Statistical Analysis Plan for TRIO-020

Title	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
Study Number	TRIO-020
Document Number	STAT-020-SAP
Version Number	2.0
Product Name	Afatinib (BIBW2992)
Indication	Advanced ER+, HER2- Postmenopausal Breast Cancer with low ER Expression
Study Phase	II
Sponsor	Translational Research in Oncology (TRIO) Suite 1100, 9925-109th Street Edmonton, Alberta, Canada
Version Date	04-Dec-2014

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Protocol Number: TRIO-020 **Product:** Afatinib (BIBW2992)

Protocol Title:

"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."

Author: Vincent Houé

Version Number: 2.0

Version Date: 04-Dec-2014

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas.

	Date	**Signature**
Vincent Houé Senior Manager of Biostatistics, TRIO		
Hélène Mansouri Global Project Coordinator, TRIO		
Karen Afenjar Global Project Coordinator, TRIO		
Richard Finn Steering Committee Chair		

SAP Changes From Version 1.0 to Version 2.0

The objective of SAP version 2.0 is to update the SAP version 1.0 to match the updated CRF version 2.2 (dated 29-Jan-2014). Some redefinitions were also applied..

Other noteworthy revisions are described below:

Section #	Changes
10.2	Prior Surgery for Breast cancer and Prior Anti-Tumor Therapy are considered as part of Disease Characteristics rather than Medical History.
10.3	This section is considered as Not Applicable as data dealing with Medical History are not collected anymore in CRF version 2.2.
11.1	Baseline Demographics and Disease Characteristics will be summarized on ITT population only. Only the treatment emergent adverse events will be considered in the outputs. Therefore, the treatment emergent flag is removed.

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse Event
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DM	Data Management
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
H- score	Immunohistochemistry staining score
HER2	Human Epidermal Growth Factor Receptor 2
ITT	Intent-to-Treat
KM	Kaplan-Meier
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated Acquisition
NE	Not Evaluated
OCRDC	Oracle Clinical Remote Data Capture
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease

PFS	Progression Free Survival
PgR	Progesterone Receptor
PR	Partial Response
TTP	Time To Progression
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SC	Steering Committee
SD	Stable Disease
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures
TRIO	Translational Research in Oncology
UE	Un-evaluable
URS	User Requirement Specifications
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the detailed statistical methodology for executing the statistical analyses to assess the antitumor activity and safety profile of letrozole in combination with afatinib (BIBW2292) versus letrozole alone in the first line treatment of ER+, HER2 negative postmenopausal Advanced Breast Cancer women with low ER expression. The data will be analyzed by TRIO. It is planned that the data from all centers that participate in this study will be used.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to compare the progression-free survival (PFS) of the drug combination letrozole plus afatinib (BIBW2292) to letrozole alone in the first line treatment of ER+, HER2 negative postmenopausal Advanced Breast Cancer women with low ER expression.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the Overall Survival (OS) between the two treatment arms
- To compare the Objective Response Rate (ORR) between the two treatment arms
- To compare the Time to Tumor Progression (TTP) between the two treatment arms
- To assess the safety and tolerability in the two treatment arms

2.3 Exploratory Objectives

TRIO plans to examine the molecular profiles of tumor tissue submitted by the subjects to identify factors that may influence biological and clinical responses to afatinib and letrozole including but not limited to Estrogen Receptor (ER) and Progesterone Receptor

(PgR) statuses, H-score and the EGFR related downstream pathways. The analyses performed afterwards will be described in a separate document.

3. STUDY DESIGN

This phase II, multicenter, multinational, open-label, parallel group, randomized study will compare a two-drug regimen of letrozole plus afatinib (BIBW2292) to letrozole alone in the first line treatment of ER+, HER2 negative postmenopausal Advanced Breast Cancer women with low ER expression.

Randomization is stratified by Bone only disease (Yes vs. No) and by Prior neo/adjuvant hormonal therapy (Yes vs. No). Eligible subjects will be randomly assigned in a 1:1 ratio to either:

> **Arm A: Continuous regimen of oral letrozole 2.5 mg daily** until progression of disease or any other study treatment discontinuation criteria.
>
> OR
>
> **Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily** until progression of disease or any other study treatment discontinuation criteria.

Once the subject is discontinued from study treatment and has undergone the End of Treatment visit, the subject will enter into the follow-up phase.

This study also includes an optional exploratory research component. This optional portion is a molecular profiling assay aimed to assess the relationship of antitumor activity with the expression of selected cell cycle-related proteins and other markers that may be identified in the future. Subjects may participate in this study even if they choose not to participate in the sample banking component.

4. STUDY ENDPOINT AND COVARIATES

4.1 Efficacy Endpoints

Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from randomization until the first evidence of progression as defined by RECIST version 1.1 or death from any cause. Subjects who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment, if available, or the date of randomization if no post initiation (i.e. post-baseline) radiographic assessment is available. Symptomatic/clinical disease progression (deterioration) without documented radiologic progression will not constitute progression for the purposes of determining PFS.

It is defined as: PFS = Date of Progression/Death/Censor – Date of Randomization + 1.

	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No post-baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last tumor assessment	Censored
4	Subject lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last tumor assessment	Censored
5	Documented progression	Date of documented progression.	Progressed

		If a tumor assessment was done on multiple days, use the earliest date for that visit.	
6	Death without documented progression	Date of death	Progressed

Overall Survival (OS)

Overall survival (OS) is defined as the time from randomization to the time of death from any cause. Subjects who are alive at the end of the follow-up period, or are lost to follow-up during the study, will be censored at the last date known alive.

Duration of OS is defined as the time from randomization until death (or censoring if no death). It is defined as:

OS = Date of Death/Censor – Date of Randomization + 1

Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the proportion of randomized subjects achieving a best overall response of CR or PR per RECIST v1.1. The overall response will be determined by the investigator at each scheduled assessment (every 12 weeks +/- 1 week) based on the achievement of both measurement and confirmation criteria. The evaluation of the overall response is detailed in Table 11 and 12 of the protocol.

A **confirmed** overall response based on the achievement and confirmation of two consecutive assessments is presented below:

Confirmed Overall Response Determination		
Initial Response (Not Yet Confirmed)	**Consecutive Response (at Least 4 Weeks Later)[1]**	**Confirmed Overall Response**
PD	-	PD
CR/PR/SD	PD	SD
CR	CR	CR
CR	PR	PR
CR	nfe	SD
PR	CR	PR
PR	PR	PR
PR	nfe	SD
SD	CR/PR/SD/nfe	SD

nfe : no further evaluation

[1] The NE assessments will not be considered as a consecutive response and will be dropped in the evaluation.

The best overall response is the best **confirmed** overall response recorded from baseline until disease progression.

Time to Progression (TTP)

Time to progression (TTP) is defined as the time interval from date of randomization to date of the first documented objective tumor progression. Time to progression does not include deaths as events. Subjects who did not progress are censored at the last radiographic tumor assessment (i.e., with a cycle/visit response of CR, PR, SD, PD). If no post-baseline assessment is available, censoring will occur at date of randomization. The same censoring rules will be applied as for PFS, except that death is not considered as an event.

4.2 Safety Endpoints

Adverse Events (AE)

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE v4.0 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening and death.

Treatment Emergent Adverse Event (TEAE)

An AE will be considered treatment emergent if:

Its onset date occurred any time on or after the administration of the first dose of any study treatment up to 30 days after the last dose of study treatment (or up to any time if serious AE related to study treatment).

Related Adverse Events

Adverse events can be considered "related" and the relationship will be assessed for each component of the study treatment. If an AE is missing the relationship information (from the investigator) then this adverse event will be treated as "related" in the statistical analysis.

Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined as any AE which:

- Results in death
- Is immediately life-threatening
- Results in persistent or significant disability / incapacity
- Requires or prolongs subject hospitalization
- Is a congenital anomaly / birth defect

- Is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Laboratory Data

Hematology and blood chemistry labs will be collected in the eCRF. All those labs will be converted using recommended units by through Oracle Clinical Remote Data Capture (OCRDC).

In addition, laboratory data will be classified (by biostatistics/SAS programming) into grades according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Vital Signs

Vital sign assessments are performed in order to characterize basic body function. The parameters expected to be collected include: weight (kg) and systolic / diastolic blood pressure (mmHg).

Systolic blood pressure will be categorized as <140 mmHg, 140-160 mmHg, >160 mmHg, and Diastolic blood pressure as <90 mmHg, 90-100 mmHg, >100 mmHg.

Concomitant Medication

A medication will be regarded as previous if it started within 30 days before the randomization and stopped before randomization (medication stop date < randomization date).

A medication will be regarded as concomitant if:

- It started on or after the date of randomization and within 30 days after the date of last study treatment; **OR**
- It started prior to randomization but was ongoing at the time of the randomization.

Left Ventricular Ejection Fraction (LVEF)

Left Ventricular Ejection Fraction (LVEF) will be collected in the eCRF to assess the percent volume of blood that is pumped by the left ventricle with each cardiac contraction to detect any cardiac toxicity associated to the drugs. LVEF will be performed by MUGA scan or echocardiogram, using the same method at each assessment.

ECOG Performance Status

Performance status will be collected in the eCRF according to ECOG scale to assess how the disease affects the daily living abilities of the subject.

Drug Exposure

Exposure analyses will be based on the actual dose administered (in mg). The planned dose for Letrozole and Afatinib is the same for each subject regardless of their physical characteristics (weight).

The following variables summarizing the overall administration (not by cycle) will be derived:

Letrozole

- Number of cycles: number of cycle having a duration of intake > 0 day
- Duration of treatment (in weeks) = [(Date of last dose - date of first dose +1)]/7
- Duration of exposure (days) = Sum of each sub-administration duration (Stop Date – Start Date +1)
- Relative dose intensity (%) = [Duration of exposure (days) / Duration of treatment (days)] x 100

Afatinib

- Number of cycles: number of cycle having a duration of intake > 0 day
- Duration of treatment (in weeks) = [(Date of last dose - date of first dose +1)] /7

- Duration of exposure (days) = Sum of each sub-administration duration (Stop Date – Start Date +1)
- Cumulative dose (mg) = Sum of all (each sub-administration Duration of exposure (days) × 30 mg or 20 mg if dose reduced)
- Relative dose intensity (%) = [Cumulative Dose (mg) / (Duration of treatment (days) x 30 mg] x 100

5. STATISTICAL CONSIDERATIONS

5.1 Hypothesis for the PFS

The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups using a stratified logrank test at two-sided 10 % level of significance, i.e.:

H_0: $S_t(t) = S_c(t)$ vs H_1: $S_t(t) \neq S_c(t)$, $t \geq 0$

where $S_c(t)$ is the survival distribution function of PFS in the control arm and $S_t(t)$ is the survival distribution function of PFS in the experimental arm.

5.2 Sample Size

The following assumptions are made:

- Subjects in the control arm will have a median PFS of 9 months
- Subjects in the experimental arm will have median PFS of 14 months (PFS hazard ratio of 0.64)
- Expected accrual duration will be 18 months, which leads to about 42 months of expected entire study duration
- The α type I error rate is set to 10% (2-sided)
- The β type II error rate is set to 20% (i.e. the power of the trial will be 80%)

Under these assumptions, 150 subjects (75 per arm) will be enrolled in the trial.

5.3 Timing of Analyses

The following analyses are planned:

A first analysis of safety will be performed on the first 20 subjects who complete 28 days of treatment. The steering committee will review this formal analysis.

Interim safety analyses will, then, be performed once a year until the final analysis.

The final analysis will be performed when 127 PFS events are observed in the ITT population. The trial will stop once the last subject reaches end of study treatment visit (30 days post last drug intake) and all events required for the final analysis have been observed and collected.

6. DEFINITIONS

Baseline

The last available assessment before or at the date of start of study treatment is taken as 'baseline' assessment. If subjects have no value as defined above, the baseline results will be missing.

Complete Response

The radiological assessment Complete Response is defined using the RECIST v1.1 criteria.

Date of First Dose

The date of first dose of study drug is derived as the first date when a nonzero dose of study drug is administered and recorded on the dose administration record of the eCRF. For the sake of simplicity, the date of first dose of study drug is also referred to as the start of the study drug.

Date of Last Dose

The date of last dose of study drug is derived as the last date when a nonzero dose of study drug is administered and recorded on the dose administration record of the eCRF.

Last Contact Date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the latest complete date among the following dates which precede the cut-off date:

- All assessment dates (e.g. vital signs assessment, performance status assessment, tumor assessments, etc.)
- Medication dates including concomitant medications (start or stop)
- Adverse events dates (start or stop)
- Date of last study drug administration
- Randomization date

Partial Response (PR)

The radiological assessment Partial Response is defined using the RECIST v1.1 criteria.

Progressive Disease (PD)

The radiological assessment Progressive Disease is defined using the RECIST v1.1 criteria.

RECIST

The response to treatment will be determined according to guidelines established by the Response Evaluation Criteria In Solid Tumors (RECIST v1.1) criteria (or guidelines).

Stable Disease (SD)

The radiological assessment Stable Disease is defined using the RECIST v1.1 criteria.

Screening Phase

The screening phase is the time between the date the subject signs the informed consent and the date of randomization.

7. STUDY POPULATION

The Intent-to-treat (ITT) population will consist of all subjects who were randomized to study treatment, regardless of whether they actually received study medication. All efficacy analyses will be evaluated based on data from this population according to the treatment group they were assigned to at randomization and based on the strata they were originally assigned to at the time of randomization.

The Safety population will be used to assess clinical safety and tolerability and will consist of all subjects who were randomized and received at least one dose of study medication. This population will be based on the actual treatment received, if this differs from that to which the subject was randomized and will be used for the analysis of safety data.

8. INTERIM ANALYSIS AND EARLY STOPPING RULE

Steering Committee

The Steering Committee (SC) will be composed of the study Co-Chairs, medical, operational and statistical representatives of TRIO and a non-voting representative from the manufacturer.

The SC will have sole responsibility for the scientific conduct and integrity of the trial. Responsibilities include review and approval of the protocol document, review and approval of protocol amendments, monitoring of accrual, compliance and safety during the conduct of the trial.

9. DATA SCREENING AND ACCEPTANCE

9.1 General Principles

Data Management (DM) for this study is the responsibility of TRIO.

For the planned analyses, data acceptance will be based on the creation and review of the blinded tables, listings, and figures (TLFs). In general, TLF programs will be created prior to a database snapshot or database lock. Extracts of the clinical study data will be made prior to a snapshot or lock of the database and the TLF programs will be run with the outputs reviewed for extreme, unusual, and missing values. These will be identified to Data Management and Project Management for further investigation and potential resolution prior to a snapshot or lock of the database. As issues are detected with the data entered in the database, procedures will be reviewed and programmed if necessary to ensure resolution in subsequent data transfers.

For the final analysis, all procedures will be run to ensure previously identified data issues have been resolved. The TLF programs will be run and the outputs reviewed to ensure additional data issues have not evolved. Additionally, the following items will be specifically identified for further investigation and resolution by DM prior to acceptance of the data by Biostatistics:

- Post-baseline missing disease response by radiological tumor assessment
- Outlier lab data
- Missing baseline data (e.g., labs, vitals, etc.)

The clinical study team will identify the criteria for important protocol deviation criteria. Protocol deviations that may impact the analysis and/or the interpretation of the study results include, but are not limited to:

- No disease assessments
- Inclusion/exclusion criteria not met

- Treatment administration that is not consistent with the protocol (based on the randomized treatment for each subject)

9.2 Data Handling and Electronic Data Transfer

All clinical data will be entered directly by the sites users into the TRIO OCRDC database and will be transmitted electronically in the form of raw SAS® datasets. Once the final data queries have been generated and resolved, the database will be deemed "locked" and final data analysis files will be generated.

DM will provide all data to Biostatistics as raw SAS® data sets on a regular basis. Official data snapshots will be extracted from the clinical database for the final and updated analyses. The data used for all the analyses will be archived.

9.3 Handling of Incomplete and Missing Data

Missing and incomplete data will be identified through a review of the tables and listings created within Biostatistics. Missing and incomplete data will be identified for investigation, and possible resolution, by DM and Project Management prior to database lock (or an official database snapshot).

Missing Data: All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or "carried forward."

Partial or Missing Date for Adverse Events and Concomitant Medications:

Imputation Rules for Partial or Missing Stop Dates:

If the month and year are present, impute the last day of that month.

If only the year is present, impute December 31 of that year.

If the stop date is entirely missing, assume the event or medication is ongoing.

If a partial or complete stop date is present and the 'ongoing' box is checked, then it will be assumed that the adverse event or concomitant medication stopped and the stop date will be imputed if partial.

Imputation Rules for Partial or Missing Start Dates

Start Date		**Stop Date**						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**Missing**
		$< 1^{st}$ dose	$\geq 1^{st}$ dose	$< 1^{st}$ dose *yyyymm*	$\geq 1^{st}$ dose *yyyymm*	$< 1^{st}$ dose *yyyy*	$\geq 1^{st}$ dose *yyyy*	
Partial: *yyyymm*	$= 1^{st}$ dose *yyyymm*	2	1	2	1	n/a	1	1
	$\neq 1^{st}$ dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	$= 1^{st}$ dose *yyyy*	3	1	3	1	n/a	1	1
	$\neq 1^{st}$ dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

9.4 Outliers

Outliers will be identified through a review of TLFs. Procedures will be created to specifically look for outlier data within the laboratory and vital sign parameters.

For laboratory parameters, vital signs and clinical parameters, extreme values will be identified for investigation by Data Management and Project Management, as described in the Procedure User Requirement Specifications (URS).

Additional procedures may be created to assess potential outlier data for other parameters.

All confirmed outlier data will be included in the analyses presented in this statistical analysis plan.

9.5 Testing Validation Plan

SAS® version 9.1 or higher on the Windows system will be used for all TLFs creation. The verification of the outputs, the analysis datasets as well as the review of all programs and macros created specifically for this study, will be conducted as outlined in TRIO Standard Operating Procedures and Standard Guidelines.

10. STATISTICAL METHODS OF ANALYSIS

Categorical variables will be summarized in frequency tables, with the counts and percentage of subjects in each category. Percentages given in the summary tables will be rounded and thus may not always add up to exactly 100 percent. For continuous variables, summary statistics will include N, mean, standard deviation, Q1, median, Q3, minimum and maximum values (range).

SAS® version 9.1 or higher will be used for the statistical analyses.

10.1 Disposition of Subjects

The disposition of subjects will be tabulated using the ITT population. Number (percent) of subjects who were in each analysis population (e.g. the ITT and Safety populations), discontinued, and ongoing as of data cut-off date will be summarized by treatment group. The reason for discontinuation (both from treatment and from study participation) will be summarized considering the categories specified in the eCRF pages. Listings of disposition information and analysis population will be provided as well.

Violations of the inclusion/exclusion criteria, as well as other important protocol violations will be summarized and listed for the ITT population, by treatment arm.

The stratifications factors Bone only disease (Yes vs. No) and Prior neo/adjuvant hormonal therapy (Yes vs. No) will also be described by treatment group.

10.2 Demographic and Disease Characteristics

The following demographic and baseline characteristics will be summarized and listed for the ITT population by treatment group:

Demographics:

Age, *INT (Date of randomization – Date of birth) / 365.25)*

INT = integer part

Due to the fact, only the year of birth is collected (YYYY), we assume the full date to be 31-Dec-YYYY

Menopausal Status

Weight at Baseline

ECOG Status at Baseline

Disease Characteristics:

Time from initial diagnosis to randomization

Primary Tumor Side

Histopathological Type at Initial Diagnosis

Histological Grade at Initial Diagnosis

Stage IV Disease at Initial Diagnosis (Yes/No)

Time from Metastatic / Locally Recurrent Disease to randomization

Disease Status at Registration

Prior Surgery for Breast cancer and Prior Anti-Tumor Therapy

10.3 Medical History

Not Applicable.

10.4 Study Drugs Administration

Number of cycles, Duration of treatment, Cumulative dose (for Afatinib only) and Relative dose intensity (RDI) will be summarized by treatment for the safety population.

The relative dose intensity will be additionally presented categorized (i.e., number and percentage of subjects with relative dose intensity of <60%, 60-<80%, 80-<90%, 90-<110%, ≥110%).

The number and percentage of subjects with dose interruptions/discontinuations or reduced (Afatinib only), along with their respective reasons will be summarized.

For Afatinib, the compliance will be summarized by visit following this calculation :

> *Compliance (%) = [Number of tabs taken* / Sum of each sub-administration duration in a visit] x 100

When the total number of tabs taken does not equal the number of tabs dispensed minus the number of tabs returned, the reasons will also be summarized.

10.5 Efficacy Analyses

Efficacy data for the primary endpoint and the secondary endpoints will be analyzed for the ITT population. Sensitivity analyses and subgroup analyses will be conducted as appropriate. Summaries and figures of the efficacy endpoints will be generated by randomization group.

10.5.1 Progression Free Survival (PFS) - Primary Endpoint

Progression-free survival will be summarized using Kaplan-Meier (KM) curves and compared between treatment arms using a stratified log-rank test, stratifying for Bone only disease (Yes vs. No) and by Prior neo/adjuvant hormonal therapy (Yes vs. No). The Kaplan-Meier estimate of the PFS survival distribution function will be computed for each treatment group using PROC LIFETEST with method=KM option in SAS. The results will also be plotted graphically (Kaplan-Meier curves) by each treatment arm. The plots will also display the number of subjects at risk at equidistant time points.

For each randomization group, the Kaplan-Meier estimates for the median PFS time, the first and third quartiles will be presented, along with approximate 95% confidence intervals (CI).

The effect of treatment on PFS will also be compared using a stratified Cox proportional hazards regression mode using the stratification variables at randomization as strata. This model will generate estimates of the stratified treatment hazard ratio, respectively. Additional stratified Cox regression models might be employed to explore the effects of additional prognostic variables (considered as covariates in the model) on PFS. The hazard ratio with two-sided 95% confidence interval will be derived from the stratified Cox proportional hazards model using PROC PHREG with ties=EXACT option in the model.

A sensitivity analysis will be performed on Progression free survival to assess the robustness of the results. Therefore, subjects receiving any non-protocol anti-cancer therapy during the treatment period before an assessment of disease progression will be

censored on the last available assessment date prior to initiating medication or the date of surgery or radiotherapy.

10.5.2 Overall Survival (OS) – Secondary Endpoint

The treatment groups will be compared using the stratified log-rank test and the survival curves will be estimated, together with corresponding summary statistics. The survival curves for each treatment group will be generated using the Kaplan-Meier methodology. The effect of treatment on OS will also be compared using a stratified Cox proportional hazards regression mode using the stratification variables at randomization as strata.

10.5.3 Objective Response Rate (ORR) – Secondary Endpoint

The objective response rates observed in the treatment groups will be compared adjusting for the stratification variables using the Cochran-Mantel-Haenszel (CMH) test.

A 95% CI will be calculated for each response rate. The best overall response outcome (CR/PR/SD/PD/Unevaluable [UE]) will be summarized and tabulated for the ITT population by treatment group and by the stratification variables using the Cochran-Mantel-Haenszel test as appropriate.

10.5.4 Time to Progression (TTP) – Secondary Endpoint

The treatment groups will be compared using the stratified log-rank test and the survival curves will be estimated, together with corresponding summary statistics. The survival curves for each treatment group will be generated using the Kaplan-Meier methodology. The effect of treatment on TTP will also be compared using a stratified Cox proportional hazards regression mode using the stratification variables at randomization as strata.

10.6 Safety Analyses

Safety analyses will be performed on the safety population.

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA version 16.0 or later) will be used to code all adverse events to a system organ class and a preferred term.

Subject incidence of Treatment Emergent Adverse Events will be tabulated by system organ class, preferred term and toxicity grade for all adverse event, serious, treatment-related, and serious treatment-related adverse events. Each of these outputs will include tabulation for each system organ class and preferred term as reported by the investigator based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Summary tables will be provided separately for Treatment Emergent Adverse Events leading to investigational product discontinuation and Treatment Emergent Adverse Events leading to study withdrawal.

All AEs leading to deaths will be summarized (not only TEAEs). An AE will be considered as leading to death if it has a grade 5.

Detailed listings for all adverse events and listings and/or narratives will be provided for serious and significant adverse events, deaths, and treatment discontinued due to adverse events. A flag will be used to identify which adverse events are considered as treatment emergent or not.

10.6.2 Performance Status, Physical Exams, Vital Signs, and Laboratory Evaluations

Summary of ECOG Performance Status results at each scheduled time point (including baseline) and the change from baseline will be presented. A shift table will be provided as well from baseline status to the worst status of post-baseline time points.

Vital sign measurements (only systolic and diastolic blood pressure) will be summarized at each visit (maximum value on day of dosing) and over the study, using descriptive statistics. In addition, shifts from baseline will be tabulated, by cycle (maximum value on

day of dosing) and over the study, with systolic blood pressure categorized as <140, 140-160, >160 mmHg, and diastolic blood pressure as <90, 90-100, >100 mmHg.

Body weight and change from baseline will be summarized by visit.

LVEF and change from baseline will be summarized by visit.

Laboratory parameters for Hematology and Blood chemistry results at each scheduled time point (including baseline) and the change from baseline will be presented. A shift table will be provided as well from baseline status to the worst status of post-baseline time points.

10.6.3 Concomitant Medication

The number and proportion of subjects receiving each reported medication will be summarized by each treatment arm as coded using World Health Organization Drug Dictionary (WHODD).

A listing of all concomitant medications by subject will also be provided.

11. LIST OF PLANNED TABLES, FIGURES, LISTINGS

11.1 Planned Tables

Title	Population	Description
Subject Disposition	ITT	Tabulates the disposition of all subjects, including the number of subjects randomized, the number of subjects that received investigational product and the number of subjects that were randomized and never received investigational product. The reason for drug discontinuation will also be summarized. The reason for study discontinuation will be summarized.
Stratification Factors	ITT	Tabulates the stratification factors Bone only disease (Yes vs. No) and Prior neo/adjuvant hormonal therapy (Yes vs. No).
Protocol Deviations	ITT	Tabulates the protocol and the eligibility deviations.
Baseline Demographics	ITT	Tabulates summary statistics of the demographics (Age, Menopausal Status, Weight and ECOG Status at Baseline).
Disease Characteristics	ITT	Tabulates the Time from Initial Diagnosis to Randomization, the Primary Tumor Side, the Histopathological Type at Initial Diagnosis, the Histological Grade at Initial Diagnosis, the Stage IV Disease at Initial Diagnosis and the Disease

Title	Population	Description
		Status at Registration, Prior Surgery for Breast cancer and Prior Anti-Tumor Therapy.
Study Drug Exposure	Safety	Tabulates the Number of Cycles, the Duration of Treatment, the Cumulative dose, the Relative dose intensity, Reductions. The number of subjects with dose interruptions/discontinuation or reduction will also be summarized.
Progression-Free Survival	ITT	Summary of PFS results including treatment comparison results.
Progression-Free Survival	ITT	Summary of PFS results including treatment comparison results (sensitivity analysis).
Overall Survival	ITT	Summary of OS results including treatment comparison results.
Objective Response Rate	ITT	Summary of ORR results including treatment comparison results.
Time to Progression	ITT	Summary of TTP results including treatment comparison results.
TEAEs Overview	Safety	Tabulates the number of TEAEs, serious TEAEs, Grade 3-4 TEAEs, Treatment Related TEAEs, Serious and Treatment Related TEAEs, Fatal TEAEs.
Treatment Emergent Adverse Events (TEAEs)	Safety	Summary by system organ class and preferred term for each treatment group.

Title	Population	Description
Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Serious Treatment Emergent Adverse Events (TEAEs)	Safety	Summary by system organ class and preferred term for each treatment group.
Serious Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Related Letrozole Treatment Emergent Adverse Events (TEAEs)	Safety	Summary by system organ class and preferred term for each treatment group.
Related Letrozole Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Related Afatinib Treatment Emergent Adverse Events (TEAEs)	Safety	Summary by system organ class and preferred term for each treatment group.
Related Afatinib Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Serious Related Letrozole Treatment Emergent Adverse Events (TEAEs)	Safety	Summary by system organ class and preferred term for each treatment group.
Serious Related Letrozole Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Serious Related	Safety	Summary by system organ class and preferred

Title	Population	Description
Afatinib Treatment Emergent Adverse Events (TEAEs)		term for each treatment group.
Serious Related Afatinib Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Grade 3-4 Treatment Emergent Adverse Events (TEAEs)	Safety	Summary by system organ class and preferred term for each treatment group.
Grade 3-4Treatment Emergent Adverse Events (TEAEs) per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Treatment Emergent Adverse Events (TEAEs) leading to drug discontinuation	Safety	Summary by system organ class and preferred term for each treatment group.
Treatment Emergent Adverse Events (TEAEs) leading to drug discontinuation per Grade	Safety	Summary by system organ class and preferred term for each treatment group.
Fatal Treatment Emergent Adverse Events	Safety	Summary by system organ class and preferred term for each treatment group.
ECOG Performance Status	Safety	Summary of ECOG performance status results at each time point, change from baseline at each time point. In addition, a shift table will be presented.
Blood Pressure	Safety	Summary of systolic and diastolic blood pressure results at each time point. In addition, shift tables

Title	Population	Description
		will be presented.
Weight	Safety	Summary of weight results at each time point, change from baseline at each time point.
Hematology	Safety	Summary of hematology parameters at each time point. In addition, shift tables will be presented.
Blood Chemistry	Safety	Summary of blood chemistry parameters at each time point. In addition, shift tables will be presented.
Concomitant Medications	Safety	Summary of administered concomitant medications by preferred name.

11.2 Planned Listings

Title	Population	Description
Subject Accountability	ITT	Listing of all subjects population and treatment arms.
Subject Withdrawal	ITT	Listing of all subjects who withdrew from the study/treatment, including the reason for withdrawal.
Study Drug Exposure	Safety	Listing of all subjects investigational product administration information.
Treatment Emergent Adverse Events	Safety	Listing of all treatment emergent adverse event. Listing will include subject number, system organ class and preferred term of adverse event, date of onset, date of resolution, CTCAE v4.0 Grade, action taken, relationship and outcome.
Serious Treatment Emergent Adverse Events	Safety	Listing of all serious treatment emergent adverse event. Listing will include subject number, system organ class and preferred term of adverse event, date of onset, date of resolution, CTCAE v4.0 Grade, action taken, relationship and

Title	Population	Description
		outcome.
Treatment Emergent Adverse Events Leading to Drug Discontinuation	Safety	Listing of all treatment emergent adverse event leading to drug discontinuation. Listing will include subject number, system organ class and preferred term of adverse event, date of onset, date of resolution, CTCAE v4.0 Grade, action taken, relationship and outcome.
Fatal Treatment Emergent Adverse Events	Safety	Listing of all adverse event leading to death (grade = 5). Listing will include subject number, system organ class and preferred term of adverse event, date of onset, date of resolution, CTCAE v4.0 Grade, action taken, relationship and outcome.
Deaths	ITT	Listing of all subjects who died, including cause of death, study day of death.
Vital Signs (Blood Pressure)	Safety	Listing of all vital signs results for each subject.
ECOG Performance Status and Physical Exam (Weight)	Safety	Listing of ECOG PS and Weight at each assessment.
Hematology	Safety	Listing of all hematology parameters.
Blood Chemistry	Safety	Listing of all blood chemistry parameters.
Concomitant Medications	ITT	Listing of all concomitant medications.
Efficacy Parameters	ITT	Listing of all efficacy parameters for each subject, including Progression-Free Survival, Overall Survival, Objective Response Rate, Time to Progression.

11.3 Planned Figures

Title	Population	Description
Progression-Free Survival	ITT	Kaplan-Meier plot of Progression-Free Survival.
Overall Survival	ITT	Kaplan-Meier plot of Overall Survival.
Time to Progression	ITT	Kaplan-Meier plot of Time to Progression.