NOVARTIS

Department: Novartis Oncology

Non-Interventional Study Protocol

Study Protocol Number: CRAD001JGB14

Title	A phase IV multicentre, open-label, non-interventional study of postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer treated with Afinitor® (everolimus [RAD001]) in combination with exemestane, after progression following therapy with a non-steroidal aromatase inhibitor.
Abbreviated Title/Acronym	BOUDICA: oBservatiOnal stUdy in locally aDvanced or MetastatIc hormone reCeptor positive breast cAncer.
Protocol version identifier	Final Version 43.0; 12th October 2015
Date of last version of protocol	12th June 2015
Release date	16th October 2015
EU PAS register number	ENCEPP/SDPP/9076
Active substance	Everolimus (RAD001)
Medicinal product	Afinitor®
Product reference	EU/1/09/538/004, 006 and 008

Procedure number	Not Applicable
Marketing authorisation holder(s)	Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom
Joint PASS	No
Research questions and objectives	In a randomised phase III, double-blind, placebo-controlled study (BOLERO-2), Afinitor in combination with exemestane was compared with exemestane plus placebo in 724 postmenopausal women with hormone receptor positive (HR+) advanced breast cancer (ABC) who had a recurrence or progression on letrozole or anastrozole. The median duration of follow-up of the patients was 18 months. Median progression-free survival (PFS) was 7.8 months for Afinitor plus exemestane versus 3.2 months for exemestane plus placebo (Hazard Ratio [HR]: 0.45; 95% Confidence Interval [CI]: 0.38 to 0.54; P<0.0001). Subsequently, in July 2012, Afinitor in combination with exemestane was approved for the treatment of postmenopausal women with oestrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-), ABC after progression on a non-steroidal aromatase inhibitor (NSAI) in the United States (USA), European Union (EU) and many other countries and has become an option in United Kingdom (UK) clinical practice. UK audit data and anecdotal evidence to date has suggested a higher incidence of adverse events (AEs) than expected from the reported safety profile in the BOLERO-2 trial. The primary objective of this observational study is to describe, in patients commencing treatment with Afinitor in combination with exemestane for ABC after progression on a NSAI, two specific toxicities, namely stomatitis* and non-infectious pneumonitis (NIP)* in terms of: • incidence, severity, length of time to onset, duration and clinical course;

- specific management (prophylaxis and intervention);
- any potential predisposing factors

*Definition of CTCAE (Common Terminology Criteria for Adverse Events): Non-infectious pneumonitis (NIP) and stomatitis (V4.0 2009)

	Grade 1	Grade 2	Grade 3	Grade 4
Non-infectious pneumonitis (NIP)	Asymptomatic, X-ray images only; no management required	Symptomatic; medical management; daily activities restricted	Severe symptoms; limited personal activities. Oxygen therapy indicated	Life-threatening. Emergency intervention indicated (tracheotomy or intubation)
Stomatitis	Asymptomatic or mild symptoms: no management required	Moderate pain; no interference during oral administration; diet adapted accordingly	Severe pain during oral administration	Life-threatening. Emergency intervention indicated

Secondary objectives are:

- to determine the dosing, schedule and duration of treatment with Afinitor and exemestane including any dose modifications/durations and reason(s); frequency of monitoring; prior and subsequent treatments and reason(s) for discontinuation
- to evaluate investigator-assessed progression-free survival with Afinitor plus exemestane. Investigator-assessed disease progression may be based on clinical examination or radiographic or laboratory features, mirroring routine practice.
- to capture changes in Quality of Life (QoL) scores over time and investigate the relationship between Health-Related Quality of Life (HRQoL), as measured by the EuroQol five-dimensional questionnaire (EQ-5D) and subjective well-being scores in ABC;
- documentation of adverse events (AEs).

	This non-interventional study will prospectively collect UK specific data on the use of Afinitor in combination with exemestane in routine clinical practice.
Country of study	United Kingdom
Authors	[redacted], BSc (Hons), [redacted]; Dr [redacted] PhD, Novartis Pharmaceuticals UK Ltd; Dr [redacted] MD, Novartis Pharmaceuticals UK Ltd.

Dr [redacted]
Qualified Person for Pharmacovigilance or delegate — Signature — Date

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham, West Sussex, RH12 5AB UNITED KINGDOM
MAH contact person	Dr [redacted], PhD [redacted] Novartis Pharmaceuticals UK Ltd [redacted] UNITED KINGDOM

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2 List of abbreviations

ABC	Advanced Breast Cancer
AE	Adverse Event
AI	Aromatase Inhibitor
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 Isosyme
DS&E	Drug Safety and Epidemiology
4E-BP1	Eukaryotic Initiation Factor 4E Binding Protein 1
ECOG	European Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
eIF-4E	Eukaryotic Initiation Factor 4E
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	EuroQoL five dimensions patient questionnaire (descriptive system of health-related quality of life states consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression)
ER	Oestrogen Receptor
EU	European Union
EU PAS	European Union Post-Authorisation Study
FKBP-12	FK506 Binding Protein 12
HER	Human Epidermal growth factor Receptor
HR	Hazard Ratio
HR+	Hormone Receptor Positive
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging

mRNA	Messenger RiboNucleic Acid
mTOR	Mammalian Target Of Rapamycin
mTORC1	Mammalian Target of Rapamycin Complex 1 (RAPTOR)
mTORC2	Mammalian Target of Rapamysin Complex 2 (RICTOR)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NIP	Non-Infectious Pneumonitis
NIS	Non-Interventional Study
NSAI	Non-Steroidal Aromatase Inhibitor
PASS	Post-Authorisation Safety Study
PgR	Progesterone Receptor
PFS	Progression-Free Survival
PI3K-Akt	Phosphatidyl-Inositol 3-kinase (PI3K)/Akt Pathway
PR	Partial Response
QoL	Quality of Life
RAD001	Everolimus
S6K	Serine / threonine p70S6 Kinase
SAE	Serious Adverse Event
SERM	Selective Oestrogen Receptor Modulator
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
UK	United Kingdom
US	United States
WHO	World Health Organisation

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person or Organisation
Main protocol authors	[redacted] BSc (Hons), LLM, HonFICR [redacted] Dr [redacted] Ph.D Novartis Pharmaceuticals UK Limited [redacted]
Chief Investigator	Dr [redacted], M.D. [redacted]
Marketing authorisation holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham, West Sussex, RH12 5AB

4 Abstract

Title	A phase IV multicentre, open-label, non-interventional study of postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer treated with Afinitor (everolimus [RAD001]) in combination with exemestane, after progression following therapy with a non-steroidal aromatase inhibitor.
Abbreviated Title/Acronym	BOUDICA: oBservatiOnal stUdy in locally aDvanced or metastatIc hormone reCeptor positive breast cAncer.
Version and Date	Final Version 4.0: 12th October 2015
Name and affiliation of main authors	[redacted], BSc (Hons), LLM, HonFICR [redacted], United Kingdom [redacted] Dr [redacted] Ph.D Novartis Pharmaceuticals UK Limited [redacted] [redacted]
Rationale and Background	Endocrine therapy options for postmenopausal women with oestrogen receptor positive (ER+) advanced breast cancer (ABC) include selective non-steroidal aromatase inhibitors (NSAI); anastrozole and letrozole, the steroidal aromatase inhibitor (AI) exemestane, the oestrogen receptor (ER) antagonist (fulvestrant), and the selective ER modulator (SERM) tamoxifen. Blocking of oestrogenic signaling with tamoxifen has been the main approach in treatment for ER+ breast cancer for over 30 years. Tamoxifen is indicated for treatment across the whole continuum of breast cancer, ranging from risk reduction in women with high risk of developing breast cancer to treatment in multiple lines of metastatic disease. Aromatase inhibitors reduce peripheral oestrogen synthesis by blocking the conversion of androgens to oestrogens, which is the primary way oestrogens are produced in postmenopausal women. Aromatase inhibitors are generally prescribed as the first line of therapy for the treatment of postmenopausal women with ER+ breast cancer (Beslija 2009, Cardoso 2011, NCCN 2011.2). Despite the broad spectrum of available options of endocrine therapy for patients with ER+ ABC, all patients will eventually develop resistance to initial treatment and their disease will progress. Prior to the positive outcomes from the BOLERO-2 study, (a prospective, multinational, randomised, double-blind, placebo-controlled phase III study), there were no treatments specifically approved for use after recurrence or progression on an AI in this setting. Available options, based on common

	clinical practice and several treatment guidelines (e.g. National Comprehensive Cancer Network [NCCN] treatment guidelines 2009), included fulvestrant and exemestane. As a consequence of the need for new treatment options for postmenopausal women after failure of prior AI therapy, the purpose of the BOLERO-2 study was to compare treatment with exemestane plus Afinitor to exemestane plus placebo in postmenopausal women with ER+ locally advanced or metastatic breast cancer following progression on a non-steroidal aromatase inhibitor (NSAI). The combination of Afinitor with exemestane showed significant improvement in efficacy, in terms of progression-free survival (PFS), response rate, and clinical benefit rate, relative to exemestane monotherapy (Baselga 2011). The median PFS by local assessment was 7.8 months for Afinitor plus exemestane versus 3.2 months for exemestane plus placebo (HR: 0.45; 95% CI: 0.38-0.54; P<0.0001). Overall response rate (12.6% vs 1.7%; P<0.0001) and clinical benefit rate (51.3% vs 26.4%; P<0.0001) were superior in the Afinitor plus exemestane arm versus exemestane plus placebo. Analyses by central assessment showed a median PFS of 11 months with Afinitor versus 4.1 months with placebo (Hazard Ratio [HR]: 0.38; 95% Confidence Interval [CI]: 0.31–0.48; P <0.0001) confirming the results of the primary PFS analysis (Piccart 2012, Baselga 2012). The combination of Afinitor and exemestane received a marketing authorisation in the United States of America (USA), European Union (EU) and many other countries based on the results of the BOLERO-2 study.
Research question and objectives	Following EU approval on 23rd July 2012 and subsequent introduction of Afinitor in combination with exemestane for the management of ER+ ABC after progression on a NSAI into United Kingdom (UK) clinical practice it is desirable to gain information on how Afinitor is being used and the resultant outcomes. Of particular interest are two adverse events (AEs), stomatitis and non-infectious pneumonitis (NIP), both of which are class effects of rapamycin derivatives. Understanding the time course of these AEs will allow appropriate patient education, inform the frequency of monitoring and aid in the development of prevention and management strategies. It may also be possible to identify predisposing factors that increase individual patient risk.
Study design	This open-label, non-interventional study (NIS) will prospectively collect UK specific data on the use of Afinitor in combination with exemestane in patients with metastatic or locally advanced ER+ breast cancer after progression on therapy with an NSAI in routine clinical practice. Dosage and scheduling of Afinitor in the treatment of these patients will follow the recommendations of the summary of product characteristics (SmPC) and the treating physician.
Population	Approximately two hundred postmenopausal women greater than 18 years of age with ER+ locally advanced or metastatic breast cancer for whom a decision has been taken to initiate treatment with Afinitor in combination with exemestane are eligible for this study. There are no exclusion criteria except the contraindications listed in the SmPC. 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 a NIS.
Variables	**Primary Outcome Measures:** The primary objective of this study is to describe two specific toxicities, namely stomatitis and NIP, in patients commencing treatment with Afinitor in combination with exemestane for ABC after progression on a NSAI. The descriptions will comprise incidence, severity, length of time to onset, duration, clinical course, specific management (prophylaxis and intervention) and will look to identify any potential predisposing factors on the likelihood of development. **Secondary Outcome Measures:** • to determine the dosing, schedule and duration of treatment with Afinitor and exemestane including any dose modifications/durations and reason(s); frequency of monitoring; prior and subsequent treatments and reason(s) for discontinuation. • to evaluate investigator-assessed progression-free survival (PFS) with Afinitor plus exemestane. Investigator-assessed disease progression may be based on clinical examination or radiographic or laboratory features, mirroring routine practice. • to capture changes in Quality of Life (QoL) scores over time and investigate the relationship between Health-Related Quality of Life (HRQoL), as measured by the EuroQol five-dimensional questionnaire (EQ-5D) and subjective well-being scores in ABC;
Data sources	Initiation of participating sites will be performed by Novartis or an appropriate third party. Before study initiation, a Novartis representative (or their designee) will review the protocol and electronic case report form (eCRF) with the physicians and their staff. Sites enrolling patients in this study will record data on the eCRFs which will capture, check, store and analyse the data. After the collection of informed consent and at enrolment into the study, patients will be assigned a unique subject number. All data collected will only be identified by the subject number and date of birth. Data will be collected from scans and laboratory reports captured within the medical notes of enrolled patients to determine baseline demographics and disease characteristics, exposure to study products and concomitant medication. Any history of stomatitis will also be captured along with potential predisposing factors. Changes in HRQoL will be assessed by the EQ-5D patient reported outcome questionnaire (Global Health Status QoL score). In addition, patients will be asked to complete four key subjective well-being questions taken from the Integrated Household Survey in England. Concomitant medications entered into the database will be coded using the World Health Organisation Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities terminology.

Study size	Approximately two hundred patients will be studied across 25 centres, based on disease incidence, sample size in comparison with the overall population, and the expected recruitment within the enrolment period.
Data analysis	All analyses will be performed by Novartis or a contracted designee. All the patients enrolled in the study will be described. The reference population for analysis will be patients who were enrolled and received follow-up, meeting eligibility criteria with at least one follow-up visit completed. Data from all centres that participate in this protocol will be combined for analysis. All data will be analysed [redacted] Descriptive statistics include n, mean, standard deviation, median and ranges for continuous variables and frequencies and percentages for categorical variables and will be provided unless otherwise specified. For patients with screening assessments who do not enter the treatment period, data will only be listed. Further technical details and discussion of the following statistical considerations will appear in the Statistical Analysis Plan, which will be finalised prior to database lock and the analysis. For all analyses, baseline value will be defined as the latest assessment prior to first study drug administration.
Milestones	Study Start (First Patient First Visit): March 2015 Recruitment End (Last Patient First Visit): December 2016 Study End (Last Patient Last Visit): December 2017 Final report of study results: March 2018 Publication date: June 2018

5 Amendments and updates

Table 5-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	16 January 2015	Abbreviated Title	Boudica oBservatiOnAl stUdy In locally aDvanced or metastatIc hormone reCeptor positive breast cAncer	Boadicea already assigned to an alternative study
2	16 January 2015	11 Management and reporting of adverse events	Review of text against revisions of EMA Pharmacovigilance Guideline GVP Module VI Management and Reporting of Adverse Reactions to Medicinal Products	Protocol adheres to Global SOP-7015232 and GVP VI
3	16 January 2015	6 Milestones	Updated	Amended study timelines
4	17 January 2015	9.2 Setting	Updated	Removed previous mTORi as an exclusion criterion
5	17 January 2015	9.6 Data Management	Updated	Protocol deviations will be reviewed continuously
6	12 June 2015	6 Milestones	Updated	Amended study timelines
7	12 October	9.3.Variables	Updated	Informed consent
8	12 October	9.2 Setting	Updated	Patients can progress onto further clinical studies f

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Final protocol released	December 2014
Study start (first patient first visit)	May 2015
Start of data collection	May 2015
Recruitment end (last patient first visit)	December 2016
Study end (last patient last visit)	December 2017
End of data collection	January 2017
Final report of study results	March 2018
Publication date	June 2018

7 Rationale and background

7.1 Background

7.1.1 Overview of breast cancer epidemiology and current treatment

7.1.1.1 Epidemiology of breast cancer

Breast cancer is the most frequently diagnosed cancer in women accounting for 1.38 million (23%) of all new cancer cases and is the leading cause of cancer related deaths in females worldwide causing more than 400,000 deaths yearly [Jemal et al 2011]. The presence of

hormone receptors (ER and/or progesterone receptor [PgR]) is one of the most important prognostic factors detected in approximately 70% of all invasive breast cancers. Endocrine therapy is the core treatment modality in patients with HR+ ABC.

7.1.2 Treatment options for ER+ advanced breast cancer

Endocrine therapy options for postmenopausal women with ER+ ABC include the selective non-steroidal aromatase inhibitors (NSAIs; anastrozole and letrozole), the steroidal aromatase inhibitor (AI; exemestane), the ER antagonist (fulvestrant), and the selective ER modulator (SERM; tamoxifen). Blocking of oestrogenic signaling with tamoxifen has been the main approach in the treatment for ER+ breast cancer for over 30 years. Tamoxifen is indicated for treatment across the whole continuum of breast cancer, ranging from risk reduction in women with high risk of developing breast cancer to treatment in multiple lines of metastatic disease. Aromatase inhibitors reduce peripheral oestrogen synthesis by blocking the conversion of androgens to oestrogens, which is the primary way oestrogens are produced in postmenopausal women. Aromatase inhibitors are generally prescribed as the first line of therapy for the treatment of postmenopausal women with ER+ breast cancer [Beslija 2009, Cardoso 2011, NCCN 2011.2]. Despite the broad spectrum of available options of endocrine therapy for patients with ER+ ABC, all patients will eventually develop resistance to initial treatment.

An emerging mechanism of endocrine resistance is aberrant signaling via the phosphatidylinositol 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway [Burstein 2011]. Also, hyperactivation of the PI3K/mTOR pathway is observed in endocrine resistant breast cancer cells, and treatment with mTOR inhibitors, including rapamycin analogues, reverses this resistance [Miller 2010]. In addition, growing evidence supports a close interaction of the mTOR pathway with ER signaling. A substrate of mTOR Complex 1 (mTORC1), S6 kinase 1 (S6K1), phosphorylates the activation domain of activation function 1 of the ER, responsible for ligand independent receptor activation [Yamnik 2009; Yamnik and Holz 2010].

Afinitor is a rapamycin derivative that inhibits mTOR through allosteric binding to mTORC1 but not mTORC2 [Efeyan and Sabatini 2010]. Afinitor combined with AIs in preclinical models of ER+, hormone sensitive and hormone resistant breast cancer, results in G1 arrest and enhanced apoptosis [Boulay 2004]. In the clinic, Afinitor monotherapy demonstrated clinical activity in patients with ABC who had mostly ER+ tumours and had received previous endocrine therapy [Ellard 2009]. In this trial, 19 of the 49 patients enrolled were ER+/HER2-; one complete response (CR), two partial responses (PRs), three stable disease for longer than six months, and six stable disease for less than six months were reported in this subgroup. Median PFS in this subset of 19 patients was 3.5 months (95% CI: 1.9–5.5 months, data source: National Cancer Institute [NCI]-Canada). An additional PR was reported in a patient with ER+ HER2-unknown tumour [Ellard 2009].

More recently, the combination of Afinitor with exemestane showed significant improvement in efficacy, in terms of PFS, response rate, and clinical benefit rate (CBR), relative to exemestane monotherapy [Baselga 2011]. The median locally assessed PFS was 7.8 months for Afinitor plus exemestane versus 3.2 months for exemestane plus placebo (HR: 0.45; 95% CI: 0.38-0.54; P<0.0001). The overall response rate (12.6% versus 1.7%;P<0.0001) and CBR (51.3% versus 26.4%; P<0.0001) were superior in the Afinitor plus exemestane arm compared with the exemestane plus placebo arm. Analyses by central assessment showed a median progression free survival (PFS) of 10.6 months with Afinitor versus 4.1 months with placebo (HR: 0.38; 95% CI: 0.31–0.48; P <0.0001) confirming the results of the primary PFS analysis [Piccart et al 2012, Baselga 2012]. The combination of Afinitor and exemestane has received a marketing authorisation in the USA, EU and many other countries based on the results of this study.

7.1.3 Role of mammalian target of rapamycin in ER+ advanced breast cancer

The mammalian target of rapamycin (mTOR) is a key protein kinase which acts as a nutrient sensor and monitor of the cellular metabolic state regulating protein synthesis and ultimately cell growth, proliferation, and survival. The mTOR serves a key role in normal mammalian cell physiology, and is centrally involved in tumour-cell physiology (e.g. facilitating cell cycle progression from G1 to S phase) and, consequently, inhibition of this target has received considerable attention as an anti-cancer approach, as reviewed by [Bjornsti and Houghton 2004; Abraham and Gibbons 2007]. mTOR regulates global messenger ribonucleic acid (mRNA) translation [Beuvink 2005]. Indeed, downstream from mTOR is the serine/threonine kinase p70S6 kinase (S6K) which phosphorylates key residues on the ribosomal protein S6, permitting its activation and full function as a protein involved in ribosomal biogenesis. The mTOR kinase also modulates phosphorylation of eukaryotic initiation factor 4E binding protein 1 (4E-BP1), releasing its inhibition of eukaryotic initiation factor 4E (eIF-4E) and consequently permitting efficient cap-dependent translation [Bjornsti and Houghton 2004].

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance. Research into the mechanisms of resistance has shown that various signal transduction pathways are activated to escape the effect of endocrine therapy. For example, the PI3K/Akt/mTOR pathway is constitutively activated in AI resistant and long-term oestrogen deprivation boundary cap cells [Tokunaga 2006; Santen 2005; Campbell 2001]. Selective inhibitors of mTOR, sirolimus or rapamycin, demonstrated a significant growth inhibition particularly in long-term oestrogen deprivation boundary cap cells [Yue 2007]. Rapamycin and its analogues partially inhibit mTOR through allosteric binding to mTORC1 but not mTORC2 [Efeyan and Sabatini 2010]. However, prolonged exposure to rapamycin also results in mTORC2 inhibition [Sarbassov 2004].

In addition, there is growing evidence which supports a close interaction between the mTOR pathway and ER signaling. A substrate of mTOR complex 1 (mTORC1), called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand independent receptor activation [Yamnik 2009; Yamnik and Holz 2010].

7.1.4 Overview of Afinitor® (Everolimus [RAD001])

Afinitor® (everolimus [RAD001]) is a derivative of rapamycin. It is a selective mTOR inhibitor drug class, specifically targeting the mTOR signal transduction complex 1-raptor (regulatory-associated protein of mTOR complex, mTORC1 [Raptor]). Both rapamycin and Afinitor potently inhibit proliferation of endothelial cells [Yu and Sato 1999, Lane 2009] and have anti-angiogenic activity in vivo [Guba 2002, Tsutsumi 2004, Mabuchi 2007, Lane 2009].

Afinitor exerts its activity through high affinity interaction with the intracellular receptor protein FK506 binding protein 12 (FKBP12). The FKBP12/Afinitor complex binds to mTORC1, inhibiting its signaling capacity. The mTORC1 signaling is effected through modulation of the phosphorylation of downstream effectors, the best characterised of which are the translational regulators S6K1 and 4E-BP. Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumour growth and expression of hypoxia induced factors such as HIF-1; the latter resulting in reduced expression of factors involved in the potentiation of tumour angiogenic processes such as the vascular endothelial growth factor. Afinitor is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel associated smooth muscle cells. Consistent with the central regulatory role

of mTORC1, Afinitor has been shown to reduce tumour cell proliferation, glycolysis and angiogenesis in solid tumours *in vivo*, and thus provides two independent mechanisms for inhibiting tumour growth: direct anti-tumour cell activity and inhibition of the tumour stromal compartment.

7.1.5 Clinical experience of Afinitor in HR+ breast cancer

Several randomised trials evaluated Afinitor in HR+ breast cancer and showed evidence of efficacy of Afinitor in this patient population.

7.1.5.1 Afinitor monotherapy

In a multicentre, randomised phase II study, a daily dose of Afinitor (10mg) was evaluated in patients with mostly HR+ ABC who had received prior endocrine therapy. In this trial, 19 of the 49 patients enrolled were ER+/HER2-; one CR, two PRs, three stable disease for longer than six months, and six stable disease for less than six months were reported in this subgroup. Median PFS in this subset of 19 patients was 3.5 months (95% CI: 1.9–5.5 months, data source: NCI-Canada). An additional PR was reported in a patient with ER+ HER2-unknown tumour [Ellard 2009].

7.1.5.2 Afinitor in combination with endocrine therapy

The combination of Afinitor with endocrine therapy has been assessed in different disease settings.

A neoadjuvant randomised 270 patient phase II study compared the combination of Afinitor and letrozole to letrozole alone. The overall response rate in the Afinitor arm was higher than that with letrozole alone (68% versus 59% (palpation, P=0.062) and 58% versus 47% (ultrasound, P=0.035), respectively. Additionally, there was a greater anti-proliferative response, with a decrease of the Ki67 proliferation index to <1 in 57% of patients in the Afinitor arm and in 30% of patients in the placebo arm (P<0.01). This reduction in Ki67 was observed only two weeks after initiation of trial therapy [Baselga et al 2009].

In the randomised phase III, double-blind, placebo-controlled study (BOLERO-2 Study), Afinitor in combination with exemestane was compared with exemestane alone in 724 postmenopausal women with HR+ ABC who had a recurrence or progression on letrozole or anastrozole. The median duration of the follow up of the patients was 18 months. Median PFS was 7.8 months for Afinitor plus exemestane versus 3.2 months for placebo plus exemestane (HR: 0.45; 95% C;, 0.38-0.54; P<0.0001). Centrally assessed PFS analyses showed a median PFS of 11.0 months for the Afinitor plus exemestane arm versus 4.1 months for the placebo plus exemestane arm (HR: 0.38; 95% CI; 0.31-0.48; P<0.0001). Subgroup analyses showed consistent PFS benefit with combination therapy across all patient subsets. By local assessment, three complete responses (CRs, 0.6%) and 58 partial responses (PRs, 12.6%) were reported for the Afinitor plus exemestane arm, versus only four PRs (1.7%) for the placebo plus exemestane arm. The CBR also was increased with Afinitor plus exemestane therapy (51.3%) versus placebo plus exemestane (26.4%) (P<0.0001). These differences in objective response rate and CBR were also supported by a central radiology review [Piccart et al 2012].

In a 111-patient randomised phase II study in postmenopausal women with ER+ ABC previously pretreated with AIs, the combination of Afinitor and tamoxifen showed a significant improvement in PFS (8.6 months versus 4.5 months, P=0.0021) and overall survival (median not reached versus 24.4 months, P=0.0137) relative to tamoxifen alone [Bachelot et al 2012]. Although the results of the phase II trial were encouraging, the small sample size limits their relevance to clinical practice.

7.1.5.3 Safety profile of Afinitor

The following adverse events are considered to be class effects of mTOR inhibitors: stomatitis/oral mucositis/ulcers, infections and infestations, rash and similar events, cytopaenia, haemorrhages, non-infectious pnuemonitis, hyperglycaemia/new-onset diabetes mellitus, renal events, and thromboembolism. The more common metabolic AEs reported with mTOR inhibitors result from inhibitory effects on mTOR-regulated lipid and glucose pathways, while infections stem from the immunosuppressive properties of these agents. Virtually all AEs associated with mTOR inhibitors can be managed effectively with dose modification and/or supportive intervention.

The safety profile of Afinitor observed in the BOLERO-2 study was consistent with prior experience in the oncology setting with events of predominantly low grade (grade 1 or 2) reported. An increased risk of NIP, infection, and stomatitis in the Afinitor plus exemestane arm relative to the control arm (exemestane plus placebo) was observed.

The most common AEs suspected to be related to treatment, with an incidence ≥10%, reported in association with Afinitor plus exemestane therapy were consistent with what was previously reported: stomatitis, rash, fatigue, decreased appetite, diarrhoea, dysgeusia, nausea, pneumonitis, weight decreased, anaemia, epistaxis, hyperglycaemia, thrombocytopenia, and pruritus (see Table 7.1).

The most common grade 3-4 AEs suspected to be related to treatment with an incidence of ≥2% were: stomatitis, hyperglycaemia, anaemia, pneumonitis, fatigue, elevated alanine and aspartate transaminase concentrations, elevated γ-glutamyltransferase concentrations, dyspnoea, neutropenia, and thrombocytopenia. No new safety concerns emerged from the BOLERO-2 study compared with previous experience with Afinitor monotherapy or combination therapy.

Further details related to Afinitor safety can be found in the everolimus Investigator's Brochure.

Table 7-1 BOLERO-2 Study: Most common Adverse Events (≥10 percent of Patients)

	Afinitor plus exemestane (n = 482), %					Placebo plus exemestane (n = 238), %				
	Grade					Grade				
Adverse event (preferred term)	**All**	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**
Stomatitis	59	29	22	8	0	12	9	2	1	0
Rash	39	29	9	1	0	7	5	2	0	0
Fatigue	37	18	14	4	<1	27	16	10	1	0
Diarrhoea	34	26	6	2	<1	19	14	4	1	0
Nausea	31	21	9	<1	<1	29	21	7	1	0
Decreased appetite	31	19	10	2	0	13	8	4	1	0
Weight decreased	28	10	16	2	0	7	3	5	0	0
Cough	26	21	4	1	0	12	8	3	0	0
Dysgeusia	22	18	4	0	0	6	6	0	0	0
Dyspnoea	22	10	6	5	<1	11	8	2	1	<1
Headache	23	17	6	<1	0	15	13	2	0	0
Arthralgia	21	15	5	1	0	17	11	6	<1	0
Peripheral oedema	21	14	6	1	0	6	5	1	<1	0
Anaemia	21	4	10	7	1	5	2	2	<1	<1
Back pain	15	10	5	<1	0	11	6	3	2	0
Epistaxis	17	16	2	0	0	1	1	0	0	0
Vomiting	17	11	6	1	<1	13	9	3	1	0
Pyrexia	16	13	3	<1	0	7	6	1	<1	0
Pneumonitis	16	7	6	3	0	0	0	0	0	0
Constipation	15	11	3	1	0	13	8	5	<1	0
Back pain	15	10	5	<1	0	11	6	3	2	0
Pruritus	14	11	3	<1	0	7	5	2	0	0
Insomnia	14	10	4	<1	0	8	6	3	0	0
Asthenia	14	7	6	2	<1	4	3	1	<1	0
AST increased	14	6	5	3	<1	6	2	2	1	0
Hyperglycaemia	14	4	5	5	<1	2	1	1	<1	0
ALT increased	12	5	4	3	<1	5	1	2	2	0
Dry mouth	11	10	1	0	0	7	7	<1	0	0
Alopecia	11	9	1	0	0	12	12	0	0	0
Nasopharyngitis	10	9	1	0	0	9	7	2	0	0
Pain in extremity	10	6	3	<1	0	12	5	5	2	0
Urinary tract infection	10	3	7	<1	0	2	<1	2	0	0
GGT increase	10	2	2	5	2	9	1	1	5	2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase.

7.1.6 Overview of exemestane

Exemestane is an irreversible steroidal aromatase inhibitor efficacious in treating postmenopausal patients with ABC. It is indicated for adjuvant treatment of postmenopausal women with ER+ early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of five consecutive years of adjuvant hormonal therapy. It is also indicated for the treatment of ABC in postmenopausal women whose disease has progressed following tamoxifen therapy (in the USA) or anti oestrogen therapy (in the EU). Exemestane is initially recognised by the aromatase enzyme as a false substrate and then transformed through a nicotinamide adenine dinucleotide phosphate hydrogen dependent mechanism to an intermediate that binds irreversibly to the enzyme causing inactivation. Exemestane significantly lowers circulating oestrogen concentrations (oestradiol, oestrone and oestrone sulfate) but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone [Aromasin prescribing information, Pfizer-Pharmacia, 2005].

The recommended daily dose of exemestane is 25mg taken orally. Exemestane is rapidly absorbed from the gastrointestinal tract and its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, extensively bound to plasma proteins and it appears to be more rapidly absorbed in women with breast cancer (T_{max} 1.2 hours) than in healthy women (T_{max} 2.9 hours). The terminal half-life is 18-24 hours and maximal E2 suppression is reached in seven days [Demers 1993, Plourde 1995 and Buzdar 2003]. Exemestane is metabolised by cytochrome P450 isosyme (CYP) 3A4 and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including 1A2, 2C9, 2D6, 2E1 or 3A4. Although no formal drug-drug interaction studies have been conducted, significant effects on exemestane clearance by CYP inhibitors appear unlikely [Aromasin prescribing information, Pfizer-Pharmacia, 2005, Hutson 2005, and Buzdar 2003].

The most frequently reported AEs for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Others include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia, and peripheral and leg oedema. Thrombocytopaenia and leucopaenia have been reported occasionally. Reductions in bone mineral density can occur with long term use of exemestane. There were 1058 patients treated with exemestane 25mg once daily in the clinical trials program. Exemestane was generally well tolerated, and AEs were usually mild to moderate. Adverse events occurring in greater than 10% of patients include hot flushes (14%), nausea (12%), insomnia, headache, increased sweating, joint and musculoskeletal pain and fatigue [USPI; Aromasin SmPC August 2008 (UK as RMS for EU MRP)]. Androgenic effects were reported in a limited number of patients (4.3%) [Buzdar 2003].

Refer to the package insert of the local supply of exemestane for more details.

7.2 Rationale for the study

The combination of Afinitor (everolimus, RAD001) with exemestane in the BOLERO-2 study [Baselga 2012] was associated with a statistically significant and clinically meaningful increase in the median PFS, versus exemestane alone. Following approval of Afinitor for breast cancer and introduction of this combination for the management of ER+ ABC after progression on a NSAI into UK clinical practice it is desirable to gain information on how Afinitor is being used and the resultant outcomes, especially with regard to specific toxicities.

7.2.1 Stomatitis

Stomatitis is a very common adverse event of therapy with Afinitor and exemestane, often occurring soon after starting treatment and frequently regressing during the course of treatment [Porta 2011]. The frequency of all grade stomatitis and related events from the BOLERO-2 study was higher in the Afinitor and exemestane arm (67%) than in the control arm (12%). Grade 3 events occurred in 8% and <1% of patients, respectively but no grade 4 events were observed.

In the Afinitor and exemestane arm, more than one-third of all stomatitis events (grade ≥2) were reported in the first two weeks (cumulative risk, 14%). The cumulative risks of stomatitis at six and 48 weeks were 26% and 37%, respectively, for Afinitor and exemestane versus 3% for exemestane and placebo (Figure 1 below).

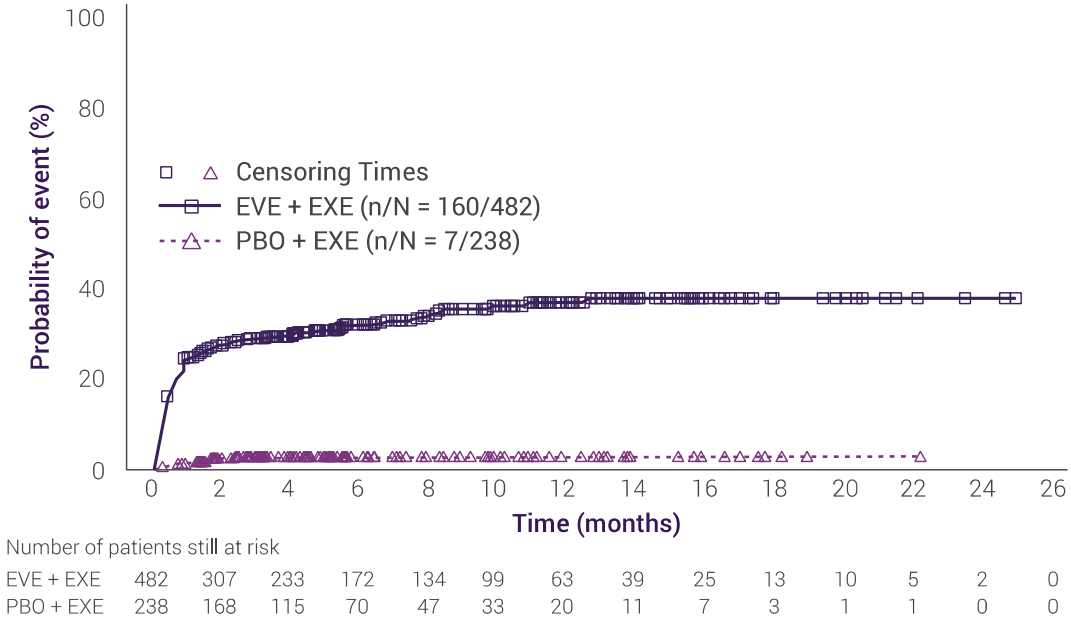

Figure 1: Cumulative risk estimates for initial onset of grade ≥2 stomatitis [Rugo 2014]

Abbreviations: EVE, everolimus; EXE, exemestane; PBO, placebo.

Among 39 patients with grade ≥3 stomatitis in the Afinitor plus exemestane arm, 97% experienced resolution to grade ≤1 following dose interruption/reduction after a median of 3.1 weeks, and 82% had complete resolution after a median of 7.4 weeks. In the control arm, the median time to resolution from grade 3 to grade ≤1 was 2.6 weeks (time to complete resolution was not assessable; one of two patients had complete resolution).

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 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 with Afinitor can be provided. 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. The study will also attempt to identify pre-disposing risk factors.

7.2.2 Non-infectious pneumonitis

Non-infectious pneumonitis (NIP) is a class effect of rapamycin derivatives. Cases of NIP (including interstitial lung disease) have also been described in patients taking Afinitor. Some of these have been severe and, on rare occasions, a fatal outcome was observed. A diagnosis of NIP should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms. Diagnosis is generally suspected in individuals receiving mTOR inhibitors who develop these symptoms or in asymptomatic individuals in whom a routine chest computed tomography (CT) scan reveals a new ground glass or alveolar infiltrate. In a performed and presented analysis of pneumonitis in breast cancer patients treated with Afinitor [Jerusalem 2009], the observed incidence of NIP in four Novartis-Sponsored studies ([C2222], Baselga 2009; Awada 2008; [J2101], Hurvitz 2009; [J2102] Cardoso 2009) totaling 238 patients did not exceed 3%. In the fifth study involving 49 patients (NCIC CTG, Ellard 2009), the incidence was approximately 10-fold higher. In a more recent study [Omarini 2014], the incidence of NIP was higher than expected compared with the data of the BOLERO-2 study (39% versus 12%). However, most of these were asymptomatic. Severe grade 3-4 cases occurred at the same frequency as in the BOLERO-2 study (4% versus 3%, respectively).

Although such marked differences remain poorly explained, the following points deserve consideration:

- Different monitoring methods across the studies have been applied: more extensive chest assessment by CT scans occurred in studies NCIC CTG, J2101, and J2102;
- Sponsor management guidelines for NIP based on CTCAE grade were developed in 2006, therefore fully implemented only in the J2101 and J2102 studies;
- The regular premedication with corticosteroids before the infusion of weekly chemotherapy could in part explain the low incidence observed in studies J2101 and J2102.

Overall, 20% of patients in the Afinitor plus exemestane arm of the BOLERO-2 study had NIP or related events, compared with <1% in the exemestane alone arm. Grade 3 events occurred in 4% of patients and one grade 4 event was reported. The time course for pneumonitis differed from stomatitis, with few early events and no appreciable plateau. Approximately one-quarter of events (grade ≥2) occurred within the first 12 weeks (cumulative risk, 5%). Cumulative risks of pneumonitis (grade ≥2) in the Afinitor plus exemestane arm were 10% and 16% at 24 and 48 weeks, respectively (Figure 2). Among patients with grade 3 pneumonitis in the experimental arm, 80% experienced resolution to grade ≤1, typically following dose interruption/reduction, after a median of 3.8 weeks. Complete resolution of grade ≥3 pneumonitis was reported in 75% of patients, after a median of 5.4 weeks.

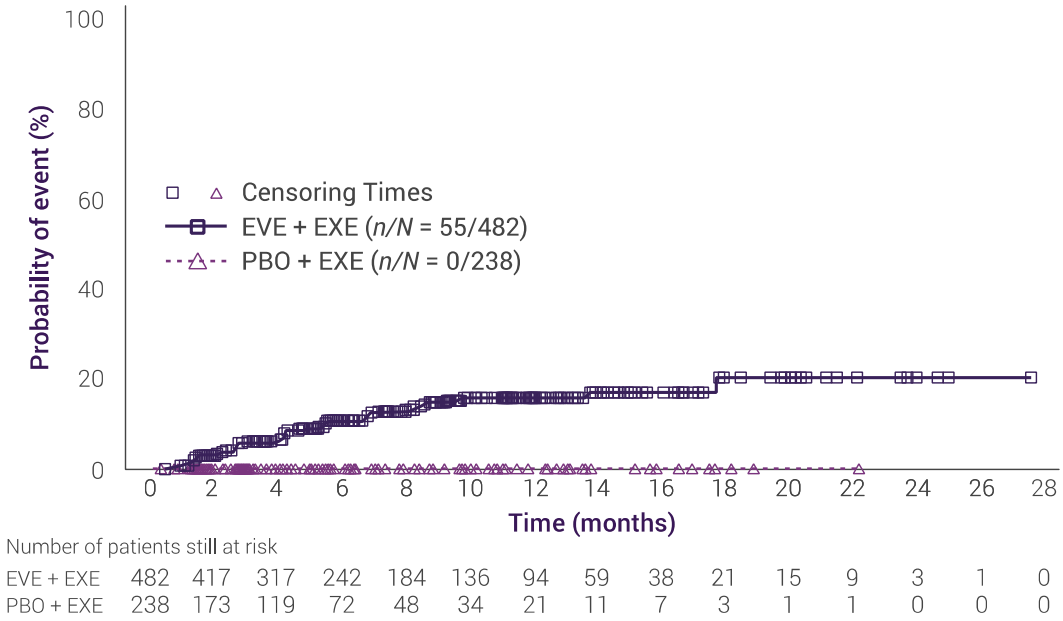

Figure 2: Cumulative risk estimates for initial onset of grade ≥2 non-infectious pneumonitis [Rugo 2014]

Abbreviations: EVE, everolimus; EXE, exemestane; PBO, placebo.

8 Research question and objectives

This NIS will prospectively collect UK specific data on the use of Afinitor in combination with exemestane. United Kingdom audit data [Omarini 2014, Thanopoulou 2014] and anecdotal evidence to date has suggested a higher AE incidence than expected from the reported safety profile in the BOLERO-2 study. Of particular interest are two AEs, stomatitis and NIP, both of which are class effects of rapamycin derivatives. Understanding the time course of these AEs will allow appropriate patient education, inform frequency of monitoring and aid in development of prevention and management strategies. The study will also attempt to identify any predisposing risk factors for the development of these two AEs.

8.1 Primary objective:

The primary objective of this observational study is to describe, in patients commencing treatment with Afinitor in combination with exemestane for ABC after progression on a NSAI two specific toxicities, namely stomatitis* and NIP* in terms of:

- incidence, severity, length of time to onset, duration and clinical course,
- specific management (prophylaxis and intervention).

The study will also collect data on any possible potential predisposing factors and will include collection of data on past incidence.

*Definition of CTCAE (Common Terminology Criteria for Adverse Events): Non-infectious pneumonitis (NIP) and stomatitis (V4.0 2009)

	Grade 1	Grade 2	Grade 3	Grade 4
Non-infectious pneumonitis (NIP)	Asymptomatic, X-ray images only; no management required	Symptomatic; medical management; daily activities restricted	Severe symptoms; limited personal activities. Oxygen therapy indicated	Life-threatening. Emergency intervention indicated (tracheotomy or intubation)
Stomatitis	Asymptomatic or mild symptoms: no management required	Moderate pain; no interference during oral administration; diet adapted accordingly	Severe pain during oral administration	Life-threatening. Emergency intervention indicated

8.2 Secondary objectives:

- to determine the dosing, schedule and duration of treatment with Afinitor and exemestane including any dose modifications/durations and reason(s); frequency of monitoring; prior and subsequent treatments and reason(s) for discontinuation
- to evaluate investigator-assessed progression-free survival with Afinitor plus exemestane. Investigator-assessed disease progression may be based on clinical examination or radiographic or laboratory features, mirroring routine practice.
- to capture changes in Quality of Life (QoL) scores over time and investigate the relationship between Health-Related Quality of Life (HRQoL), as measured by the EuroQol five-dimensional questionnaire (EQ-5D) and subjective well-being scores in ABC;
- documentation of adverse events (AEs).

9 Research methods

9.1 Study design

This is an open-label, NIS of oral Afinitor (everolimus [RAD001]) in combination with exemestane in patients with metastatic or locally advanced ER+ breast cancer after progression on therapy with a NSAI. Afinitor (10mg daily) in combination with exemestane (25mg daily) will be prescribed in accordance with the SmPCs and supplied by pharmacy.

This is a NIS and, therefore, does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to local prescribing information and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study.

The planned observation period per patient starts with initiation of treatment with Afinitor in combination with exemestane, but ends on completion of the observation phase. The observation phase completes once the last patient has been on study for 12 months. All antineoplastic therapies (surgery, medication, radiotherapy) for advanced breast cancer both

prior to initiation of Afinitor plus exemestane and post discontinuation should be recorded on the relevant eCRF pages. The treating physician will be asked to complete, if possible, at every patient visit the appropriate electronic case report form (eCRF). Below is the recommended assessment schedule that most likely mirrors the patterns of routine clinical care of most patients being treated with Afinitor (everolimus) in breast cancer. More frequent visits may be considered appropriate by the treating physician. Under these circumstances an appropriate eCRF should be completed for each visit. Data will be entered into an electronic data capture system allowing for continuous access to data and any potential re-evaluations of the study design or conduct.

Table 9-1 Follow-up schedule

Time of data entry	At start of documentation	After approx. 2 weeks	Approx. Month 1	Approx. Months 3, and at 3-month intervals thereafter	At end of treatment
Obtain patient's written informed consent*	X				
Inclusion/exclusion criteria	X				
ECOG performance status	X				
Demography	X				
Physical examination	X				
Vital signs	X				
ER, PgR status and Ki67	X				
Relevant medical history/current medical conditions	X				
Concomitant medications	X				
Date of initial diagnosis	X				
Date of metastatic relapse (if applicable) and sites involved	X				
Prior antineoplastic therapies (surgery, medication, radiotherapy) for advanced breast cancer	X				
Prior history of stomatitis	X				
Metastatic sites involved at initiation of Afinitor and exemestane	X				
Prescription of Afinitor and exemestane	X		X	X	X
Current tumour treatment with Afinitor (dosage, dose reduction, pauses in treatment, reason for dose adjustment)		X	X	X	X
PFS				X	X
Patient Quality of Life questionnaires	X	X	X	X	X

Standard well-being questionnaire	X	X	X	X	X
Planned prophylactic measures and stomatitis treatment	X	X	X	X	
AEs/SAEs (including stomatitis and NIP)		X	X	X	X
Reason for discontinuing treatment including sites of progression					X
Antineoplastic therapies since discontinuation of Afinitor plus exemestane					X

* Please note that this study allows up to 4 weeks to consent a patient on to the study.

9.2 Setting

Approximately 200 postmenopausal women will be recruited in 25 UK centres. Patients will be greater than 18 years of age with ER+ locally advanced or metastatic breast cancer for whom a decision has been taken to initiate treatment with Afinitor (everolimus [RAD001]) in combination with exemestane.. There are no restrictions regarding the last anticancer treatment prior to enrolment. Participating patients may not take part in any clinical study in parallel to this, as this does not constitute routine medical practice and would thus be counter to the objectives of a NIS. Treatment may not be administered for the purpose of inclusion in the NIS, but must be given exclusively for the purpose of medical and therapeutic need.

9.2.1 Inclusion criteria

- Postmenopausal women with ER+ locally advanced or metastatic breast cancer;
- Aged ≥18 years of age;
- A decision has been taken to initiate Afinitor plus exemestane;
- Given written and signed informed consent to participate in the study.

9.2.2 Exclusion criteria

There are no exclusion criteria except the contraindications listed in the SmPC. Participating patients may not take part in any clinical study in parallel to this whilst on Afinitor plus exemestane, as this does not constitute routine medical practice and is, therefore, counter to the aims of an NIS. On progression, patients can be enrolled onto further clinical studies which will be captured in the eCRF until the end of the study.

9.3 Variables

9.3.1 Patient demographics and other baseline characteristics

In this non-interventional study, diagnostic measures and medically indicated examinations are documented only if they were conducted in accordance with normal routine practice. Prior to enrolment into this study, it is necessary to obtain the patient's written informed consent. Patients can be consented up to four weeks after treatment with Afinitor plus exemestane is initiated. The study aims to collect the following parameters at baseline where available:

- European Cooperative Oncology Group (ECOG) Performance Index – if conducted
- General demography including age and gender;

- Medical history and current medical conditions;
- Concomitant medications;
- History and current disease status (including ER, PgR and Ki67 status if available, date of original diagnosis, date of first metastatic relapse if applicable and site involvement);
- Previous anticancer treatments for metastatic disease. The following information must be collected if available for all previous anticancer therapies: start date, end date, best response and reason for treatment discontinuation. Any history of stomatitis whilst on cancer therapy will also be collected if possible.
- Date of the prescription of Afinitor plus exemestane including dosage, reason for prescribing, date on which treatment will commence;
- Details of any planned prophylactic measures for stomatitis;
- EQ-5D questionnaire and subjective well-being assessment.

To determine eligibility at the screening visit, the following assessments may be performed and information captured:

- Physical examination and weight;
- Vital signs including blood pressure and heart rate;
- Safety laboratory assessments such as haematology, biochemistry, serum lipid profile, coagulation and urinalysis should be performed locally at the Investigator's discretion. Hepatitis screening will include: hepatitis B virus DNA, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody and hepatitis C virus ribonucleic acid polymerase chain reaction. If, at screening, laboratory results are out of range and clinically significant, these results should be captured on the medical history/current medical conditions eCRF;
- Tumour assessments at baseline may include clinical examination or radiographic or laboratory features, mirroring routine practice.

Thereafter, standard care would ideally be for patients to be contacted at 2 weeks, monthly then monthly to three monthly. The frequency of the visits will vary from patient to patient and due to clinician preference. Patients will be asked to complete the HrQoL and SWB questionnaires each time they attend the clinic. The HrQoL and SWB questionnaires will also be complete 30 days after trial end if possible as part of the end of trial visit.

9.3.2 Primary outcome variable: stomatitis and non-infectious pneumonitis

Instances of stomatitis and NIP will be assessed using the following variables:

- Incidence, severity, length of time to onset, duration and clinical course;
- Specific management of these events (including prophylaxis and interventions) will also be captured;

The expectation is that individuals participating in this study will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. Computed Tomography scans and pulmonary function tests may be conducted, as clinically indicated, if there are symptoms that indicate that the patient has developed NIP. If NIP develops, the guidelines below should be followed. Table 9-2 provides dose modification instructions for stomatitis and NIP.

Table 9-2 Management of non-infectious pneumonitis and stomatitis

Adverse Reaction	Severity (Worst Grade)	Recommended Investigation	Management	Afinitor® Dose Adustment
Stomatitis	Grade 2 (symptomatic, but can eat and swallow modified diet)	Visual assessment	Symptomatic therapy only: mouthwashes, oral gels and sucralfate. Use water-based moisturizer to protect lips. Follow recommended oral care protocol.	Temporary dose reduction until recovery to ≤grade 1. Restart treatment at same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to ≤grade 1. Restart treatment at 5mg daily.
	Grade 3 (symptomatic and unable to adequately eat or hydrate orally)	Visual assessment, including removal of dentures or partials	Symptomatic therapy only: mouthwashes, oral gels and sucralfate. Use water-based moisturizer to protect lips. Rinse mouth four times daily with a bland rinse such as salt and soda. Follow recommended oral care protocol	Temporary dose interruption until recovery to ≤grade 1. Restart treatment at 5mg daily.
	Grade 4 (symptoms associated with life-threatening consequences)	Visual assessment, including removal of dentures or partials	Symptomatic therapy only: mouthwashes, oral gels and sucralfate. Use water-based moisturizer to protect lips. Rinse mouth four times daily with a bland rinse such as salt and soda. Follow recommended oral care protocol. Consider systemic therapy.	Discontinue treatment.
Non-infectious pneumonitis	Grade 2 (symptomatic, not interfering with ADL)	CT scan with lung windows. Consider pulmonary function testing including: spirometry, DL_{CO} and room air O_2 saturation at rest. Repeat at least every 12 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and/or BAL.	Symptomatic therapy only. Consider corticosteroids if symptoms are troublesome.	Reduce study treatment dose by one dose level until recovery to ≤grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤grade 1 within three weeks.
	Grade 3 (symptomatic, interfering with ADL; O_2 indicated)	CT scan with lung windows and pulmonary function testing including: spirometry, DL_{CO} and room air O_2 saturation at rest. Repeat at least every six weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended, if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤grade 1. May restart study treatment within three weeks at reduced dose (by one level) if evidence of clinical benefit.
	Grade 4 (life-threatening; ventilator support indicated)	CT scan with lung windows ad required pulmonary function testing, if possible, including: spirometry, DL_{CO} and room air O_2 saturation at rest. Repeat at least every six weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended, if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

9.3.3 Secondary Outcome Variables; Drug exposure

Everolimus (RAD001) dosing will commence as per current practice. Patients will be instructed to take everolimus (RAD001) orally with a large glass of water, once daily, at the same time each day with or without food. Patients will be instructed to take one tablet of 25mg exemestane orally as per the SmPC.

Confirmation of correct dosing with everolimus and exemestane will be recorded in the eCRF, with details of any interruptions in drug treatment or dosage alterations. Compliance will be assessed by the Investigator and/or study personnel at each visit using tablet counts and information provided by the patient or caregiver. This information should be included in the source document at each visit for both drugs (everolimus and exemestane).

The mean and median duration of exposure will be assessed. A record will also be maintained of any dose modifications with everolimus, including duration and reason(s).

Patients will continue to be treated at the discretion of the treating physician. Information on drug exposure will be collected on the Dosage Administration Record page of the eCRF.

After a patient's individual study involvement ends, routine clinical practice will continue under the direction of the Investigator.

9.3.4 Other Secondary Outcome Variables

Observation intervals are in line with clinical routine: after approximately two weeks, one month and thereafter at monthly to three monthly intervals after the start of treatment with Afinitor and exemestane. Patients will be assessed, as described below, and details will be recorded in the eCRF.

9.3.4.1 Clinical/demographic patient characteristics:

- **Physical examination**

Significant findings present prior to the start of the study should be documented on the Medical History/Current Medical Conditions eCRF. Significant findings after the start of the study, which meet the definition of an AE, must be recorded on the AE eCRF.

Weight should be measured at screening.

- **Vital signs**

Vital signs can be recorded on the appropriate eCRF pages.

Vital signs can be measured at screening and throughout the study in accordance with routine clinical practice. Any particular clinical findings seen before starting the study should be documented in the Relevant Medical History eCRF. The findings that are compatible with AEs after commencing the study must be documented on the AE eCRF.

- **Laboratory evaluations**

Laboratory evaluations are for the clinical management of the patients and these will not be routinely documented in the eCRF.

Any particular clinically significant findings before commencing the study must be documented in the Relevant Medical History/Current Medical Conditions eCRF. Abnormal laboratory parameters that are clinically relevant (e.g., require dose modification and/or interruption of the study drug, lead to clinical symptoms or signs or require therapeutic intervention) constitute an AE and must be recorded on the AE eCRF.

- **Haematology:**

Haematology tests may include a complete blood count, a total white blood cell count, red blood cell count, haemoglobin, haematocrit and a platelet count.

Tests may be performed at screening and then as clinically indicated during the study. In the event of grades 2, 3 or 4 haematological toxicities that require study drug dose modifications or interruptions, haematological tests should be repeated weekly until recovery to the baseline value or grade 1.

- **Clinical chemistry:**

Serum chemistry tests include urea, creatinine, lactate dehydrogenase, total protein, electrolytes (sodium, potassium and calcium), total bilirubin, gamma glutamyl transferase, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, uric acid and fasting glucose (ideally fasting state for at least 12 hours).

Serum chemistry should be performed at screening and then as clinically indicated during the study. In the event of grades 2, 3 or 4 non-haematological toxicities that require study drug dose modifications or interruptions, biochemistry tests should be repeated weekly until recovery to the baseline value or grade 1.

- **Serum lipid profile:**

A serum lipid profile assessment should be performed at screening and then as required during the study. In the event of grades 2, 3 or 4 toxicities, serum lipid tests should be repeated weekly until recovery to the baseline value or grade 1.

- **Tumour assessment**

Tumour assessment and response will be investigator assessed. Investigator assessed disease progression may be based on clinical examination or radiographic or laboratory features, mirroring routine practice.

The decision regarding patient management will remain with the local Investigator.

- **Pulmonary function tests**

Pneumonitis is a known AE associated with the use of rapamycin and rapamycin analogues. Pulmonary function tests can be performed at screening (prior to the start of the study) or during the study if clinically indicated and if warranted to exclude or manage NIP. Significant findings must be recorded on the relevant eCRF pages.

9.3.4.2 Prior and subsequent treatments

Details of all prior and subsequent treatments for ABC will be collected including the reason(s) for discontinuation.

9.3.4.3 Regimen/concomitant medication

Concomitant medications and changes in additional therapies during the study will be recorded. The impact of any concomitant medications on patient outcomes will be assessed.

9.3.4.4 Performance status

Performance status should be assessed at screening and scored using the ECOG Performance Status Scale.

The ECOG Performance Status Scale Index [Oken MM, 2008] allows patients to be classified for functional impairment. Table 9-3 defines Performance Status scores.

Table 9-3 ECOG Performance Status Scale

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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9.3.4.5 Quality of Life

The EuroQoL five dimensional questionnaire (EQ-5D) is a standardised instrument to assess health state values that has been developed, validated and published by the EuroQol Group in 1990. A copy of the questionnaire is included in Annex 3 of this protocol. The EQ-5D consists of two pages; the EQ-5D descriptive system and the EQ visual analogue scale. The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

Subjective well-being (SWB) data are being used to inform public policy in the UK and researchers are considering how these data relate to HRQoL. It has been demonstrated that health is not the only factor affecting QoL, although this has not been considered in the Breast Cancer setting. By collecting both HRQoL and SWB data, this study will add to the evidence on the relationship between the two. It will also highlight the extent to which HRQoL measures capture the full effect of disease and treatment on women with metastatic breast

cancer [HM Treasury 2010, Organisation for Economic Co-Operation and Development 2011, Dolan P 2011].

Both questionnaires are for assessment purposes only and will not form part of the patient's management. The overall score contributes to the secondary endpoints of the study. The overall and subsection scores will be documented in the clinical study report for the secondary endpoint. A change in the score in either questionnaire will not, in itself, be reported as an AE. The scores form part of the evaluation of the disease under study and are, therefore, already incorporated as study endpoints. However, should the Investigator feel that any particular individual parameter is not representative of the underlying disease or represents a clinically significant event, then this will remain reportable as an AE in line with reporting requirements and this review will be documented in the eCRF.

9.3.4.6 Adverse events

Safety will be monitored by assessing all AEs, including Serious Adverse Events (SAEs), the regular monitoring of haematology, blood chemistry, vital signs and physical condition. These assessments should be performed continuously throughout the study.

An AE is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) including death. Medical conditions or diseases present before starting the study are only considered AEs if they worsen after starting the study.

A SAE is an undesirable sign, symptom or medical condition which: 1. is fatal or life-threatening; 2. requires or prolongs hospitalisation; 3. results in persistent or significant disability/incapacity; 4. constitutes a congenital anomaly or a birth defect; 5. is medically significant, in that it may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Toxicity will be assessed using the NCI-CTCAE, version 4.03 (CTCAEv4.03, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

9.3.4.7 Study discontinuation

At a minimum, all patients who discontinue the study, whether withdrawn prematurely or otherwise and including those who refuse to return for a final visit, will be contacted for safety evaluations 30 days following end of treatment.

If a study withdrawal occurs, or if the patient fails to return for visits, the Investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment eCRF page.

At this stage, the following information will be recorded:

- Date and reason for the end of the study (end of the study, treatment withdrawal, discontinuation of follow-up/lost to follow-up, or any other reason);
- Clinical details including best response during treatment;
- Safety data.

9.3.4.8 Criteria for premature withdrawal

The planned observation period per patient starts with initiation of treatment with Afinitor in combination with exemestane, but ends on completion of the observation phase. The observation phase completes once the last patient has been on study for 12 months. All

antineoplastic therapies (surgery, medication, radiotherapy) for advanced breast cancer both prior to initiation of Afinitor plus exemestane and post discontinuation should be recorded on the relevant eCRF pages.

Patients should be followed until the end of the study except if the following conditions for early termination are met:

- Voluntary discontinuation (withdrawal of patients' consent to collect or use their data);
- Patient lost to follow-up.

All data generated up to withdrawal of consent and the reason(s) for discontinuation will be recorded. Patients who withdraw consent will not be contacted for follow-up information.

Patients who discontinue the study for any reason other than consent withdrawal should be asked to return for an early discontinuation assessment. The reason for discontinuation should be established. All available safety data will be collected for a period of one month following the last dose treatment.

For patients who are lost to follow-up (those whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should contact the patient and ask them to return for a final assessment. Every effort should be made to obtain a reason for discontinuation. The physician should document steps taken to contact the patient, e.g., dates of telephone calls and registered letters.

9.4 Data sources

Data sources will include patient medical records, including determination of the exposure to the study product and concomitant medication, as well as any adjustment in dosages. Additional sources will include laboratory reports and X-rays. The baseline characteristics, ECOG Performance Status and EQ-5D and SWB questionnaires may be entered directly into the electronic database during the study which will capture, check, store and analyse the data.

Novartis or an appropriate third party will initiate participating sites. Before study initiation, a Novartis representative (or their designee) will review the protocol and eCRF with the physicians and their staff.

Concomitant or prior medications entered into the database will be coded using the World Health Organisation (WHO) Drug Reference List. Medical History/Current Medical Conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Safety data will be available to Novartis throughout the study on the electronic database.

Data collection schedule

This is a NIS and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The observation intervals will be in line with clinical routine e.g. after approximately two weeks, one and three months and thereafter at a three-month interval after the start of treatment with Afinitor and exemestane. The

treating physician will be asked to complete the appropriate eCRF at every patient visit, if possible.

For patients who discontinue prematurely, the reason for discontinuation should be determined.

9.5 Study size

The sample size calculation of 200 patients is based on disease incidence, sample size compared with the overall population, and the expected recruitment within the enrolment period.

The sample size is based on the precision of the estimate of the incidence of the two specific toxicities defined in the primary objective (stomatitis and NIP). Stomatitis is a common AE in patients treated with Afinitor with all grade incidences reported as 71% [Thanopoulou 2014], 59% [Yardley 2013] and 56% [Baselga 2012]. All grade incidences of NIP have been reported as 36% [Thanopoulou 2014], 16% [Yardley 2013], 12% [Baselga 2012] and 39% [Omarini et al 2014].

For a sample size of 200 completed patients, Table 9-4 shows the width of 95% CIs for a range of observed incidences in subjects treated with Afinitor in combination with exemestane for 12 months. For example, when the sample size is 200, an exact (Clopper Pearson) two-sided 95.0% CI for a single proportion will extend 6.8% below to 7.2% above the observed incidence for an expected incidence of 40%.

Table 9-4 Sample Size

N=200 Incidence N (%)	Exact (Clopper Pearson) 95% CI
20 (10%)	6.2%, 15.0%.
40 (20%)	14.7%, 26.2%
60 (30%)	23.7%, 36.9%.
80 (40%)	33.2%, 47.2%
100 (50%)	42.9%, 57.1%
120 (60%)	52.9%, 66.9%
140 (70%)	63.1%, 76.3%
160 (80%)	73.8%, 85.3%

Sample size calculations were done using StatXact9®.

9.6 Data management

The study database will be produced [redacted]. The database is a fully validated system which conforms to 21 Code of Federal Regulations Part 11 and includes a full electronic audit trail of the data and limits access to identified Data Management staff. Designated Investigator site staff will not be given access to the database until they have been trained. Data from the eCRFs will be entered into the study database by Investigator site staff using electronic verification. Automatic and manual validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data.

Subsequently, the entered data will be systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Data errors or omissions will be entered on electronic Data Query Forms, which will be sent to investigational site staff who are required to respond to the query and confirm or correct the data. All relevant comments should be added to the eCRF using the Investigator Comment feature.

Data will be available to Novartis throughout the study for any recommendations regarding changes in conduct of the study. A Study Steering Committee may also be constituted for overseeing the conduct of the study and making any recommendations as needed.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using MedDRA.

Data about the study drug dispensed to the patient will be tracked using the eCRF.

Over the course of the study, protocol deviations will be determined. The Investigator must certify that data entered into the eCRF system are complete and accurate. Quality control audits of all key safety and efficacy data in the database will be made prior to locking the database.

The QoL questionnaire (EQ-5D and SWB) can be recorded directly onto the eCRF.

After completing these actions and the database is complete and accurate, it will be locked and made available for data analysis. Any subsequent database changes require joint written agreement between the Clinical Trial Leader, the Trial Statistician, the Data Manager and the Quality Manager.

9.7 Data analysis

All analyses will be performed by Novartis or a contracted designee.

All the patients enrolled in the study will be analysed. The reference population for analysis will be patients who were enrolled and received follow-up, meeting eligibility criteria with at least one follow-up visit completed.

Each Investigator taking part in the study should enroll at least one patient and not more than 15 patients will be enrolled per centre. The enrolment period is one year, however this can be re-assessed depending on how recruitment is progressing. Data from all centres that participate in this protocol will be combined for analysis.

Descriptive statistics will be provided unless otherwise specified. These include n, mean, standard deviation, median and ranges for continuous, quantitative variables and frequencies and percentages for categorical, qualitative variables. For patients with screening assessments who do not enter the treatment period, data will only be listed. Further technical details and discussion of the following statistical considerations will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

For all analyses, baseline value will be defined as the latest assessment prior to first study drug administration.

9.7.1 Analysis of the primary objective

The primary objective of this study is to evaluate (in patients commencing treatment with Afinitor in combination with exemestane for ABC after progression on a NSAI) two specific toxicities (stomatitis and NIP) in terms of: incidence, severity, length of time to onset, duration and clinical course, specific management (prophylaxis and intervention); and any preventive measures. Incidence, severity, length of time to onset, duration, and clinical course of any instances of stomatitis and/or NIP will be analysed. Specific management of these events, including variables for prophylaxis and interventions, and any preventive measures will also be investigated. Predisposing factors will also be investigated.

The analyses will be solely descriptive and comprise the description of the various items and the 95% CI.

9.7.2 Analysis of secondary objectives

The key secondary objective of this study is to report the Afinitor and exemestane dosage/schedule in routine clinical practice, including the duration of exposure and the main reasons for any dose reduction or discontinuation of Afinitor.

- Duration of Afinitor and exemestane treatment: Number of treatment days will be calculated as the difference between the date of the first dose and one day after the date of the last dose of the study. The actual duration of treatment will be calculated as the difference between the exposure period minus the number of days on which treatment was temporarily withdrawn.
- Main causes of dose reduction, dose escalation or withdrawal of Afinitor and exemestane will be captured
  .

The analyses will be solely descriptive and comprise the description of the various items and the 95% CI.

Further technical details and discussions including imputation and details regarding missing data will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

9.8 Quality control

Data entered into the 21 Code of Federal Regulations Part 11 compliant electronic database system will be validated against pre-defined criteria at the point of data entry and undergo source data verification procedures prior to further data review based on pre-defined validation rules established by Data Management. All data changes after initial data entry will be managed by data queries and have a full audit trail.

Further details regarding ensuring data quality and integrity will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

Data quality assurance

[redacted] will assure database quality by reviewing the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).The physician must give Novartis (or their designee) access to all relevant source documents to confirm their consistency with the eCRF entries. No information about the identity of the patients will be disclosed in source documents.

Site monitoring

Before study initiation or at a site initiation visit Novartis personnel will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, adherence to the protocol and Good Clinical Practice, progress of enrolment, and to ensure study treatment is being dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Formal site and compliance monitoring will be performed as described in the monitoring plan for this study which includes provisions for remote data monitoring, amendment of visit frequency due to common protocol deviations and anomalous data entries.

9.9 Limitations of the research methods

Being conducted solely in the UK means that the study results will only reflect the current status of clinical practice within the UK. Other countries will have different factors affecting their own clinical practice, such as re-imbursement issues and the availability of different competitor therapies.

10 Protection of human subjects

This clinical study was designed and will be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, including the amended Medicines for Human Use (Clinical Trial) Regulations and the European Directive 2001/20/EC & 2005/28/EC, and with the ethical principles laid down in the Declaration of Helsinki.

It is unlikely that the study will place any study patients at risk as a result of their participation.

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in NISs are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and will be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology [ISPE 2008] and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [VonElm 2008].

Regulatory and ethical compliance

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to Novartis before study initiation. Prior to study start, the Investigator is required to sign a protocol signature page confirming his or her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. The Investigator is also required to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IECs and regulatory authorities as necessary.

Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IEC-approved informed consent, or, if incapable of doing so,

after such consent has been provided by a legally acceptable representative of the patient. If a patient's representative gives consent, the patient should be informed about the study to the extent possible given his or her understanding. If the patient is capable of doing so, he or she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents. Patients can be consented up to four weeks after the initiation of Afinitor plus exemestane.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki and the appropriate regulatory requirements.

Amendments to the protocol

Protocol changes or additions can only be made in a written protocol amendment approved by Novartis and, if appropriate, the IEC. Only amendments required for patient safety may be implemented prior to IEC approval. However, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol, in which case, Novartis should be notified of this action and the IEC at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as www.clinicaltrials.gov. At study completion and finalisation of the study report, the results of this study will also be submitted for publication and/or posted in a publicly accessible database of clinical study results.

The terms applying to the scientific publication of the results and the authors participating in these publications and presentations will be defined by Novartis Pharma, which retains the copyright on all important publications, including translations into other languages.

Study documentation

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 Good Clinical Practice, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorised Novartis representatives, IEC and regulatory authority to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic

negatives, microfilm or magnetic media, X-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded.

The Investigator or site should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator or site should take measures to prevent accidental or premature destruction of these documents.

Essential written and electronic documents should be retained for at least15 years from the completion of the Clinical Trial unless Novartis provides written permission to dispose of them, or requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Confidentiality

The Investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrolment log must be kept strictly confidential to enable patient identification at the site.

Audits and inspections

Source data/documents must be available for inspections by Novartis or their designee, IECs or Health Authorities.

11 Management and reporting of adverse events

All AEs including SAEs and safety endpoints, where relevant, must be collected and recorded in the study database, irrespective of causal association. Adverse Drug Reactions (ADRs) occurring in association with exposure to a Novartis drug other than the Novartis drug of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis DS&E as a spontaneous report.

Adverse events identified for non-Novartis products should be reported to the local health authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorisation Holder; these will not be recorded in the Novartis safety database.

Adverse event reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g. haematologic abnormality that requires transfusion or haematological stem cell support), or require changes in study medication(s).

Medical conditions or diseases present before starting the study are only considered AEs if they worsen after starting the drug of interest. Adverse events that begin or worsen after the start of this study should be recorded in the AE eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History eCRF. Adverse Event monitoring should be continued for at least 30 days following the end of the study. Adverse Events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1-4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, information about deaths will be collected on a death form.

An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Afinitor, whether or not related to the medicinal product(s).

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. Adverse Events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded on the AE eCRF with the following information:

- the severity grade (1-4);
- its relationship to the drug(s) of interest (suspected or not suspected);
- its duration (start and end dates or if continuing at final examination);
- whether it constitutes a SAE.

In addition, all reports of the following special scenarios are considered an AE irrespective of whether a clinical event has occurred:

- Drug-drug or drug-food interaction;
- Drug exposure during pregnancy;
- Drug use during lactation or breast-feeding;
- Lack of effectiveness;
- Overdose;
- Drug abuse and misuse;
- Drug maladministration or accidental exposure;
- Dispensing errors or medication errors;
- Off-label use;
- Withdrawal or rebound symptoms.

Any treatment of any AE should be recorded on the AE eCRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); drug of interest dosage adjusted or temporarily interrupted; drug of interest permanently discontinued due to this AE; treatment medication adjusted; non-drug therapy given; patient hospitalised or patient's hospitalisation prolonged.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent. Assessment should be made at each visit, or more frequently if necessary, of

any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

Information about AEs already known about the medicinal product can be found in the SmPC. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Information on all AEs is included in the individual patient eCRF which must be updated and committed in the study database within 24 hours of the site becoming aware of it. Information on non-serious AEs is then transferred from the study database to Novartis DS&E [redacted] on a weekly basis.

Serious adverse event reporting

A SAE is defined as an event which:

- Is fatal or life-threatening;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition*;*
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest;
    - Social reasons and respite care without any deterioration in the patient's general condition;
- Is medically significant. This is defined as an event that jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. It may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
- Transmission of infectious agent by medicinal product.

For Afinitor the following AEs are of special interest for targeted follow-up and should be notified to Novartis Drug Safety and Epidemiology (DS&E) in the same manner as a SAE:

- Acute and congestive heart failure
- Developmental toxicity
- Afinitor amenorrhoea
- Afinitor reactivation, aggravation, exacerbation of background disease
- Afinitor NIP
- Afinitor severe infections including hepatitis reactivation
- Pregnancy and breast-feeding women
- Hypersensitivity including anaphylaxis
- Malignancy and neoplasm
- Renal impairment or failure.

To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs occurring after this 28 day period should only be reported to Novartis if the treating physician or other involved health care professional suspects a causal relationship to the drug of interest.

Recurrent episodes, complications, or progression of the initial SAE must be reported as a follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Report Form. The treating physician or other involved health care professional must assess the relationship to the drug of interest, complete the SAE report form and send the completed signed form within 24 h to the local Novartis Drug Safety & Epidemiology (DS&E) Department.. The telephone number of the contact persons in the local department of DS&E, specific to the site, are listed in the treating physician or other involved health care health care professional folder provided to each site.

Follow-up information is collected and sent in the same manner as for the original SAE Report, using a new SAE form, stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the SmPC a local DS&E Department associate may urgently require further information from the treating physician or other involved health care professional for health authority reporting.

Pregnancy

This study is in postmenopausal women, so pregnancy should not occur. However, as is routine, to ensure patient safety, any occurrence of a pregnancy in a patient on Afinitor (everolimus; RAD001) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAE experienced during pregnancy must be reported on the SAE Report Form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pregnancy Form and reported by the treating physician or other involved health care professional to the local Novartis DS&E Department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug of interest should be reported.

12 Plans for disseminating and communicating study results

Upon study completion and finalisation of the study report, the results of this NIS may be submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of

Medical Journal Editors guidelines. For non-interventional PASS studies, the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorised within two weeks after first acceptance for publication.

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Annex 1 – List of stand-alone documents

Table 0-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	1	22 October 2014	Afinitor® SmPC
2	2	December 2014	Novartis Protocol Signatory Page

Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

BOUDICA: oBservatiOnal stUdy in locally aDvanced or MetastatIc hormone reCeptor positive breast cAncer

Study reference number:

CRAD001JGB14

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	25
1.1.2 End of data collection[2]	☒	☐	☐	25

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1.3 Study progress report(s)	☐	☐	X	
1.1.4 Interim progress report(s)	☐	☐	X	
1.1.5 Registration in the EU PAS register	☐	☐	X	
1.1.6 Final report of study results.	☒	☐	☐	43

Comments:

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	20-24
2.1.2 The objective(s) of the study?	☒	☐	☐	24-25
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	26
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	36-37
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.5; Investigational study based on published data after product approval.

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	24
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	27-29
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	36-37

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	33
4.2 Is the planned study population defined in terms				

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
of:	☐	☐	☐	
4.2.1 Study time period?	☒	☐	☐	27
4.2.2 Age and sex?	☒	☐	☐	27
4.2.3 Country of origin?	☒	☐	☐	27
4.2.4 Disease/indication?	☒	☐	☐	27
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	27

Comments:

Further technical details and discussion of the following statistical considerations will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	33-36
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	33-36
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	18-19
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	30-31

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	27-37
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

6.2; Standard clinical practice and accepted adverse event coding. Further technical details and discussion of the following statistical considerations will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	37
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	37
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	37
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	37
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	37
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	37
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	37
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

8.4; Not required; patient initials and unique patient number will be allocated.

Section 9: Study size and power	Yes	No	N/A	Page Number(s)

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☒	34-37

Comments:

9.1; No formal sample size calculation. Number of patients determined from previous number of adverse events of interest (stomatitis and non-infectious pneumonitis) and the recruitment potential in 12 months.

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	34-37
10.3 Are descriptive analyses included?	☒	☐	☐	34-37
10.4 Are stratified analyses included?	☐	☐	X	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	X	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	X	

Comments:

10.1; There are no excess risks in this study which is being conducted to evaluate standard clinical practice.
10.5 and 10.6; Further technical details and discussion of the following statistical considerations will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	39
11.3 Are methods of quality assurance described?	☒	☐	☐	37
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	38-39

Comments:

11.1 and 11.4; Details regarding handling of missing data and any issues arising from data sources will be documented in a subsequent statistical analysis plan. Further technical

details and discussion of the following statistical considerations including handling of missing data will appear in the statistical analysis plan, which will be finalised prior to database lock and the analysis.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	38-40
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	38-40
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	38-40
12.3 Does the protocol address other limitations?	☒	☐	☐	38-40

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	38
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	38
13.3 Have data protection requirements been described?	☒	☐	☐	38

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	39

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	43
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	43

Comments:

Name of the main author of the protocol: Dr [redacted]

Date: 23/12/2014

Signature: [redacted]

Annex 3 – Additional information

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

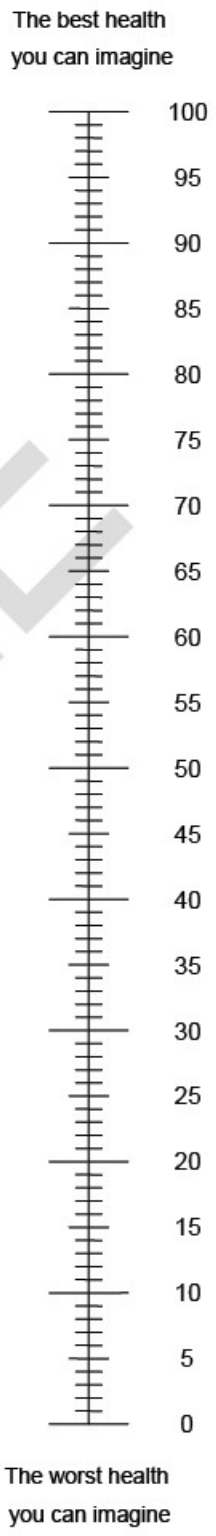
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Subjective well-being (SWB) questions taken from the Integrated Household Survey.

1. Overall, how satisfied are you with your life nowadays?
2. Overall, to what extent do you feel that the things you do in your life are worthwhile?
3. Overall, how happy did you feel yesterday?
4. On a scale on which 100 is “not at all anxious” and 0 is “completely anxious,” overall, how anxious did you feel yesterday?

- **We would like to know how anxious you feel TODAY. This scale is numbered from 0 to 100**
- **0 means completely anxious**
- **100 means not at all anxious**

- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐