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Breast Cancer Treatment with Afinitor® (Everolimus) and Exemestane for HR+ Women (CRAD001JDE53)

Observation Plan

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2 List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	German Drug Law
BDSG	German Data Protection Law
BfArM	Federal Institute for Drugs and Medical Devices
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CTC	Common Terminology Criteria (criteria for defining AEs)
DMP	Data Management Plan
EC	European Parliament and Council
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
FSA	Voluntary Self-Regulation for the Pharmaceutical Industry
GOÄ	German Fee Scale for Physicians
HER2-	Human Epithelial Growth Receptor 2 negative
HR+	Hormone Receptor positive
ITT	Intention to Treat
KBV	National Association of Statutory Health Insurance Physicians
MedDRA	Medical Dictionary for Regulatory Activities
MBOÄ	Professional Regulations for Physicians
mTOR	*Mammalian Target of Rapamycin*
NIS	Non-Interventional Study
NSAI	Non-Steroidal Aromatase Inhibitors (letrozole, anastrozole)
PEI	Paul Ehrlich Institute
PFS	Progression Free Survival
PFS FU	Progression Free Survival Follow Up
PS	Performance Status
PT	Preferred Term (MedDRA)
p.o.	per os
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOC	System Organ Class (MedDRA)
SOP	Standard Operating Procedure
TTP	Time to Progression
VFA	Association of Research-Based Pharmaceutical Manufacturers

3 Summary

Drugs in this NIS:

Afinitor® in combination with exemestane (Aromasin® or generics), in accordance with medical regulations and routine medical practice. Currently the standard dosage is deemed to be 10 mg or 25 mg daily. The treatment can be adjusted at the discretion of the physician based on individual tolerability and clinical necessity according to the recommendations in the respective Summary of Product Characteristics (dose reduction or suspension).

Afinitor® is an oral inhibitor of the *mammalian target of rapamycin* (mTOR), which is indicated in combination with exemestane for the treatment of postmenopausal patients with advanced hormone-receptor-positive (HR+), HER2/neu-negative breast cancer without symptomatic visceral metastasis after relapse or progression on non-steroidal aromatase inhibitor (NSAI).

Exemestane belongs to the group of aromatase inhibitors and prevents the synthesis of oestrogens through irreversible binding to the enzyme aromatase. The active substance is indicated for the treatment of advanced breast cancer in post-menopausal women (natural or induced menopause) following progression under anti-oestrogen therapy.

Aims of this non-interventional study:

The aim of this NIS is to acquire information from routine care

- on the impact of physical activity on efficacy and quality of life,
- on prophylaxis and management of stomatitis in routine clinical practice,
- on the sequence of treatment

in the treatment of patients with advanced or metastatic HR+ breast cancer who are treated on-label with Afinitor® und exemestane. Adverse events will be documented.

Number of participating sites:

This non-interventional, multicentre study will be conducted at approx. 400 gynaecology and oncology practices and outpatient clinics scattered throughout the regions in Germany**.**

Number and selection of patients:

Three thousand postmenopausal women with advanced breast cancer previously treated with a non-steroidal aromatase inhibitor and currently being treated with Afinitor® in accordance with routine practice and the Summary of Product Characteristics will be observed in this non-interventional study.

Patients may be included in this NIS only after being provided with information according to the current Summary of Product Characteristics and after signing the informed consent form.

Observation period:

The planned observation period per patient corresponds to the duration of the treatment with Afinitor® and exemestane, but ends no later than the end of the observation phase. This means that the last patient will be observed for a maximum of 12 months. If therapy with Afinitor® and exemestane is stopped prior to disease progression, the follow up period will be extended until progression / death of the patient. The observation intervals are not fixed, but are based on current practice and the clinical symptoms of each patient. The end of the treatment with Afinitor® and exemestane should be documented regardless of the target interval if treatment is completed before the next follow-up. The reason for discontinuing treatment and the subsequent treatment planned should thus be recorded promptly.

Evaluation parameters:

Expanding knowledge about the course of treatment

Efficacy: To evaluate efficacy, progression-free survival (PFS) is recorded according to the assessment by the treating physician for the total patient group and in relation to intensity of physical activity (subgroup analysis) and duration of treatment.

Quality of life: The following patient questionnaire on quality of life will be completed in hard copy: EORTC QLQ-C30/BR23.

Physical activity: The nature and scope of physical activity before and during treatment with Afinitor® and exemestane will be recorded using two questionnaires in hard copy: the "Godin Leisure-Time Exercise Questionnaire" and the "Physical Activity Scales (PAS)[1]" developed at the Institute for Cardiovascular Research and Sports Medicine at the Sports University in Cologne.

Stomatitis management: Documentation of the prophylaxis and the management of stomatitis, as well as the start and end dates of this side effect.

Gathering data from clinical practice on the use of drugs

Sequence of treatment: Prior treatment and the treatment following immediately are recorded: type, duration and reason for termination of previous drug treatment(s) and treatment following directly after ending treatment with Afinitor®.

Drug exposure: Identifying the number of patients in whom treatment needed to be modified, paused or terminated including the type of dose adjustments and the length of and reason for those adjustments.

Safety and tolerability

Documentation of adverse events, serious adverse events, non-serious and serious side

[1] German title: Körperliche Aktivitäts-Skalen (KAS)

effects during routine use.

Scheme of documentation

Time of data entry	At start of documentation	After approx. 2 weeks	Approx. Month 1	Approx. Months 3, 6, 9, 12 ... etc. at 3-month intervals	At end of treatment with Afinitor® and exemestane
Patient characteristics	X				
Demography and vital parameters	X		X	X	
Medical history and disease characteristics	X				
Previous treatment	X				
Current tumour history	X				
Concomitant diseases	X				
Patient questionnaires on quality of life and physical activity	X		X	X	
Patient questionnaire on stomatitis prevention		X	X	X	
Prescription of Afinitor® and exemestane	X		X	X	X
Prophylactic measures and stomatitis treatment	X	X	X	X	
Antiresorptive treatment	X				
Issuance of calendar overview	X				
AEs/SAEs		X	X	X	X
Current tumour treatment with Afinitor® (dosage, dose reduction, pauses in treatment, reason for dose adjustment)	X	X	X	X	X
Reason for discontinuing documentation					X
Reason for discontinuing treatment					X
Treatment response				X	X
Subsequent treatment					X

Contents of documentation after combination therapy with Afinitor® and exemestane

If the treatment with Afinitor® and exemestane is stopped prior to disease progression, the following data will be collected approximately every six month until progression or death of the patient:

- Follow up treatment
- Date of progression (if applicable)
- AEs and SAEs with causal connection to Afinitor® or exemestane / occurrence of death independent from causal connection (see below) starting day 31 after stopping combination therapy until day 30 after last documentation in the context of PFS follow up visit (last contact

of patient to study centre). All AEs and SAEs with causal connection to Afinitor or exemestane will be documented – inclusive progression with causal connection.

Occurrence of death will be documented independently from causal connection of the combination therapy (Afinitor® and exemestane) from day 31 after stopping combination therapy until day 30 after last documentation in the context of PFS follow up visit (last contact of patient to study centre).

Statistical methods:

The NIS will be analyzed using epidemiological methods under primary use of descriptive statistical methods.

Ethical requirements and regulations:

The NIS will be conducted in compliance with the FSA Code of Conduct (dated 07/05/2008, Federal Gazette No. 68, p. 1636) and in accordance with the recommendations of the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI) on the planning, implementation and evaluation of observational studies dated 07/07/2010 and the VFA recommendations for improving the quality and transparency of non-interventional studies dated 31/01/2007 and 23/04/2007.

Timetable:

The study will be conducted between October 2012 and December 2017.

4 Introduction and rationale

Breast cancer is the **most common cancer** in women. In Europe, breast cancer accounts for approximately 13% of all newly diagnosed cancers and causes approximately 130,000 deaths a year (Boyle et al. 2005).

Approximately 40% of newly diagnosed breast cancer patients develop **metastatic disease**. The treatment of metastatic breast cancer is palliative in nature and focuses on the reduction of tumour size, slowing disease progression and reducing the complications associated with the disease and treatment such as fatigue, bone fractures and hypercalcaemia. The average life expectancy for women with metastatic breast cancer is usually 24 to 30 months (World Health Organization Facts and Figures).

Endocrine therapies are regarded as cornerstones in the treatment of women with advanced hormone-receptor-positive breast cancer. For first-line therapy in postmenopausal patients, non-steroidal aromatase inhibitors (NSAI, e.g. letrozole and anastrozole) feature in the treatment of choice (AGO Guideline 2012). However, some patients do not respond to first-line endocrine therapy (primary or *de novo* resistance), or develop resistance to these substances during the course of

treatment (Johnston et al. 2010).

Resistance to endocrine therapy for breast cancer is known to be frequently associated with an over-activation of the PI3K/AKT/mTOR intracellular signalling pathway. This signalling pathway plays a crucial role in proliferation, survival, angiogenesis and metabolism of cells. In addition, it has been shown that there is a close **interaction between the PI3K/AKT/mTOR and the oestrogen signalling pathways** (Di Cosimo S and Baselga 2010). Thus, the simultaneous inhibition of both signalling pathways constitutes a promising therapeutic principle for overcoming resistance to endocrine therapy. Afinitor® is an orally available inhibitor of the *mammalian target of rapamycin* (mTOR), a serine-threonine kinase that is a central component of the PI3K/AKT/mTOR signalling pathway (Baselga et al. 2011).

The efficacy of the combination of an mTOR inhibitor with endocrine therapy has been demonstrated in several clinical trials. In a randomized Phase 2 study comparing **everolimus plus letrozole** with letrozole monotherapy in neo-adjuvant treatment of patients with ER-positive breast cancer, the response rate under combination therapy was significantly higher than letrozole alone (Baselga et al. 2009).

These data were confirmed by the recently announced results of the BOLERO-2 study, an international phase III, placebo-controlled approval study. BOLERO-2 examined the efficacy and safety of **Afinitor® in combination with exemestane** compared to exemestane monotherapy in patients with a previous recurrence or progression during or after letrozole or anastrozole therapy.
In the final evaluation after a median follow-up of 18 months, the combination therapy resulted in a significant prolongation of progression-free survival (PFS) from 3.2 to 7.8 months in the local radiological evaluation and reduced the risk of disease progression by 55%. These results were confirmed by an **independent central radiology diagnostic centre (PFS 4.1 vs. 11.0 months, reduction of risk by 62%).** In all subgroups examined, a significant effect in favour of everolimus was observed. The time to deterioration of the quality of life, assessed via patient questionnaires, was significantly longer under the combination therapy. After 18 months' follow-up and 200 documented events, there was a numerical advantage in terms of overall survival in favour of the combination therapy compared with the placebo arm (32.2% vs. 25.4%). The final analysis of overall survival will take place when 398 deaths are documented (Piccard et al. 2012).

Based on the results of the BOLERO-2 study, Afinitor® was authorised in combination with exemestane for the treatment of postmenopausal patients with advanced HR-positive, HER2/neu-negative breast cancer without symptomatic visceral metastasis in whom a recurrence or progression had occurred following NSAI treatment.

Currently no data are available on the **efficacy** of Afinitor® therapy for this indication in **routine use** outside of clinical trials. The product was authorised for this indication in July 2012. The terms of the authorisation permit patients who were not included in the approval study due to their previous treatment or their state of health to receive treatment with Afinitor®. This group includes metastatic

patients receiving later lines of chemotherapy. It is therefore crucial to gather data on the efficacy of Afinitor® in routine care, i.e. outside a strictly controlled clinical study with predefined inclusion and exclusion criteria. These data will make it possible to assess whether the efficacy demonstrated in the approval study is replicated in routine care.

One important objective in the palliative treatment of cancer patients is to enable them to have a good **quality of life** for as long as possible. For this reason, this NIS will examine whether the quality of life under Afinitor® changes during the course of treatment. The corresponding questionnaire must be completed by patients in the first and third months after starting treatment and thereafter at 3-month intervals.

The nature and level of physical activity could influence efficacy and/or quality of life of patients with metastatic breast cancer. Such an influence has been shown both for prevention and for the adjuvant setting (Friedensreich 2011). To date however there are hardly any studies that address this issue in metastatic patients. Some data suggest that a **positive effect of physical activity** in women with HR+ breast cancer may be more pronounced than in other breast cancer types (Carmichael et al. 2010). One of the aims of this NIS is to use patient questionnaires to determine the nature and level of physical activity and to investigate a possible correlation with efficacy and quality of life. It will also be used to evaluate whether the fatigue that is present under many therapies can be reduced by physical activity.

Stomatitis is a very common side effect of therapy with Afinitor® and exemestane, often occurring soon after starting treatment and frequently regressing during the course of treatment (Porta et al. 2011). In the acute phase, various options are available to the physician to provide relief for the patient. The nature and duration of treatment depend on both the degree of severity of the stomatitis and the specific criteria used by the individual physician. Since the data are as yet unclear, no definitive treatment recommendation for stomatitis under Afinitor® can be given. However, stomatitis occurring under treatment with mTOR inhibitors has been seen to differ in nature from the stomatitis that develops under certain chemotherapies. For this reason, this NIS will record the measures used for prophylaxis and, if necessary, treatment of stomatitis and the outcome of these measures.

Various therapeutic options are available for the treatment of postmenopausal patients with metastatic breast cancer. These include both endocrine therapies and chemotherapies (AGO Breast Commission 2012 recommendations). The decision to opt for a particular treatment is taken by the physician in light of the patient's individual situation and in agreement with the patient. In this NIS, prior therapies and therapy following Afinitor® and exemestane will be documented. The aim is to document the **sequences of treatment** used in routine practice for combined Afinitor® and exemestane therapy.

Afinitor® and exemestane are administered on the basis of the respective Summaries of Product Characteristics, guided exclusively by medical and therapeutic necessity.

5 Aims of the study

The aim of this NIS is to acquire information from routine care

- on the impact of physical activity on efficacy and quality of life,
- on prophylaxis and management of stomatitis in routine clinical practice,
- on the sequence of treatment

in the treatment of patients with advanced or metastatic HR+ breast cancer who are treated on-label with Afinitor® und exemestane. More specifically, this information includes the following observation parameters:

Primary observation parameters

Evaluation of the efficacy of the combination of Afinitor® and exemestane used in routine use in the entire patient group and in relation to the intensity of physical activity. For the subgroup analysis, the treatment courses for patients with higher activity are compared with those patients with lower activity. To evaluate efficacy, PFS under treatment with Afinitor® and exemestane is documented according to the assessment of the treating physician.

Secondary observation parameters:

Quality of life and physical activity:

- The quality of life of patients during treatment with Afinitor® (patient questionnaire EORTC QLQ-C30/BR23) and the importance of physical activity for quality of life.
  The nature and level of physical activity are assessed using the "Godin Leisure-Time Exercise Questionnaire" and "Physical Activity Scale (PAS)" questionnaires.

Drug use and treatment sequence:

- Duration of therapy with Afinitor® and exemestane in routine medical practice
- Increasing knowledge of routine treatment of breast cancer and of suitable treatment algorithms. For this purpose, prior treatments and the treatment immediately following Afinitor® will be documented, in addition to the nature and duration of previous drug treatment(s) and the reason for their discontinuation.
- Number of patients where the treatment needed to be modified, interrupted or discontinued, including type of dosage modifications, duration and cause of the interruptions.

Stomatitis management:

- Prophylaxis and treatment of stomatitis as an adverse event during routine use of Afinitor® in combination with exemestane and concomitant treatments, as well as the start and end dates.

Documentation of adverse events (AEs).

6 Study design

This is a non-interventional study pursuant to Section 4 para. 23 sentence 3 AMG, “in the framework of which information from the treatment of persons with drugs is analysed using epidemiological methods; treatment including diagnosis and monitoring shall be provided strictly in accordance with medical practice, not in accordance with a fixed study protocol; if the study drug is subject to authorization or approval pursuant to Section 21a para. 1, treatment shall also be provided in accordance with the instructions for use specified in the authorization or approval” and is conducted in line with the FSA Code of Conduct and according to the joint recommendations of BfArM and PEI on the planning, conduct and analysis of observational studies as well as the VRA recommendations on improving the quality and transparency of non-interventional studies.

The design of an NIS allows observation without the need to specify strict inclusion and exclusion criteria or interventions. It is therefore suitable for the study aims described, in particular because no requirements regarding the nature and level of physical activity are specified, likewise in relation to prophylaxis and management of stomatitis. Instead, the intention is to describe in a relatively large number of patients the routine medical treatment and the real activity situation in patient’s everyday life. In this NIS, the course of treatment is also documented for those patients who were treated on-label with Afinitor®, but were not included in the approval study due to previous treatment or their state of health.

6.1 Study sites and patients

This non-interventional, multicentre study will be conducted at approx. 400 gynaecology and oncology practices/clinics. The participating physicians will be informed of the aims and modalities of this NIS by the medical director of the NIS. The field employees of Novartis Pharma GmbH will be deployed for administrative purposes in the conduct of the NIS and will distribute all documentation materials to the participating sites.

There will be prospective documentation of the course of treatment for a total of approx. 3000 patients treated with Afinitor® in combination with exemestane according to routine practice and the respective Summaries of Product Characteristics. Patients may also be included in the documentation if treatment with Afinitor® and exemestane was started a maximum of 6 weeks before they gave their consent to participate in this NIS and they are currently receiving Afinitor® and exemestane. The planned observation period per patient corresponds with the duration of treatment with Afinitor® in combination with exemestane, but ends on completion of the observation phase. This means that the last patient will be observed for a maximum of 12 months. If the therapy with Afinitor® and exemestane is stopped prior to disease progression, the follow up period will be extended until time of progression / death of the patient. Observation intervals are not specified, but will be guided by current practice and the clinical symptoms of the respective patient, e.g. after approx. 2 weeks, 1 and 3 months and then at 3-month intervals (6, 9, 12 ... etc.) after the start of

treatment with Afinitor® and exemestane. The end of this treatment should be documented regardless of the target interval if treatment is ended before the next regularly scheduled follow-up.

The following patients are suitable for inclusion in this NIS:

- ✓ Patients who are treated with Afinitor® plus exemestane according to routine practice and the Summary of Product Characteristics or for whom treatment with Afinitor® and exemestane is indicated.
- ✓ Postmenopausal women with advanced hormone-receptor-positive, HER2/neu-negative breast cancer without symptomatic visceral metastases.
- ✓ Recurrence or progression after a non-steroidal aromatase inhibitor (e.g. anastrozole, letrozole)
- ✓ Age ≥ 18 years
- ✓ Patients who were given information about this NIS and signed an informed consent form.

There are no exclusion criteria except the contraindications listed in the Summary of Product Characteristics. Participating patients may not take part in any clinical study in parallel to this, as this does not constitute routine medical practice and is therefore counter to the aims of an NIS pursuant to Section 4 para. 23 sentence 3 AMG.

Notes on the indication for Afinitor® and exemestane and contraindications and possible side effects are provided in the enclosed Summary of Product Characteristics. Treatment may not be administered for the purpose of inclusion in the NIS, but must be given exclusively for the purpose medical and therapeutic need.

6.2 Ensuring representativeness of the number of cases

Although deliberations regarding the number of cases are based on formal statistical principles, this is not strictly planned with respect to controlling alpha errors and statistical power. The estimate of case numbers is based on considerations such as incidence of disease, sample size in relation to the overall population and anticipated recruitment within the study period.

The number of cases of approx. 3000 corresponds to >11% of the total population with this indication, assuming that during the patient recruitment phase (October 2012 to December 2016), approx. 24,000–26,000 patients would be eligible for Afinitor® plus exemestane as a treatment option according to the Summary of Product Characteristics (i.e. postmenopausal women with advanced breast cancer with no symptomatic visceral metastases following a recurrence or progression after a non-steroidal aromatase inhibitor). The number of cases of up to 3000 allows sufficiently large subgroups to be formed to make a comparative analysis with respect to efficacy and quality of life between patients with high levels of physical activity and patients with low levels of physical activity.

The representativeness of the approx. 400 participating study sites is ensured by a nearly

equal regional distribution across the country. Study sites are selected exclusively on the basis of their involvement with the care of the patient collective to be studied and the interest of the site in participating in a structured case documentation and analysis project. Since no exclusion criteria are explicitly defined (i.e. all patients who fulfil the requirements for documentation can actually be documented), the representativeness of the selection within the sites is assured.

6.3 Observation period

The approval study for Afinitor® demonstrated a statistically significant advantage of Afinitor® in combination with exemestane over placebo plus exemestane, consisting in a prolongation of PFS from 3.2 to 7.8 months according to the local radiology evaluation. The risk of progression of the cancer was reduced by 55%. These results were confirmed by an independent central radiology assessment (4.1 vs. 11.0 months, 62% reduction of risk). In order to obtain relevant results corresponding to the stated goals, the observation period corresponds with the duration of treatment with the combination of Afinitor® and exemestane, ending however no later than 31/12/2017 at the latest. The last patient will thus be observed for a maximum of 12 months. If the therapy with Afinitor® and exemestane is stopped prior to disease progression, the follow up period will be extended until time of progression / death of the patient. A patient who does not start the indicated treatment with Afinitor® and exemestane, for whatever reason, cannot be documented in the NIS. Treatment interruptions are documented over the entire treatment period. If treatment with Afinitor® and/or exemestane is discontinued permanently for whatever reason, the date of the last administration and the main reason for discontinuation are to be documented.

Timeline of the NIS:

Start of the observation phase:	October 2012
Inclusion of last patient in the documentation:	December 2016
End of the observation phase:	December 2017
Last data collection in the eCRF:	March 2018
Final report:	December 2018

Only data entered into the NIS database via web application by 31/03/2017 or questionnaires that were sent to the CRO [redacted] by 31/03/2018 can be used for the statistical analysis and will be eligible for remuneration (signature required).

6.4 Observation parameters

In this non-interventional study, diagnostic measures and medically indicated examinations are documented only if they were conducted in accordance with normal routine practice. The points described under 6.4.1 to 6.4.3 are guideline observation parameters and are solely for the purpose of orientation.

Optional intermediate examinations can be anticipated per patient corresponding to routine practice in normal conditions. Findings are to be documented at the time of inclusion and after approx. 2 weeks, 1, 3, 6, 9, 12... etc. months until the end of treatment with Afinitor® and exemestane or until the end of the observation phase, whichever occurs first.

To assess quality of life and physical activity before the start of treatment and during treatment, questionnaires in hard copy will be provided. To estimate patient compliance, patients will be given calendar overviews.

6.4.1 Observation parameters at the initial examination

Prerequisite: written consent form for participation in the study

- Date of start of observation/initial examination
- Patient history, demographic data, and characteristics of the disease
  - Date and characteristics of the initial diagnosis (month/year, tumour stage (TNM), grading, histological subtype, Ki67)
  - Diagnosis-specific history at the first evidence of metastasis (date, type of metastasis, location)
  - Previous and current treatment (radiotherapy, pharmacological treatment with start, end, and best result observed with respect to tumour response)
  - Details of previous tumour resection and metastases and their tumour biology if available
- ECOG performance status – if conducted
- Height, weight
- Current tumour status (TNM stage, location of metastases and latest imaging (CT, MRI, ultrasound, bone scintigraphy, etc.))
- Reason for switching to Afinitor® (progression, patient wish, not progression-induced switch)
- Comorbidity
- Antiresorptive treatment to prevent bone-related complications if bone metastases are present
- Planned prophylactic measures against stomatitis
- Quality of life: patient questionnaire EORTC QLQ-C30/BR23
- Physical activity: “Godin Leisure-Time Exercise Questionnaire” and “Physical Activity Scale” (PAS)
- Compliance: calendar overview provided to estimate treatment compliance
- Prescription for Afinitor® (date, dosage, pack size)
- Planned follow-up visit

6.4.2 Observation parameters two weeks after the start of documentation (prospectively after implementation of Amendment 2 in the eCRF)

If a visit takes place approx. 2 weeks after the start of documentation in accordance with routine practice, the following observation parameters are documented at this time:

- Date of follow-up
- Documentation of stomatitis treatment if any was needed and given
- Current tumour treatment with Afinitor® (dosage, dose reduction, treatment breaks, reason for dose adjustment)
- Patient questionnaire on stomatitis prophylaxis
- Documentation of adverse events
- Next scheduled follow-up

6.4.3 Observation parameters at later follow-ups

In accordance with routine practice, documentation of the following observation parameters is to be made at regular follow-up s (e.g. after 1 month, 3 months and thereafter at 3-month intervals):

- Date of follow-up
- ECOG performance status – if conducted
- Weight
- Imaging follow-up (not at month 1)
- Evaluation of response to treatment (from imaging and/or clinical assessment of status in accordance with routine practice)
- Current tumour treatment with Afinitor® (dosage, dose reduction, treatment breaks, reason for dose adjustment)
- Prophylactic measures relating to treatment management
- Quality of life: EORTC QLQ-C30/BR23 patient questionnaire
- Physical activity: “Godin Leisure-Time Exercise Questionnaire” and “Physical Activity Scale” (PAS)
- Compliance based on a calendar overview, if available
- Documentation of adverse events
- Documentation of stomatitis treatment if any was necessary and given
- Patient questionnaire on stomatitis prophylaxis
- Prescription for Afinitor® (date, dosage, pack size)
- Next scheduled follow-up

6.4.4 End of observation

The documentation of the end of treatment with Afinitor® is not bound to the target observation interval (e.g. after month 1, 3, 6 etc.), but should be carried out at the soonest possible time that is

in line with medical practice. The following observation parameters will be recorded:

- Reasons for the end of documentation (withdrawal of consent, lost to follow-up, death, discontinuation of treatment with Afinitor®)
- Date, dosage and pharmaceutical form of the last administration of Afinitor®
- Reason for ending treatment (lack of efficacy, disease progression, intolerability, poor compliance)
- Evaluation of response to treatment (from imaging and/or clinical assessment of status in accordance with routine practice)
- Follow-up treatment
- Documentation of adverse events

6.4.5. PFS Follow Up

- Date of progression or death as well as type of follow up treatment, if therapy with Afinitor® an exemestane has been stopped prior to disease progression
- Documentation of AEs and SAEs with causal connection to Afinitor® an exemestane and occurrence of death, independent from causal connection

6.5 Drugs

Afinitor® is an oral inhibitor of the *mammalian target of rapamycin* (mTOR). Afinitor® is approved in combination with exemestane for the treatment of postmenopausal patients with advanced HR-positive, HER2/neu-negative breast cancer with no symptomatic visceral metastases, after a recurrence or progression following an NSAI. Afinitor® is available as 10 mg, 5 mg and 2.5 mg tablets to facilitate any necessary dose reductions.

Exemestane belongs to the group of aromatase inhibitors and prevents the synthesis of oestrogens by irreversible binding to the aromatase enzyme. The active ingredient is indicated for the treatment of advanced breast cancer in women after natural or induced menopause following progression under anti-oestrogen treatment.

Afinitor® and exemestane are administered according to current routine practice and the recommendations of the respective Summary of Product Characteristics, based exclusively on medical and therapeutic need. The patients are treated with commercially available products. Information on dosage, warnings, precautionary measures, combination treatment and compatibility with other medication is provided in the accompanying Summary of Product Characteristics.

Dose adjustment due to toxicity

If serious and/or unacceptable side effects with a suspected correlation to Afinitor® occur, the dosage can be adjusted according to the Summary of Product Characteristics.

6.6 Study documentation

The study documents include

- Agreement to participate (two original documents: please send one copy to the CRO [redacted], the other copy is for your records)
- Patient information and informed consent form (two original documents: one copy is for the study doctor, the other one is fpr the patient. Please note: the written informed consent form must be archived by yourself)
- This observation plan
- Patient questionnaires (one questionnaire on quality of life, two questionnaires on physical activity, one questionnaire on stomatitis prophylaxis)
- The diary documenting medication intake
- A documentation guideline.

The Summaries of Product Characteristics for Afinitor® and exemestane are included. In addition, the physician is given a brochure for patients with suggestions and information on “physical activity with advanced breast cancer”. To support exercise, the physician can also give patient a pedometer with which they can observe their own activity on a voluntary basis.

All documentation in the database is labelled with the acronym of the NIS and a unique sequential patient number consisting of the site number, and a patient number assigned in ascending order (e.g. for site 100 with 5 patients: patient 100/01 to patient 100/05). **In order to identify a patient for a potential comparison of the data collected with the patient record (source data verification – SDV) the participating physician must keep a separate identification list that makes it possible to link the number of a specific patient to her name, date of birth, and age internally within the practice.** The identification list is intended to be retained exclusively by the participating physician. It must be ensured that the number on the patient questionnaires on quality of life and physical activity correspond with the patient number in the database. These questionnaires are to be completed by the patients themselves.

6.7 Study logistics

The Novartis Pharma GmbH field employees involved will be trained in the regulatory framework parameters, the FSA Code of Conduct and the recommendations of BfArM/PEI and the VFA.

The study documents will be distributed by the field employees. No advertising for the drug under investigation in this NIS that has any temporal or substantive link to the study-related activities of the field employee is permitted. The physician must be free to decide whether to participate; no attempt must be made to influence this decision in any way. The drug is prescribed exclusively on the basis of therapeutic need, a decision for which the physician has responsibility.

The documentation of follow-up examinations is to be carried out by the physician in electronic form only via the internet in the electronic Case Report Form (eCRF).

6.8 Remuneration

Remuneration for giving the patient information, complete documentation and the immediate notification of any serious adverse events (no later than 24 hours of their becoming known) will be made based on an assessment of services.

The average remuneration of EUR 850.00 per completely documented observation of a patient for the average observational period of 10 months is constituted as follows:

- Documentation of the start of observation € 150.00
- Observation at week 2 € 100.00
- Observations at month 1, 3, 6, 9...etc. € 125.00
- Documentation of the end of observation (one occasion) € 100.00
- Documentation of progress or death following discontinuation of the therapy with Afinitor® and exemestane (every six month until progress / death € 110.00

At 5% of the participating sites, on-site monitoring will be conducted in compliance with the applicable data protection provisions to ensure the confidentiality of patients' personal data. Remuneration for this on-site monitoring, if conducted, will consist of an additional € 150.00. This payment covers preparations and follow-up for the monitoring visit and availability during monitoring.

Separate remuneration of € 75.00 per fully completed questionnaire will be paid for the additional time involved in filling out the questionnaires that may be required for the risk management plan (as amended).

7 Adverse Events

7.1 Definition

The term "adverse event" (AE) describes any adverse or unintended manifestation (e.g. abnormal laboratory finding), symptom, or any illness **coinciding with** the use of a Novartis drug or **the drug(s) studied in this NIS**, regardless of whether a causal relationship with this drug is suspected. The drug studied in this NIS means the drug that is the subject of this study and includes combination or comparator products if they have been specified as part of the study aims. **The drugs in this BRAWO study are Afinitor® and exemestane.** Adverse events that occur **after the time of the initial administration of** Afinitor® and exemestane are recorded in the BRAWO NIS. Medical conditions or diseases that were already present before the initial administration of Afinitor® and exemestane in this study are considered an "adverse event" only if they became worse after starting treatment with Afinitor® and exemestane.

In addition, all the events or situations listed below are considered adverse events, regardless of whether or not a clinical symptom occurred:

- **Interaction** between drugs and/or between the drug(s) and food, with or without clinical

symptoms

- **Exposure to drugs** during **pregnancy** or **lactation** (irrespective of the outcome)
- **No efficacy or inadequate efficacy** of a compound after exhausting the recommended dose range, with or without clinical symptoms
- **Accidental or deliberate overdose**, with or without clinical symptoms
- **Drug abuse** and **drug misuse, dependence**
- **Withdrawal/discontinuation/rebound phenomenon,** with or without symptoms in each case
- **Medication and administration errors**, i.e. incorrect or accidental administration or delivery, including taking another person's medication, , or confusion of names (e.g. Lamisil mistaken for Lamictal), with or without symptoms in each case
- **Progression** or **deterioration of the underlying disease** with a suspected causal relationship, see Section 7.8
- **(Unexpected) positive effects**
- **Occupational / accidental exposure**
- **Quality defects**

Adverse events are classified as **serious** (SAE, see 7.2) or **non-serious** adverse events (NSAE, see 7.4).

All adverse events that occur are to be documented according to the type of event, first occurrence, duration and intensity in the patient observation form (eCRF). In addition, it must be documented whether a causal relationship has been seen, and if so, with what drug (see 7.5). Countermeasures initiated (e.g. pharmacological treatment, dose adjustment/ discontinuation/pause of medication), relevant concomitant medication, relevant investigation and laboratory findings and the outcome of the adverse event must also be reported.

Please ensure that the events are entered in full in the report form (eCRF) from the point of view of clear categorisation (e.g. pre-existing diseases, adverse event observed) and evaluation (e.g. causality) from the perspective of the reporting physician/medical professionals. Adverse events should be documented by a physician or other medical professional involved in the case (e.g. nurse, dentist, pharmacist), but must always be confirmed by the treating physician or the physician participating in the NIS. Hospital discharge reports, other findings and laboratory results should be sent only if requested by Novartis. Please note that **conscientious and fully completed documentation** facilitates quick, accurate data capture and, if necessary, reporting and **allows follow-up requests to be** avoided.

The incidence and profile of AEs occurring during the observational period are evaluated based on the currently applicable MedDRA version-coded reported events (System Organ Class [SOC] and Preferred Term [PT]).

Adverse events (SAEs and NSAEs) are recorded **irrespective of the causal relationship up**

to 30 days after the end of treatment with Afinitor® and exemestane within this NIS and processed according to the procedures described below. Adverse events with a suspected causal relationship with Afinitor® in the BRAWO NIS can be documented after this period.

All AEs and SAEs with causal connection to Afinitor® and exemestane of patients who stopped therapy with Afinitor and exemestane prior to disease progression and who entered PFS follow up period have to be documented in eCRF and reported starting day 31 after stopping treatment until day 30 after last visit (please refer to section 7.2 and 7.3). Occurrence of death have to be documented in eCRF and reported as SAEs independently from causal connection from day 31 after stopping treatment with Afinitor® and exemestane until day 30 after last visit (please refer to section 7.2).

After the end of the observation period specified for the BRAWO NIS (end of the observation period) in the observation plan in Section 6.3, reported **adverse events (SAEs and NSAEs) must be included in this NIS irrespective of the causal relationship up to 30 days after the end of the observation period and processed according to the procedures described.** After these 30 days, all adverse events (SAEs and NSAEs) subsequently reported to CRO [redacted] will be forwarded to Novartis outside this NIS, i.e. not included in the study.

7.2 Serious Adverse Events

- are fatal,
- are life-threatening[1],
- require or prolong hospitalisation,
- lead to inability to work, persistent or severe disability or incapacity[3],
- result in a congenital anomaly or birth defect,
- are medically significant[4].

1 Refers to an adverse event that carries a fatal risk for the patient at the time of the reaction. It does not refer to a reaction that could hypothetically result in death if it developed to a higher level of severity or complications.
2 This refers to inability to work as a result of permanent damage to health
3 Disability is considerable incapacity or permanent damage
4 Medically significant adverse events (AEs) are AEs that are not immediately fatal or life threatening or necessitate hospitalisation, but can considerably impair the patient. AEs are also medically significant if they require intervention/treatment to prevent a condition corresponding to the criteria for the definition of an SAE.

Inpatient treatment is not considered to be a serious adverse event if one of the following points applies:

a) Hospitalisation, that is part of the standard of care or surveillance of the disease investigated in the NIS and that is not due to worsening of the disease

b) Elective admission or hospitalisation, that was already planned before inclusion in the NIS for the treatment of pre-existing diseases without relation to the disease investigated in the NIS and without deterioration since application of the drugs studied in this NIS

c) Hospitalisation for social reasons and for short-term care without deterioration of the patient's general condition or the disease investigated in this study.

The decision as to whether an event constitutes an SAE depends only on whether one of the formal criteria named above is present and is ***independent of the assessment of whether there is a causal relationship between taking a drug and the occurrence of the SAE***.

Reporting periods for SAEs

All serious adverse events are to be documented **fully** in the electronic case report form (eCRF) under the "Adverse Events" tab and submitted in the system **within 24 hours of becoming known**.
Exception: In the event that entering an SAE in the eCRF is impossible for technical or other reasons, the SAE report can also be faxed as a hard copy "SAE report" directly to [redacted].

[redacted]

Fax: [redacted]

If sent by fax, the date of the fax is to be written on the original report form, which remains in the study documentation in the study site.
If the information on the serious adverse event is provisional in nature, it should be finally completed as soon as possible and sent to Novartis within 24 hours after the **new information becomes known as an SAE follow-up**.
Recurring manifestations, complications or progression or deterioration of the initial SAE must be reported to Novartis as a follow-up to the original report within 24 hours of becoming known. An SAE assessed to be completely independent of a previously reported SAE should be reported as a new event.

7.3 Non-serious adverse events

Non-serious adverse events (NSAEs) do **not** fulfil the formal criteria specified in 7.2. **All non-serious adverse events** must be documented in the system and sent **within 10 days** of becoming known.
Exception: In the event that entering an NSAE in the eCRF is not possible for technical or other reasons, a paper form for documenting and reporting the AE directly to [redacted] can be

requested and then forwarded to the following fax number.

[redacted]
[redacted]
[redacted]
Tel: [redacted]
Fax: [redacted]

If sent by fax, the date of the fax is to be written on the original report form, which remains in the study documentation at the study site.

If the information on the non-serious adverse event is provisional in nature, it should be finally completed as soon as possible and sent to Novartis as an NSAE follow-up.

7.4 Details of the causality assessment

For assessing the causal relationship between Afinitor®, exemestane and/or other concomitant medication and the event that has occurred, the options **"no causal relationship" or "causal relationship suspected"** are available. A physician's causality assessment is required and must be documented in all cases.

Relationship with Afinitor®, exemestane and/or other concomitant medication

It should be noted that many different aspects can play a role in assessing causality. These aspects can include the individual patient, the underlying disease, any concomitant medication or non-pharmacological factors.

No causal relationship	There is no reasonable possibility of a causal relationship between Afinitor®, exemestane and/or other concomitant medication with the AE.
Causal relationship suspected	There is a reasonable possibility of a causal relationship between Afinitor®, exemestane and/or other concomitant medication with the AE.

7.5 Handling side effects of other drugs from Novartis

Adverse events that are suspected to be in causal connection with Novatis drugs other than the drugs studied in this NIS will have to be announced in the range of the legal notification to the Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) and Novartis DS&E (Novartis Pharma GmbH, Abteilung Arzneimittelsicherheit, Roonstraße 25, 90429 Nürnberg Fax: [redacted]) as a spontaneous message (individual case message outlying the study). This includes suspicions of side effects under therapy with a Novartis drug which are known already before or during the screening visit and which have not yet been reported.

7.6 Side effects of drugs from other manufacturers

Suspected cases of side effects in connection with drugs from other manufacturers that are not included in the defined aims or reason for conducting the non-interventional study must be reported by the participating physician to the supreme federal authority (BfArM or PEI), the Drugs Committee of the German Medical Association (AkdÄ) or to the marketing authorisation holder of the respective product (exception: suspected interaction with a Novartis product, see 7.6). The study drugs in this NIS are Afinitor® and exemestane.

7.7 Progression of the underlying disease (tumour progression)

Deterioration of the underlying disease (tumour progression) during treatment with Afinitor® must be documented as an adverse event (AE) only if a causal relationship with Afinitor® treatment is suspected or if as a result of disease progression one or more of the formal criteria for a serious adverse event (SAE) listed under point 7.2 applies.

7.8 Abnormal laboratory values or test results

Abnormal laboratory values or **test results should be documented as an adverse event only if** they

- are above or below normal/reference values **AND**
- represent a change in terms of deterioration of the respective parameter compared with the baseline finding. This condition does not apply if there is no previous baseline value, **AND**
- the changed laboratory parameters
    - are considered clinically relevant **OR**
    - are associated with clinical symptoms **OR**
    - require therapeutic intervention **OR**
    - lead to a dose reduction and/or temporary suspension or permanent discontinuation of Afinitor® and/or exemestane.

Changes in a quantifiable parameter are to be documented as a **serious adverse event** if the formal criteria for an SAE are fulfilled (see 7.2). Reporting deadlines and reporting procedures are the same as those specified under 7.2 (Serious adverse events) and 7.4 (Non-serious adverse events).

7.9 Documentation of exposure during pregnancy and use during lactation

The authorisation for the combination of Afinitor® with exemestane is for postmenopausal patients. If it is nevertheless taken by a mother during pregnancy and/or lactation, all pregnancies that existed or occurred during this NIS, regardless of whether they are associated with an AE/SAE or not, must be reported to the address given above within 24 hours of becoming known using the

report form for pregnancies. Any use during lactation must also be documented and reported in the same way.

7.10 Patient questionnaires (e.g. quality of life questionnaires)

The events that enquired about in the validated and standardized patient questionnaire EORTC QLQ-C30/BR23 and the questionnaires on physical activity need not be documented additionally in the eCRF as adverse events. These entries describe the respective clinical picture and its course and are therefore analysed and presented separately. However, the physician involved must review all completed questionnaires (EORTC QLQ-C30/BR23, questionnaires on physical activity, questionnaire on stomatitis prophylaxis), also taking into account the answers relating to the presence of adverse events (AEs) in the patient questionnaire filled out at the previous assessment time, reporting these by documenting them in the eCRF. Any additions made that go beyond the respective questionnaire layout must be checked by the participating physician for the presence of an AE or SAE and documented in the eCRF if necessary.

8 Ethics

8.1 Consultation with the ethics committee

In accordance with the joint recommendations of BfArM and PEI on the planning, implementation and evaluation of observational studies and the VFA recommendations for improving the quality and transparency of non-interventional studies, an ethics committee with responsibility for the medical director, constituted according to federal state law, will be consulted before the start of the study. In this case, this is the ethics committee of [redacted].

8.2 Patient information and informed consent form

Every patient must be given information by the treating physician about the aims and the nature and scope of documentation before being included in the NIS. Because an authorised drug is being observed in the NIS, specific patient information that goes beyond the scope of the instructions for patients is not needed.

A patient may not be included in the NIS without her written consent to having her data documented in the NIS and to having her patient file viewed for comparing data. Processing of personal data for the purpose of comparing the data collected with the patient's medical record (SDV) is subject to EU Directive 95/46/EC and national data protection regulations.

8.3 Data protection

The protection of patient data is assured. Patient data collected in the NIS are documented in pseudonymised form in the observation form, i.e. marked only with a number (patient number) and without indicating the name, initials, date of birth or address of the patient.

If the study results are published, the personal data may be used only in pseudonymised form. The personal data may be viewed only by persons who are authorised by the sponsor and required to maintain confidentiality and by the responsible regulatory authorities where necessary to check that the non-interventional study was properly conducted.
The medical personnel responsible for transferring the data from the patient file must be informed of their data protection responsibilities.

9 Legal and regulatory principles, reporting requirement

This NIS is conducted in accordance with the Novartis Pharma GmbH internal SOPs, which are based on the following recommendations and guidelines:

- Section 4 para. 23 sentence 3 of the German Drug Law (AMG)
- The non-interventional study is notified before its start to the Federal Institute of Drugs and Medical Devices (BfArM), the National Association of Statutory Health Insurance Physicians and the Central Federal Association of Health Insurance Funds pursuant to Section 67, para. 6 AMG.
- Section 63 b of the German Drug Law (AMG)
- Directive 2001/83/EC of the European Parliament and of the Council and amendment with Directive 2010/84/EU of the European Parliament and of the Council
- Pharmacovigilance Guidelines of Volume 9A of 'The Rules Governing Medicinal Products in the EU'
- Guideline on good pharmacovigilance practices (GVP), Module VI – Management and reporting of adverse reactions to medicinal products
- Joint recommendation(s) of the Federal Institute of Drugs and Medical Devices and Paul Ehrlich Institute for the planning, conduct and evaluation of observational studies (7.7.2010)
- The study is also registered before the start in the publicly accessible register for NIS at the VFA (http://www.vfa.de/de/forschung/nisdb/).
- VFA recommendations on improving the quality and transparency of non-interventional studies dated 31/01/2007 and 23/04/2007
- FSA Code of Conduct on collaboration with professionals – Federal Gazette dated 07/05/2008

10 Data Management

10.1 Data Management Plan

All quality assurance measures in data management are set out in a project-specific data management plan (DMP) and specified for the individual phases of data management:

- Automatic plausibility checks for data input

- Data query plan, with catalogue of questions that lead to queries at the study site
- Implementation of an audit trail in accordance with FDA CFR21 Part 11 Standard
- Ensuring the integrity of data through documented closure of the data bank
- Data handling report for handling ongoing data inconsistencies relevant for the analysis. The data handling report is an integral part of the statistical analysis plan (SAP).

All data management processes are based on the SOP of CRO [redacted].

10.2 Data Collection and Data Query

All documentation is undertaken by the treating physician online in the electronic case report form (eCRF), with the exception of the patient questionnaires, which are in hard copy. The validated eCRF web application is located on a secure server of [redacted]. Programmed validations check the entries in the web application for plausibility and correctness when they are input and automatically generate the corresponding feedback. Open queries can be seen in the current status and are to be processed. Data input is checked centrally by [redacted] according to the agreements made. Free text input of new or updated data entered via the web application is checked for possible hidden adverse events. Open queries are followed up in the system regularly and communicated to the system. Handling of queries should be done online by the site via the eCRF module. In exceptions, a generated query can also be mailed or faxed to the site for processing, which is completed and signed by the treating physician and sent to [redacted] to be entered into the database. A signed copy of this data query form is kept by the physician. The patient questionnaires are to be completed by hand using a ballpoint pen. During or at the latest at the end of the NIS at the site of the participating physician, the completed questionnaires are sent to [redacted] for central recording (one copy) and registration in the study database. Follow-up procedures and reporting lines for SAE reports and the cumulative AE reporting are in accordance with the SOPs of Novartis Pharma GmbH.

After data entry, queries can be made at the study sites. Searches for incompletely documented AEs or undocumented (hidden) AEs are made in an online data query and according to the respective SOPs of Novartis Pharma GmbH.

11 Monitoring/comparison with the patient record (SDV)

At the participating study sites, on-site monitoring complying with the provisions of current data protection legislation to ensure the confidentiality of the personal data of patients and in accordance with the monitoring plan will be conducted. The goals of the source data verification (SDV) to be conducted in this monitoring are:

- Checking that the patient's written informed consent for SDV is present
- Comparison of documentation data and source data for the following variables:

- Prerequisites for documentation
- Demographic data
- Examination times including documentation of examinations conducted at these times
- Documentation of SAEs and NSAEs
- Afinitor® and exemestane administration
- Treatment response and reasons for discontinuation of treatment
- Treatment/management of stomatitis, if applicable
- Any concomitant diseases

Monitoring will be conducted by a representative, designated by Novartis. The representative will be trained and certified in a monitoring training programme. The results of the SDV will be documented in a monitoring report.

The study site will be paid €150.00 as remuneration for the time spent on the monitoring visit based on the Fees Schedule for Physicians (GOÄ).

12 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be prepared by [redacted] before the start of the NIS, in which

- the statistical database on which the analysis is based is specified, including all adjustments, implementations, and calculations of derived parameters
- the specifications of the analysis collective will be presented in detail
- The (inferential) statistical methods will be specified.

12.1 Statistical analysis rationale

All variables measured in this NIS will be analysed and reported using appropriate statistical methods. The NIS will be analysed using epidemiology methods with primary use of descriptive statistical methods. If inferential statistical methods are used to determine confidence intervals, parameter comparisons stating the probabilities of exceeding limits or (multivariate) statistical methods for evaluating covariates, their results are considered to be purely descriptive. In this exploratory context, no alpha adjustments in multiple statistical comparisons are made.

The following intermediate analyses are planned: focus on physical activity and stomatitis management 6 months after inclusion of approx. 500 patients in the documentation, focus on PFS 12 months after the inclusion of approx. 500 patients in the documentation, and focus on stomatitis prophylaxis, incidence and treatment and on PFS 18 months after inclusion of approx. 500 patients in the documentation.

12.2 Descriptive statistical methods

Variables reaching at least interval level will be presented in tabular form including their sample values (number of valid and missing values, minimum, maximum, 5th percentile, first quartile, third quartile, 95th percentile, median, mean, standard deviation).

For variables at the nominal and ordinal level, distribution of the absolute and relative frequencies will be indicated.

For adverse events, incidences will be reported based on the patient population included and incidence density (number of events/sum of person times in years) according to the MedDRA system organ class and preferred term for adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs). Times of events and survival time analyses will be analysed using the Kaplan-Meier methodology. The derivation and rating of these event times is described in the SAP.

12.3 Missing values and discontinuation of treatment

Handling of missing values and dropouts is to be described and explained in the SAP.

12.4 Analysis sets

The analysis is based on the population of patients with documented administration/prescription of Afinitor® for whom at least one follow-up under treatment is available.

12.5 Analysis software

The statistical analysis will be performed using SAS® in the version current at the time of the evaluation.

13 Study reports and publication

The project manager at Novartis and the medical director are responsible for presenting the final report in English within 12 months after completion of the statistical analysis. The results of the study will be published jointly. Before publication by the medical director of the study, Novartis will be entitled to make a statement on the manuscript/abstract.

A progress report based on the classification of the study as a post-authorisation safety study (PASS) will be made at least once a year. The results will be taken into consideration in the periodic safety update report (PSUR) for Afinitor®. In the event of relevant findings (safety concerns), the progress report will be submitted to the responsible supervisory authority.

14 Documentation and archiving

The sponsor is responsible for archiving the study documentation for at least 10 years.

According to the MBOÄ (Professional Regulations for Physicians), participating physicians are

obligated to archive the identification list and the documentation of treatment provided in the NIS for at least 10 years.

15 References

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