Clinical trial results:
A randomized open-label Phase II study of letrozole plus afatinib (BIBW2992) versus letrozole alone in first-line treatment of advanced ER+, HER2- postmenopausal breast cancer with low ER expression

Summary

EudraCT number	2013-002192-18
Trial protocol	ES
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	TRIO020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02115048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Translational Research In Oncology
Sponsor organisation address	Suite 1100 9925-109 Street , Edmonton, Canada, T5K 2J8
Public contact	Project Management, Translational Research In Oncology, 011 +33 1 58 10 09 09, TRIO020.contact@trioncology.org
Scientific contact	Project Management, Translational Research In Oncology, 011 +33 1 58 10 09 09, TRIO020.contact@trioncology.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of letrozole plus afatinib and of letrozole alone on progression-free survival (PFS) in the first line treatment of ER+, HER2 negative postmenopausal ABC women with low ER expression.

Protection of trial subjects:

Regular assessment and monitoring of adverse events is required throughout trial treatment period and up until 30 days after last intake of trial medication (last intake of letrozole in the single agent arm or last intake of afatinib + letrozole or letrozole -if afatinib previously discontinued- in the combination arm). Recommendations regarding monitoring and adequate management of specific events are provided below. CTCAE version 4.0 is used to assess the severity of adverse events.

Letrozole dose modification: No dose adjustment is permitted for letrozole.

Afatinib dose modification: Patients are monitored closely for toxicity and the dose of afatinib may be adjusted as indicated in tables below. Dose reduction to 20 mg is allowed depending on the type and severity of toxicity encountered. Patients requiring more than one dose reduction will be discontinued from afatinib.

Dose escalation is not allowed once afatinib dose has been reduced.
For toxicities requiring dose adjustment (see sections 5.4.2 to 5.4.7), afatinib will be held for up to 14 days to allow patient to recover to a grade ≤ 1, and will be resumed at 20 mg.

Dose reduction should always follow a treatment pause in order to allow recovery to grade ≤ 1 toxicity. Nevertheless, the initial trial visits schedule should be kept unchanged (every 4 weeks regardless of any additional visits and treatment pauses).

If despite optimal care and afatinib pause, patient has not recovered to grade ≤ 1 within 14 days and is not deriving obvious clinical benefit from trial treatment, the patient should not receive any further treatment with afatinib. Letrozole should be discontinued within the frame of the trial and the patient must be discontinued from the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Bosnia and Herzegovina: 7
Country: Number of subjects enrolled	United States: 15

Worldwide total number of subjects	44
EEA total number of subjects	22

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty-four (44) patients were enrolled in the study from 26 participating sites located in the USA, Spain, Bosnia and Romania. Enrollment ended prematurely with only 44 patients (initially planned for 150 participants). Early enrollment closure was documented with protocol amendment 3 (approved 09 May 2016).

Pre-assignment

Screening details:

Informed consent procedures were completed prior to performing any trial specific procedures. Patients who did not meet the eligibility criteria were considered screen failures. Patients who met all eligibility criteria were randomized using the following factors: Bone only disease- Yes vs. No, and Prior neo/adjuvant hormonal therapy- Yes vs. No.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial is open-label. There is no blinding of the treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Continuous regimen of oral letrozole 2.5 mg.

Arm type	Active comparator
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole is standard of care in this population. Commercial Letrozole was used. Commercial Letrozole contains 2.5 mg letrozole as the active ingredient. Packaging depends on the commercial letrozole available locally. Patients were instructed to swallow their letrozole tablets without regard to food. Patients were encouraged to take their dose at approximately the same time each day.

Arm title	Arm B

Arm description:

Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily.

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole is standard of care in this population. Commercial Letrozole was used. Commercial Letrozole contains 2.5 mg letrozole as the active ingredient. Packaging depends on the commercial letrozole available locally. Patients were instructed to swallow their letrozole tablets without regard to food. Patients were encouraged to take their dose at approximately the same time each day.

Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

It is supplied by the manufacturer Boehringer Ingelheim (BI). Two dose strengths of 20 and 30 mg afatinib are used in the trial to allow for any dose adjustment. At each monthly visit, patients should be given a 30-tablet bottle. Treatment was divided into treatment cycles, which are each 4 weeks (28 days) in duration. However, treatment was given continuously unless treatment schedule adjustments were needed. Patients took a single oral dose of afatinib each day for the first and subsequent cycles. The medication was taken at the same time each day (± 2 hours) at least one hour before food intake and at least three hours after the last food intake. Afatinib tablets should be swallowed whole with water, and if not possible, afatinib tablets can be dispersed in approximately 100 ml of noncarbonated drinking water. The glass should be rinsed with approximately 100 ml of water which should also be consumed. The dispersion can also be administered through a gastric tube.

Number of subjects in period 1	Arm A	Arm B
Started	23	21
Completed	23	21

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Continuous regimen of oral letrozole 2.5 mg.	
Reporting group title	Arm B
Reporting group description:	
Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	23	21	44
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	14	10	24
From 65-84 years	9	11	20
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.1	64.29	
standard deviation	± 7.58	± 7.24	-
Gender categorical Units: Subjects			
Female	23	21	44
Male	0	0	0
Menopausal Status Units: Subjects			
Pre-Menopausal	0	0	0
Post-Menopausal	23	21	44
ECOG Performance Status Units: Subjects			
ECOG PS 0	12	14	26
ECOG PS 1	11	7	18
Weight Units: kg			
arithmetic mean	77.39	69.59	
standard deviation	± 16.25	± 11.14	-

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Continuous regimen of oral letrozole 2.5 mg.	
Reporting group title	Arm B
Reporting group description:	
Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily.	

Primary: Progression Free Survival

End point title	Progression Free Survival[1]

End point description:

Progression Free Survival (PFS) is defined as the time from randomization until date of progression (assessed by RECIST) or death due to any cause, whichever occurs first. For evaluation of PFS, for each patient, the beginning date was taken as a randomization date. If the status at the last assessment date was “Non complete response/ Non progressive disease” or “Complete response”, then the patient was considered censored at that time. If the status at the last assessment for any tumor was “Progressive disease”, then the patient was considered as having an event at that time. Two patients who died during the study were also considered as having event at the time of death.

Since enrollment was terminated early (only 44 patients enrolled), preventing appropriate statistical calculations, efficacy has not been assessed - this incudes PFS, overall survival (OS), objective response rate (OR), and time to tumor progression (TTP). TPP analysis was not performed due to lack of OS data.

End point type	Primary

End point timeframe:

Every 12 weeks up to 9 months (average) for subjects in the control arm or up to 14 months (average) for subjects in
the experimental arm.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Enrollment ended prematurely with only 44 patients (initially planned for 150 participants). Early enrollment closure was documented with protocol amendment 3 (approved 09 May 2016).

As such, the data collected for all patients are described per arm, but no statistical comparison can be made (appropriate statistical evaluation cannot be completed due to low recruitment). TPP was not analyzed due to a lack of OS data.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: Patients				
Failed (Progressed or Died)	4	2		
Censored	14	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival is defined as the time from randomization until death to any cause. For subjects in which treatment is discontinued for reasons different than progression disease: after treatment and up to documentation of disease progression: Overall Survival is assessed every 12 weeks.

Since enrollment was terminated early (only 44 patients enrolled), preventing appropriate statistical calculations, efficacy has not been assessed - this incudes PFS, overall survival (OS), objective response rate (OR), and time to tumor progression (TTP). TPP analysis was not performed due to lack of OS data.

End point type	Secondary

End point timeframe:

Under treatment: every 4 wks up to 9 months (average) for subject in the control arm or up to 14 months (average)
for subjects in the experimental arm. After documentation of disease progression up to the end of the study: every 6
months up to 42 months

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percentage				
Died	2	0		
Censored	16	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

As per RECIST.

Since enrollment was terminated early (only 44 patients enrolled), preventing appropriate statistical calculations, efficacy has not been assessed - this incudes PFS, overall survival (OS), objective response rate (OR), and time to tumor progression (TTP). TPP analysis was not performed due to lack of OS data.

End point type	Secondary

End point timeframe:

Every 12 weeks up to 9 months (average) for subjects in the control arm or up to 14 months (average) for subjects in the experimental arm.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percentage				
Complete Response (CR)	2	1		
Death	2	0		
Progressive Disease (PD)	2	2		
Non-CR/ Non-PD	12	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumour Progression

End point title	Time to Tumour Progression

End point description:

As per Response Evaluation Criteria In Solid Tumors (RECIST). Time to progression (TTP) is defined as the time interval from date of randomization to date of the first documented objective tumor progression. Two patients who died were not accounted for in this analysis. For one of those patients, the last status and the last assessment date was used; however such data is not available for the second patient.

Since enrollment was terminated early (only 44 patients enrolled), preventing appropriate statistical calculations, efficacy has not been assessed - this incudes PFS, overall survival (OS), objective response rate (OR), and time to tumor progression (TTP). TPP analysis was not performed due to lack of OS data.

End point type	Secondary

End point timeframe:

Every 12 weeks up to 9 months (average) for subjects in the control arm or up to 14 months (average) for subjects in
the experimental arm.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Percentage				

Notes:

[2] - Analysis was not performed due to lack of 'Overall Survival' data.

[3] - Analysis was not performed due to lack of 'Overall Survival' data.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events

End point title	Incidence of Adverse Events

End point description:

Subject's incidence of adverse events will be tabulated by system organ class, preferred term and toxicity grade by treatment arm. Adverse events leading to death or drug discontinuation, drug related

and serious adverse events will also be summarized by treatment arm.
For subjects in which treatment is discontinued for reasons different than progression disease, after treatment and up to documentation of disease progression, the assessment of incidence of adverse events will be assessed every 12 weeks.

** Enrollment was closed prematurely due to low recruitment (only 44 participants enrolled) compared to what was initially planned (150 participants), therefore no statistical evaluations were completed. Adverse event data collected are described per arm but no statistical comparison was made.

End point type	Secondary

End point timeframe:

Under treatment: every 4 wks up to 9 months (average) for subjects in the control arm or up to 14 months (average)
for subjects in the experimental arm. After documentation of disease progression up to the end of the study: every 6
months up to 42 month

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: percentage				
Patient having at least one TEAE	16	20		
Patient having at least one serious TEAE	5	2		
At least one TEAE related to letrozole	6	11		
At least one TEAE related to afatinib	0	18		
At least one serious TEAE related to letrozole	0	0		
At least one serious TEAE related to afatinib	0	1		
Patient having at least one grade 3/4 TEAE	7	3		
TEAE leading to discontinuation - letrozole	1	1		
TEAE leading to discontinuation - afatinib	0	1		
Fatal TEAE	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (serious and non-serious) were reported from the time the patient takes their first dose. All events were followed up to 30 days after the last intake of trial medication. Only serious events are reported between consent and first dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Arm A

Reporting group description:

Continuous regimen of oral letrozole 2.5 mg.

Reporting group title	Arm B

Reporting group description:

Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)	2 / 21 (9.52%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Multiple fractures			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Subarachnoid haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 23 (69.57%)	20 / 21 (95.24%)	
Investigations			
Weight increased			
subjects affected / exposed	2 / 23 (8.70%)	4 / 21 (19.05%)	
occurrences (all)	2	6	
Weight decreased			
subjects affected / exposed	2 / 23 (8.70%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 23 (4.35%)	6 / 21 (28.57%)	
occurrences (all)	1	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)	15 / 21 (71.43%)	
occurrences (all)	2	26	
Nausea			
subjects affected / exposed	3 / 23 (13.04%)	3 / 21 (14.29%)	
occurrences (all)	5	4	
Stomatitis			
subjects affected / exposed	0 / 23 (0.00%)	6 / 21 (28.57%)	
occurrences (all)	0	8	
Abdominal distension			
subjects affected / exposed	1 / 23 (4.35%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	1 / 23 (4.35%)	6 / 21 (28.57%)	
occurrences (all)	1	11	
Dry skin			
subjects affected / exposed	1 / 23 (4.35%)	5 / 21 (23.81%)	
occurrences (all)	1	7	
Dermatitis acneiform			
subjects affected / exposed	0 / 23 (0.00%)	4 / 21 (19.05%)	
occurrences (all)	0	4	
Pruritus			
subjects affected / exposed	1 / 23 (4.35%)	3 / 21 (14.29%)	
occurrences (all)	2	3	
Alopecia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 23 (17.39%)	2 / 21 (9.52%)	
occurrences (all)	8	2	
Back pain			
subjects affected / exposed	4 / 23 (17.39%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Bone Pain			
subjects affected / exposed	0 / 23 (0.00%)	4 / 21 (19.05%)	
occurrences (all)	0	4	
Musculoskeletal pain			
subjects affected / exposed	1 / 23 (4.35%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Infections and infestations			
Paronychia			
subjects affected / exposed	0 / 23 (0.00%)	6 / 21 (28.57%)	
occurrences (all)	0	6	
Urinary tract infection			

subjects affected / exposed	0 / 23 (0.00%)	5 / 21 (23.81%)	
occurrences (all)	0	8	
Upper respiratory tract infection			
subjects affected / exposed	3 / 23 (13.04%)	1 / 21 (4.76%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2013	• Updated Inclusion Criterion 5 by changing it from "ER positive breast cancer. Local testing should demonstrate that the tumor is ER positive. Central testing (required for all subjects) must demonstrate that the tumor is ER+ low amplification (H-score <160)." to "ER positive breast cancer. Local testing should demonstrate that the tumor is ER positive. Central testing (required for all subjects) must demonstrate that the tumor is ER+ with low expression (H-score [1-159])." • Updated Inclusion Criterion 9 by changing the part for AST and ALT from "Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 x upper limit of normal (ULN) or AST and ALT £ 5 x ULN if liver function abnormalities are due to liver metastasis." to "Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) < 2.5 x upper limit of normal (ULN)." • Added exclusion criteria 17: patients with known history of keratitis, ulcerative keratitis or severe dry eye • Updated the section on adverse event management and treatment schedule adjustments • Updated section on Management of Rash by adding a guidance for Rash grade 4. • Updated Table 7: Treatment Schedule Adjustments by adding Acute kidney injury ans Keratitis symptoms • Added note 7 to Table 9 Schedule of activities: During treatment phase, blood tests must be obtained up to 5 days prior to the visit and will assess the following parameters : Hematology: Hemoglobin, Absolute Neutrophils Count (ANC), Platelets. Blood chemistry: AST, ALT, Alkaline Phosphatase, Total Bilirubin and Creatinine.

12 November 2013	• Updated the number of participating sites from 26 to 25 • Updated section 1.3 Investigational Medicinal Product Overview • Updated section 1.3.2 Clinical Pharmacokinetic and Safety • Updated section 1.4 Rationale • Updated section 2.3 Exploratory Objectives (Optional) • Updated Exclusion Criterion 15 by changing it from "Concomitant treatment with strong inhibitor of P-gP" to "Concomitant treatment with strong inhibitor of P-gP. Patients having received treatment with strong P-gP inhibitors had to have discontinued treatment at least 7 days before the start of study drugs. " • Added Exclusion Criterion 18 and excluded the participation in the active phase of other clinical trials of investigational agents in which last study treatment had been administered within 2 weeks prior to randomization. • Updated the Clinical pharmacokinetic and safety section according to IB v14. • Updated section 5.2.1.1 Afatinib to notify that "In the future, afatinib supplies for clinical trials might be switched to the marketed product image which is identical to the description provided above with the only difference that 20mg film-coated tablets are white to slightly yellowish. Updated section 5.2.3.1 Afatinib to clarify that "Unused/expired afatinib should be destroyed locally once accountability performed and reconciled." Instead of being returned to BI. Updated section 5.3.3 by changing from "By default, subjects are treated until disease progression. The investigator will also discontinue the treatment if any of the following conditions is met : Intercurrent illness that warrants trial treatment discontinuation or unacceptable toxicity, such as interstitial lung disease Subject's decision to withdraw Death Pregnancy Investigator's decision Discontinuation of the study by the sponsor" (More provided in clinical study report)
09 May 2016	• Closed study enrolment due to the following reasons: discontinuation of the Breast cancer program with afatinib at Boehringer Ingelheim (BI), low recruitment in the study, approval of palbociclib (IBRANCE) in a similar target population and therefore accessibility to patients to other therapeutic options with unlikelyhood that afatinib might provide a better benefit to patients than palbociclib. • Removed the follow-up period of the study because of the small number of patients randomized in the study (44 instead of 150 pts expected as per the statistical method) resulting in survival information that would not have been relevant. Therefore patients were not to be followed after the end of therapy visit planned as close as possible to 30 days after the last intake of any study treatment. • Removed the primary and secondary objectives as with such a small number of patients randomized in the study, the assessment of progression-free survival, overall survival, objective response rate, time to tumor progression would not provide statistically relevant information. • The following sections were updated: • 2. Objectives • 2.3 Exploratory objectives • 3. Study design • 4. Subject selection • 5.1 protocol treatment • 5.2.1.1 Afatinib • 5.2.1.2 Letrozole • Protocol treatment discontinuation • 5.4.1 General rules • 6.1.1 Informed consent • 6.2 Study participation discontinuation • 8. Statistical Considerations • 9.1 Steering Committee

31 July 2018	• Discontinuation of patient treatment at the latest on 30 November 2018 due to the discontinuation of the Breast cancer program with afatinib at Boehringer Ingelheim (BI). • At the time of this protocol amendment there were only 2 patients still in treatment in arm B for whom options were evaluated in order to be able to allow continuation of afatinib after the date of 30 November 2018. Only one patient benefited from this option as the other patient had progressed by 30 November 2018. • The following sections were updated: • 1.2 Current treatment overview • 1.3 Investigational medicinal product overview • 1.4 Rationale • 2.1.2 Secondary objectives • 3 Trial design • Figure 1 Footnote • 5.2.2.1 Afatinib • 5.2.2.2 Letrozole • 5.3.3 Protocol treatment discontinuation • 6.2 Trial Participation and Discontinuation • 6.3 Schedule of Procedures • Table 9 Footnotes • 7.1.1 Period of Observation • 7.3.2 SAE information provided by TRIO to BI • 8. Statistical Considerations • 8.1 Populations for analyses • 8.6 Criteria for trial termination • 9.1 Steering Committee • 9.7 Data Protection • 10 Bibliography

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrolment was closed prematurely with only 44 participants enrolled compared to what was initially planned (150 participants). Thus, preventing appropriate statistical evaluation (primary/secondary objectives no longer applicable as per protocol).

Notes: