Universitair Ziekenhuis Brussel

-TITLE OF THE PROTOCOL
A phase II, open label study of everolimus with fulvestrant in postmenopausal women with hormone receptor-positive HER-2 negative AI and fulvestrant treated, locally advanced or metastatic breast cancer (mBC), who progressed on or after mTor inhibitor based treatment

- EUDRACT NUMBER : 2013-000665-36

- INVESTIGATIONAL MEDICINAL PRODUCT : Everolimus

ANNUAL SAFETY REPORT

FIRST CLINICAL TRIAL AUTHORIZATION DATE: 14/08/2013

DATE OF THIS REPORT: 07/12/2017

NAME AND ADDRESS OF THE SPONSOR:

Dr/Prof De Grève
UZ Brussel
Medische Oncologie Centrum
Laarbeeklaan 101
B-1090 Brussel

INTRODUCTION:

Full title of trial	A phase II, open label study of everolimus with fulvestrant in postmenopausal women with hormone receptor-positive HER-2 negative AI and fulvestrant treated, locally advanced or metastatic breast cancer (mBC), who progressed on or after mTor inhibitor based treatment
Short title	UZB-MO-CF-01
Date of the protocol	15-sep-2012
IMP(s) under investigation (generic name(s))	Everolimus
Registered names(s) of the IMP(s) under investigation/ delivered by : "name of the company"	Afinitor® / DELIVERED BY Novartis Pharma S.A./N.V.
Date of the first approval of the IMP	03/08/2009
Dosage and route of administration	5mg – 10mg PO
Trial Objectives	- The primary objective of a phase II academic study is to investigate whether the combination of everolimus and fulvestrant can restore sensibility to fulvestrant in postmenopausal women with ER+ HER-2 advanced breast cancer who received a previous everolimus + exemestane treatment. - The secondary objective is to determine the disease response to the combination of fulvestrant and everolimus. - The secondary exploratory objective is to explore the tolerability of the combination, the correlation of response with steady state plasma levels of everolimus (pharmacokinetic), correlation of response with the activated mTOR pathway on tumor tissue (biomarkers) and the correlation of early metabolic response with final outcome.

Study population	Postmenopausal women with hormone receptor-positive, HER-2 negative AI and fulvestrant treated, locally advanced or metastatic breast cancer, who progressed on prior fulvestrant and on or after everolimus plus exemestane treatment. Patients can have a maximum of one line of prior chemotherapy for advanced disease.
Trial design	This is a Belgian, multi-center, open-label, single arm, phase II study designed to investigate whether the combination of everolimus and fulvestrant can restore sensitivity to fulvestrant in postmenopausal women with ER+ HER2- advanced breast cancer who received previous everolimus + exemestane treatment and were progressive on prior fulvestrant. None of these treatments needed to be the last treatment before inclusion in this study. - Screening period: Once patient eligibility is confirmed, the patient will be enrolled. All screening evaluations will be performed within 21 days prior to Treatment Day1. Whenever possible a new tumor biopsy will be performed and frozen tissue banked at baseline in order to permit correlative biomarker investigations. -Treatment phase: Patients will start study treatment on Day 1and will be treated with 10 mg daily doses of everolimus in combination with fulvestrant 500 mg IM once every four weeks, to be initiated simultaneously. Dose adjustment (reduction, interruption) according to safety findings will be allowed. After each dose reduction plasma levels of everolimus will be determined. During the study, visits will be performed every Month and at the end of treatment. Study treatment will continue until one of the following conditions applies, whichever comes first: - tumor progression, - unacceptable toxicity according to investigator's judgment, - death, - discontinuation from the study for any other reason, withdrawal of consent. Further treatment after progression will be at the investigator's discretion.
Trial start date	16/10/2013
Trial end date	01/06/2017
Target number of subjects for whole trial	35
How many subjects have been enrolled since the trial started	6
Countries concerned by this trial	Belgium
Reporting period	**FROM** 01/01/2017**TO** 01/06/2017

Contact details for person making this notification

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PART 1: REPORT ON THE SAFETY OF SUBJECTS

1.1 Overview of data:

The trial is still ongoing and the database has not been locked.

1.2 Serious Adverse Events:

	Current Reporting Period	*Cumulated since the beginning of the trial*
Number of subjects enrolled	0	6
Number of SAEs observed	0	0
Number of SARs observed	0	0
Number of SUSARs observed	0	0

1.3 Non-serious Adverse events:

	Current Reporting Period	*Cumulated since the beginning of the trial*
NON SERIOUS ADVERSE EVENTS		
***n* non serious adverse events in *x* patients**	**0 / 01-Jan-2017**	**51 / 01-Aug-2014**
SEVERITY OF ADVERSE EVENTS		
n Mild	**0**	**51**
n Moderate	**0**	**5**
n Severe	**0**	**3**
RELATIONSHIP TO THE TRIAL MEDICATION		
certain	**0**	**25**
probable	**0**	**13**
possible	**0**	**0**
unlikely	**0**	**0**
not related	**0**	**19**

1.4 New findings related to the safety of the IMP

There have been no new findings related to the safety of the IMP in this trial.

1.5 Impact of New findings for the Subjects of the Trial:

There have been no new findings related to the safety of the IMP(s) in this trial.

1.6 Implications for the Population of the Trial

There have been no safety findings that have implications for any specific populations in this trial.

1.7 Analysis of the Safety Profile of the Tested IMP

By reviewing the safety data of the five included patients no unknown side effects were discovered. The severity of the adverse events was essentially mild and already known in all cases.
Three of the six patients were still responding after a mean of eight months follow-up. The risk benefit ratio is certainly positive for the included patients responding after 4 lines of hormone therapy.

1.8 Measures Proposed to Minimise Risks Found

There have been no risks identified related to the safety of the IMP(s) in this trial.

PART 2: LINE LISTING

THIS LINE LISTING MUST BE SENT ON A 6 MONTH BASIS TO THE COMPETENT AUTHORITIES AND TO THE LEADING ETHICS COMMITTEE.

There were no Suspected Serious Adverse Reactions in this trial; therefore no line listings have been completed.

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ANNUAL SAFETY REPORT: SERIOUS CASES BY SYSTEM ORGAN CLASS
SPONSOR NAME: UZ Brussel
EUDRACT: 2013-000665-36
STUDY SHORT TITLE: UZB-MO-CF-01
PRODUCT RECEIVED: Everolimus
Route of administration as per protocol: PO
Daily dosage as per protocol: 10mg

SOC: see MedDRA list

Subject ID/Case	Case (SAR n°)	Country	Date of Birth	Sex	Daily Dose of IMP	Dates of Treatment	Date of Onset of AE	Adverse Reaction MedDRA Lowest Level Term	Expected	Event serious code	Causality Investigator / Sponsor	Ongoing reaction with: Dechallenge/ Rechallenge	Unblinding Results	Outcome	Comments
* = Previous ASR		*BE*							*YES/NO*	*Required intervention /caused or prolonged hospitalisation /results in death /life threatening/ persistent or significant disability/ congenital anomaly/ other /none*	*Certain; probable :possible; unlikely; conditional; unassessable*	*YES; NO; NA / YES; NO; NA*	*N/A*	*Resolved / Resolved with sequelae / Ongoing / Unknown / Fatal + date of death*	

PART 3: SUMMARY TABULATIONS

SYSTEM ORGAN CLASS	LOWEST LEVEL TERM	IMP Everolimus	
		SAE	SUSAR
		0	0

There were no Suspected Serious Adverse Reactions in this trial; therefore no summary tabulation has been compiled.

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CONCLUSIONS

-This Annual Safety report does not contain new data which modify the security profile of the IMP.

- The overall benefit/risk assessment is not modified.

- No following measures are taken for the safety of the patients.

This document has been approved by:

Signature ---------- Date: 9/12/2017

9/12/2017

Name Christel Fontaine

Title Dr.

Department Oncology

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