen and/or progesterone receptor-positive before the start of primary endocrine therapy
6. Endocrine therapy for 5 years (maximum deviation ± 12 months)
7. Therapy break (from the preliminary therapy) maximum 12 months
8. Informed consent prior to randomisation

Old text:

Exclusion criteria:

1. Premenopausal patients or patients with non-determinable menopausal status at randomisation
2. Manifest secondary malignancy or status post secondary malignancy
3. General contraindications and/or hypersensitivity to anastrozole
4. Carcinoma in situ of any size with or without Paget's disease of the nipple or T4 tumours at the time of initial diagnosis
5. Receptor determination unknown or negative at the time of diagnosis or at the start of the primary endocrine therapy
6. **Age > 80 years**
7. Known hepatic and/or renal impairment
8. Performance index >2 as per WHO
9. Regular use of hormone products and hormone replacement therapy (HRT) for more than 6 months since the primary breast cancer surgery
10. Serious concomitant disease preventing implementation of adjuvant therapy in line with the protocol and/or controlled follow-up
11. Lack of patient cooperation

12. Legal incapacity and/or other circumstances preventing the patient from understanding the nature, significance and implications of the clinical trial
13. Existing psychiatric disease as per ICD at study enrolment (especially alcohol dependency)

Amended text:

Exclusion criteria:

1. Premenopausal patients or patients with non-determinable menopausal status at randomisation
2. Manifest secondary malignancy or status post secondary malignancy **(exceptions: simultaneous bilateral breast cancer, oestrogen and/or progesterone receptor-positive on both sides, at the time of diagnosis; cervical carcinoma in situ and basal cell skin cancer)**
3. General contraindications and/or hypersensitivity to anastrozole
4. Carcinoma in situ of any size with or without Paget's disease of the nipple or T4 tumours at the time of initial diagnosis
5. Receptor determination unknown or negative at the time of diagnosis or at the start of the primary endocrine therapy
6. Known hepatic and/or renal impairment
7. Performance index >2 as per WHO
8. Regular use of hormone products and hormone replacement therapy (HRT) for more than 6 months since the primary breast cancer surgery
9. Serious concomitant disease preventing implementation of adjuvant therapy in line with the protocol and/or controlled follow-up
10. Lack of patient cooperation
11. Legal incapacity and/or other circumstances preventing the patient from understanding the nature, significance and implications of the clinical trial
12. Existing psychiatric disease as per ICD at study enrolment (especially alcohol dependency)

Affected protocol point:

Point 1.1. Study summary/study schedule (protocol, page 11) and point 4. Design (protocol, page 21.)

Old text:

Planned recruitment end:	December 2008
Planned end of the maximum treatment phase:	December 2013
Planned end of follow-up:	December 2018

Amended text:

Planned recruitment end:	**December 2009**
Planned end of the maximum treatment phase:	**December 2014**
Planned end of follow-up:	**December 2019**

Affected protocol point:

Point 1.2. Flow chart (protocol, page 12)

Old flow chart

1.2. Flow chart

Parameter	Screening	6 months	12 months	24 months	36 months	48 months	60 months	6 years	7 years	8 years	9 years	10 years
Verification of inclusion and exclusion criteria	x											
Medical history	x											
Clinical examination	x	x	x	x	x	x	x	x	x	x	x	x
Gynaecological examination	x		x	x	x	x	x					
Ultrasound or CT of abdomen	x		x	x	x	x	x					
Chest x-ray or CT	x		x	x	x	x	x					
Bilateral or unilateral mammogram	x		x	x	x	x	x	x	x	x	x	x
Measurement of bone density (optional)	x		x	x	x****	x****	x****					
Survey of fracture rate		x	x	x	x	x	x					
LFP*	x		x	x	x	x	x					
RFP**	x		x	x	x	x	x					
TU marker*** (optional)	x		x	x	x	x	x					
SAE/AE		See point 9						See point 9				

Legend: * LFP: GOT,GPT, AP, total bilirubin;** RFP: Serum creatinine; *** TU marker: CEA, CA 15-3;****only for patients in Arm B (5 years of anastrozole)

New flow chart

1.2. Flow chart

Parameter	Screening	6 months	12 months	24 months	36 months	48 months	60 months	6 years	7 years	8 years	9 years	10 years
Verification of inclusion and exclusion criteria	x											
Physical examination *	x	x	x	x	x	x	x	x	x	x	x	x
Gynaecological examination	x**		x***	x***	x***	x***	x***					
Ultrasound or CT of abdomen	x		x	x	x	x	x					
Chest x-ray or CT	x		x	x	x	x	x					
Bilateral or unilateral mammogram	x		x	x	x	x	x	x	x	x	x	x
Measurement of bone density (optional) (thoracic/lumbar spine)	x		x	x	x	x	x					
Survey of fracture rate		x	x	x	x	x	x					
TU marker**** (optional)	x		x	x	x	x	x					
SAE/AE		See Chapter 9 of the protocol						See Chapter 9 of the protocol				

Legend: * Including assessment of general status to record WHO status

** Including ultrasound

*** Follow-up examination according to the current state of scientific knowledge

**** TU marker: CEA, CA 15-3

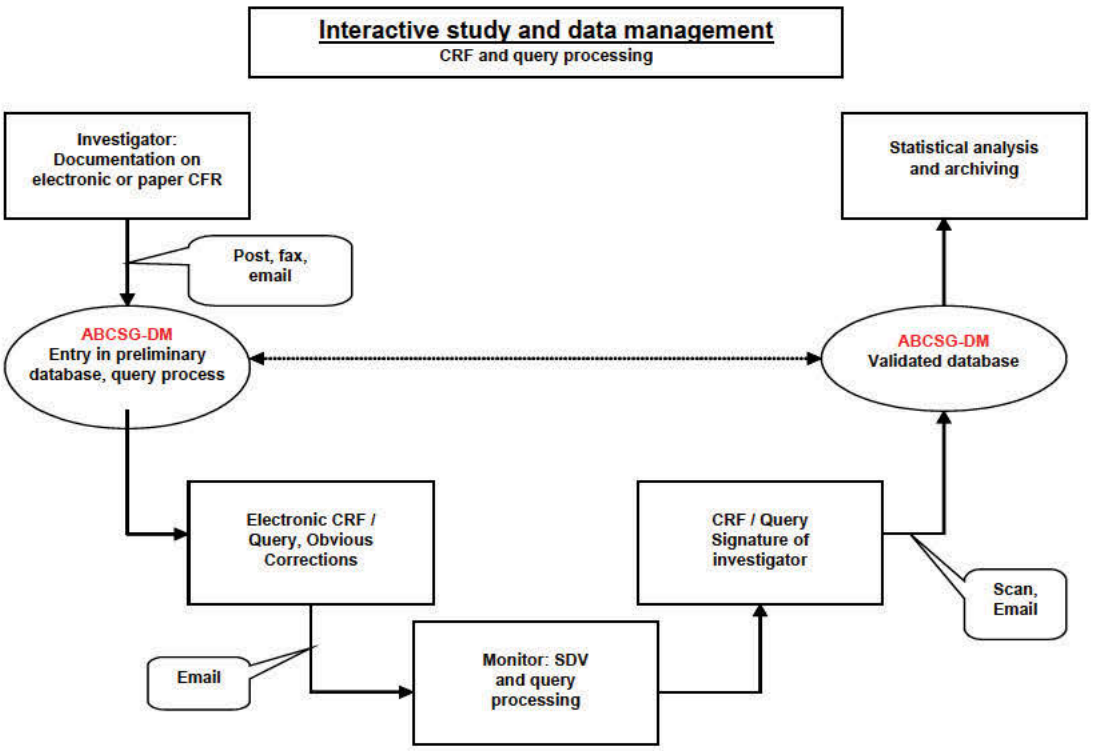
Affected protocol point:

Chapter 11. Data management (protocol, page 36–39)

Old text:

11. DATA MANAGEMENT

Data is managed by the ABCSG in cooperation with the contract research organisation CRS Creative Research Solutions GmbH using the IntTrial® system. IntTrial® is a modular system based on the universal PDF format for creating, evaluating and archiving study CRFs. The following diagram provides an overview of the "CRF flow" on IntTrial®:



11.1. Patient identification list

All patient-related data will be recorded in anonymous form. Each patient is assigned a patient number at randomisation that uniquely identifies them by their initials and date of birth. The investigator will keep a confidential patient list, in which the identifying data is linked to the patients' full name and optionally the insurance number.

11.2. Data collection / documentation sheets

11.2.1. Documentation

At the study sites, all data required by the study protocol as well as objective and subjective information must be entered directly into the relevant medical files/original patient documentation before documentation in the CRF.

All data collected during the study is entered into the designated documentation forms (CRFs) by the investigator or a person who has previously been authorised in writing. These provide a mirror image of the requirements according to the protocol.

If an examination has not been completed, this will be indicated with "n.d.". If information is not available, this will be documented with "n.a.".

The IntTrial® system allows the investigator to document study data electronically ("on-screen"; "e-CRF") or conventionally on a paper CRF. The study CRF is made available on CD-ROM. The CD-ROM contains all CRF pages both in the form of fillable PDF documents (e-CRF) and as a print version, which can be printed out and completed by hand.

After completion on computer, the CRF pages are sent to Data Management by email. Alternatively, the pages can also be printed out and either faxed or sent by mail. A copy of each page sent is kept at the site, either in electronic or paper form.

In the case of conventional documentation, the print template of the CRF is used. Fully completed pages are sent by post or faxed to Data Management. All entries must be made in permanent black or blue ballpoint pen to ensure the legibility of all copies.

It is important that documentation is completed soon after therapy. Documentation should therefore be completed and sent to Data Management within 7 days of a visit.

The completed CRF pages are sent to:

ABCSG Data Management

FAO [redacted]

Theresiengasse 32

1180 Vienna, Austria

Study fax: [redacted]

Study email: [redacted]

11.2.2. Subsequent corrections to documentation

Once a CRF page has been completed on the computer and forwarded to Data Management, the page can no longer be corrected by the investigator and resubmitted to Data Management. The CRF page is entered into the preliminary database and further adjustments may only be carried out again during SDV.

If a CRF page is accidentally sent to Data Management twice, the second page will not be input, but simply archived. SDV is performed on the first version of the respective CRF page.

The same rules apply to paper CRFs. Since in this case, entries are made by hand, corrections made during documentation are made in accordance with the usual rules. An incorrect entry is crossed out, however, the deleted entry must remain recognisable. The corrected value should be written next to it. The date of the change and signature/initials of the investigator or authorised person must be added to each correction. The use of correction fluid is prohibited.

11.3. Data acquisition

Data acquisition is carried out by the person responsible for data management. Data entry takes place on an ongoing basis, in parallel with the clinical trial.

11.3.1. Data entry / obvious corrections / queries

CRFs received by Data Management are included in the preliminary study database. A system consisting of the Cardiff Teleform Reader, the Teleform Verifier and MS-SQL is used for the input process with IntTrial®. The input process is divided into automatic data acquisition, followed by a manual check by the data entry staff, with each value being checked subsequently.

A copy of each CRF page is automatically archived in electronic format as an indexed PDF. Corrections of obvious mistakes in the documentation (obvious corrections) are made immediately during input by the input staff and the changes are logged in the database. Missing, contradictory or illegible entries are also logged as queries in the database.

11.3.2. Creating an electronic copy of CRFs for source data verification (SDV)

To enable the study data to be monitored, the data from each CRF page included in the preliminary study database is exported into a blank CRF form. The obvious corrections made as well as the queries logged in the database are exported into the form.

These CRF pages are then made available to the competent monitor for source data adjustment. During SDV, queries already listed are processed and the CRF page is signed by the investigator after any corrections are made. A copy of the signed CRF remains at the site and the original is given to the monitor.

11.3.3. Data entry / database validation / database lock

The signed CRF pages are forwarded by the monitor to Data Management and then entered into the database again from there. This data is then validated by a final query process, based on checks for validity, consistency and plausibility.

Query forms to clarify any queries are passed on to the investigator for processing via the monitor. After processing, these are sent back to Data Management, and a copy is retained at the site.

After clarification of all possible queries using query forms, the database is closed. The analysis and statistical analysis is carried out using SAS® (Statistical Analysis Software) version 8.

11.4. Original data in the CRF

All data collected within this protocol must be available as original data in the respective medical history. Direct entries in the CRF are not considered to be source data.

11.5. Storage of CRFs

Once the study is completed, the documentation remains with the ABCSG. The originals of all central study documents including the documentation sheets are stored at the study site for at least 15 years after the end of the study. CRFs can also be stored on image carriers or other data storage devices.

During the study, one copy of the CRF remains with the respective investigator. The investigator also retains the administrative documents produced (correspondence with the Ethics Committee, BUMI, AstraZeneca, study site etc.), the patient identification list, signed informed consent forms, copies of documentation sheets and the general study documentation (protocol, amendments) for the period of time stated above.

Original data on study patients (medical files) must be stored in accordance with the archiving term applicable to the study sites, however, for a minimum of 15 years.

If the investigator does not stay at the study site for whatever reason (e.g. retirement, appointment elsewhere), the retention of the documents must be handed over to a successor, who consequently takes on the responsibility, and this must be documented in writing. Both AstraZeneca and the ABCSG must be informed of such a transfer in writing.

Amended text:

11. DATA MANAGEMENT

Data is managed by the ABCSG using the "Macro" (InferMED) data management system via the "DATAPORT" web portal. "MACRO" is a piece of software developed for use in controlled single or multi-centre clinical studies of all phases (I-IV). Documentation is web-based (eCRF) and is supported by active online support.

System compliance with the requirements of international guidelines such as "ICH Good Clinical Practice" and "FDA 21 CFR Part 11" is essential for "MACRO". An audit trail is created for the entire course of the study, which shows any changes e.g. in terms of the data entered, the date and time of entry and the added comments.

"MACRO" also provides the possibility for easy detection of discrepancies in the individual data sets (e.g.implausibilities selected by Edit Check programming, missing values etc.) through the use of various marks (icons). This allows the employees from Monitoring and Data Management to generate queries (=discrepancies) quickly, which in turn can be processed by the investigator in a timely manner. Through automatic assignment of specific "marks" (icons) by the system, the processing status of the queries (= discrepancies) is visible and can be tracked up to final completion.

Employees from Monitoring also have the option to use other "marks" (= icons) to indicate the status of source data verification (SDV) (e.g. planned, completed, pending, discontinued).

Due to the web-based processing, all entries, changes, queries etc. are visible to authorised persons immediately after implementation. This reduces the processing time and means that all data is available more quickly for statistical evaluation.

11.1. Patient identification list

All patient-related data will be recorded in anonymous form. Each patient is assigned a patient number at randomisation that uniquely identifies them together with their initials. The investigator will keep a confidential patient list, in which the identifying data is linked to the patients' full name and optionally the insurance number.

11.2. Data collection / documentation sheets

11.2.1. Documentation

At the study sites, all data required by the study protocol as well as objective and subjective information must be entered directly into the relevant medical files/original patient documentation before documentation in the web-based CRF (eCRF).

Patient data that is relevant for the study is collected in the "MACRO" data management system via the "DATAPORT" web portal directly at the site by the investigator or by study personnel with documentation authorisation. Only in exceptional cases will a hard-copy CRF be provided for the site. In this case, entries must be made in block letters or in easily legible script using a black or blue pen. The data documented on hard-copy CRFs is recorded in "MACRO" by data entry staff from the ABCSG using "double data entry".

Correct collection and input of data is checked by the competent monitor via the Internet and is marked accordingly in the system using a designated icon. Any queries (=discrepancies) are generated by the monitor via the internet and are immediately visible to both the investigator and Data Management as soon as they are created on the system.

11.3. Data management (data review)

The eForms marked as source data verified by Monitoring are checked for consistency and plausibility by Data Management. Any queries (=discrepancies) are generated via the Internet and are therefore visible to both the investigator and monitor as soon as they are created in the system by means of "marks" (icons). Data Management locks all eForms that it finds to be fully correct, meaning they are protected from further processing. "Marks" indicate this processing status.

The individual working steps carried out by Data Management are specified in SOPs (= standard operating procedures) and WIs (= working instructions).

Justification for the amendment:

- The age limit in the inclusion and exclusion criteria is being raised (reason: there are a number of sprightly patients who will tolerate the study follow-up phase well and can remain compliant. The primary objective of the study will not be affected by a potential increase in the incidence of deaths that are not breast cancer related.)

- Correction of the permitted N-stages of the tumour from N1 to N+ (reason: it is expected that all patients, regardless of their N-stage at the time of diagnosis will benefit from extending the therapy with anastrozole beyond 5 years)

- Addition to the exclusion criterion: "Manifest secondary malignancy or status post secondary malignancy" with the following exceptions: a) simultaneous bilateral breast cancer, oestrogen and/or progesterone receptor-positive on both sides at the time of diagnosis (reason: because of the simultaneity of the tumour occurrence, such a carcinoma is interpreted as a multi-centric carcinoma); b) in-situ carcinoma of the cervix and basal cell carcinoma of the skin, is a correction of the data in the CRF and protocol, as these exceptions were defined in the CRF (reason: the probability of relapse in these carcinomas is minimal.)

- Extension of the recruitment phase for 1 year (reason: the annual recruitment rate was overestimated in the study planning phase.)

- The flow chart will be adjusted following the protocol amendments as per Amendment 1.

- The Data Management System of ABCSG is being changed from the PDF-format based IntTrial® system (CRS – Creative Research Solutions GmbH) to the web-based MACRO® data management system (software from InferMED). This change was prompted by the withdrawal of support for IntTrial® on the part of the system developer.

Initiators of the amendment:

Coordinating Investigator: [redacted]
Biometrics: [redacted]
Sponsor: AstraZeneca Österreich GmbH, Medical Director: [redacted]

AstraZeneca

Agreement for Protocol Amendment No. 2

Title:	A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy
Study no.:	1033AU/0003
Version:	Final Version dated 30/10/2008

I agree with the contents of this protocol amendment.

....

Date [redacted]

[redacted]

Coordinating Investigator

University Clinic for Surgery

Währinger Gürtel 18–20

1090 Vienna, Austria

Agreement for Protocol Amendment No. 2

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final version dated 30/10/2008

I agree with the contents of this protocol amendment.

. . . .

Date Assoc. Univ. [redacted]

[redacted]

Responsible statistician

Special Facility for Medical Statistics and Information Technology

Institute of Clinical Biometrics

Medical University of Vienna

Spitalgasse 23

1090 Vienna, Austria

Agreement for Protocol Amendment No. 2

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final Version dated 30/10/2008

I agree with the contents of this protocol amendment.

. . . .

Date [redacted]

[redacted]

Medical Director at AstraZeneca Österreich

Schwarzenbergplatz 7

1037 Vienna, Austria

AstraZeneca

Clinical Study Protocol Amendment

Amendment Number	3
Drug Substance	Arimidex (Anastrozole)
Study Code	1033AU/0003, ABCSG Protocol 16, S.A.L.S.A.
Date	2009-11-27

S.A.L.S.A. (Secondary adjuvant, long-term study with Arimidex®):
A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

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Sponsor:

AstraZeneca Österreich GmbH, Schwarzenbergplatz 7, A-1037 Vienna, Austria
Tel.: [redacted]
Fax: [redacted]

Study sites affected by the amendment

The amendment applies to all participating study sites in this study.

The study protocol shall be amended as follows:

Affected protocol point:

Point 1.1. Study summary/study schedule (protocol, page 11; amendment 2, page 3) and point 4. Design (protocol, page 21; amendment 2, page 3)

Old text:

Planned recruitment end:	December 2009
Planned end of the maximum treatment phase:	December 2014
Planned end of follow-up:	December 2019

Amended text:

Planned recruitment end:	**June 2010**
Planned end of the maximum treatment phase:	**June 2015**
Planned end of follow-up:	**June 2020**

Affected protocol point:

10.6. Substitution of patients (protocol, page 35)

Old text:

No patient who meets the inclusion and exclusion criteria and who stops taking part in the study early for any reason will be replaced.

Amended text:

No patient who meets the inclusion and exclusion criteria and who stops taking part in the study early for any reason will be replaced. **Patients who are found to not meet the inclusion and exclusion criteria at study enrolment during monitoring can be replaced.**

Justification for the amendment:

- Extension of the recruitment phase for 6 months (reason: the annual recruitment rate was overestimated in the study planning phase.)
- Substitution of ineligible patients (reason: the required number of evaluable patients will be guaranteed by substitution.)

Initiators of the amendment:

Coordinating Investigator: [redacted]
Statistics: [redacted]
Sponsor: AstraZeneca Österreich GmbH, Medical Director: [redacted]

AstraZeneca

Agreement for Protocol Amendment No. 3

Title:	A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy
Study no.:	1033AU/0003
Version:	Final version dated 27/11/2009

I agree with the contents of this protocol amendment.

....

Date [redacted]

[redacted]

Coordinating Investigator

University Clinic for Surgery

Währinger Gürtel 18–20

1090 Vienna, Austria

Agreement for Protocol Amendment No. 3

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final version dated 27/11/2009

I agree with the contents of this protocol amendment.

. . . .

Date [redacted]

[redacted],

ABCSG statistician

Austrian Breast and Colorectal Cancer Study Group

Nußdorfer Platz 8

1190 Vienna, Austria

Agreement for Protocol Amendment No. 3

Title: A Prospective, Randomised, Open, Multicentre Phase III Study to Assess the Efficacy of Secondary Adjuvant Endocrine Anastrozole Therapy for 2 Further Yrs vs 5 Further Yrs in Patients With HR +ve Breast Cancer After 5-yr Primary Adjuvant Endocrine Therapy

Study no.: 1033AU/0003

Version: Final version dated 27/11/2009

I agree with the contents of this protocol amendment.

. . . .

Date [redacted]

[redacted]

Medical Director

AstraZeneca Österreich GmbH

Schwarzenbergplatz 7

1037 Vienna, Austria