Statistical Analysis Plan – OS Follow-up addendum

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A Randomised, Double-blind, Parallel-group, Multicentre, Phase III Study to Compare the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Anastrozole (ARIMIDEX™) 1 mg as Hormonal Treatment for Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer Who Have Not Previously Been Treated With Any Hormonal Therapy (FALCON)

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Global Product Statistician

PPD

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
DCO	Data cut off
FACT-B	Functional Assessment of Cancer Therapy – Breast
ITT	Intention to Treat
ORR	Objective response rate
OS	Overall Survival
PFS	Progression-free survival
PT	Preferred term
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TLFs	Tables, listings, and figures
TOI	Trial Outcome Index

AMENDMENT HISTORY

Date	Brief description of change
20 October 2017	First draft – addendum to SAP Edition 3 (27 April 2016)
3 May 2022	Second draft – per protocol version 6.0 (17 December 2021), change of final overall survival (OS) analysis trigger from when 75% of patients have died to: when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled; summaries of data on protocol deviations and concomitant medication are also generated; retain OS TLF original numbering and add a suffix for OS analysis

1. STUDY DETAILS

1.1 Study objectives

The only objective of the study relevant to the overall survival (OS) follow-up analysis is the secondary objective:

> To compare the OS of patients treated with fulvestrant 500 mg versus patients treated with anastrozole 1 mg.

1.2 Study design

The study design relevant to the OS is as follows:

After the data cut-off for the primary progression-free survival (PFS) analysis, all the remaining patients, regardless of whether they are still receiving randomised treatment, will enter the survival follow-up phase. An interim analysis of OS data will be performed at the time of the PFS analysis and an updated survival analysis will be performed when at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled, July 11, 2014. After the updated survival analysis, data collection will cease for this study and the patient's treatment will be unblinded.

1.3 Number of subjects

The sample size calculations are described in the main SAP.

2. ANALYSIS SETS

All patients, defined as everyone who signed informed consent, will be used to summarise patient disposition.

The Intention to Treat (ITT) analysis set, as defined in the main SAP, will be used to analyse OS, and to summarise post-discontinuation anti-cancer therapy, important protocol deviations, concomitant medications, best overall tumour response to first subsequent therapy, Quality of Life (QoL) questionnaires: Functional Assessment of Cancer Therapy – Breast (FACT-B) and EQ-5D.

The Safety analysis set as defined in the main statistical analysis plan (SAP), will be used to summarise serious adverse events (SAE), deaths and exposure.

2.1 Violations and deviations

Important protocol deviations post the data cut-off (DCO) for the primary PFS analysis will be summarised and listed by treatment group.

3. FOLLOW-UP OUTCOME VARIABLES

3.1 Disposition and anti-cancer therapy variables

Patient disposition is defined as the number of patients who enrolled; randomised; received treatment, or not; continued to receive treatment, or not, at DCO for the updated OS analysis; were ongoing, or terminated, at DCO.

Post-discontinuation disease-related anticancer therapy is defined as the medications recorded on the Post-Withdrawal Cancer Therapy (CAPRXPOST) CRF page.

Concomitant medications will be listed and summarised by treatment group for the survival follow-up phase.

3.2 Overall survival

Overall survival is defined in section 3.2.1 of the main SAP.

3.3 Best response to first subsequent breast cancer therapy

Best response to first subsequent cancer therapy, as collected on the Post-Withdrawal Cancer Therapy CRF page, will be summarised overall and by type of therapy.

3.4 Safety

Deaths and SAEs are the only safety variables to be summarised in the Follow-up analysis, as described in section 3.3 of the main SAP.

3.5 Exposure to study drug

Derivations of exposure to study drug remain unchanged from the PFS analysis, specifically total duration of fulvestrant will be derived, in months, as follows:

{[earliest of (last dose date +28) or death date] – first dose date +1} / (365.25/12)

Total duration of anastrozole will be derived, in months, as follows:

(last dose date - first dose date +1) / (365.25/12)

3.6 Quality of Life (QoL) questionnaires

FACT-B scores will be derived as described in section 3.4 of the main SAP

EQ-5D scores will be derived as described in section 3.5 of the main SAP.

4. ANALYSIS METHODS

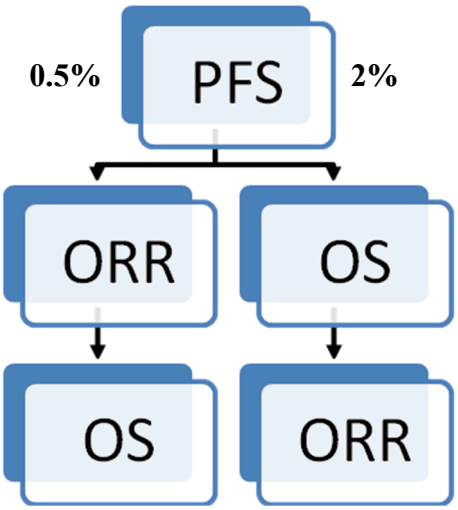
4.1 General principles

General principles of the analysis methods are unchanged from section 4.1 of the main SAP.

4.1.1 Multiple testing strategy

The key secondary endpoints of OS, and ORR will be tested using a multiple testing procedure (MTP) with an alpha-splitting and recycling strategy (Burman et al 2009). With this approach, the endpoints of OS, and ORR will be tested in a pre-defined order as shown below. The secondary endpoints of CBR, EDoR, EDoCB, FACT-B and EQ-5D will not be included in this MTP.

Figure 1 Multiple testing procedure



The primary endpoint (PFS) was tested at a single time point when 309 progression events have occurred (143 in the fulvestrant group and 232 in the anastrozole group). The secondary endpoints of OS and ORR were tested in the MTP using a weighted proportion of alpha (test mass; the total test mass equals alpha) and test mass that became available after each rejected hypothesis was recycled to secondary endpoints not yet rejected. This testing procedure stopped when the entire test mass was allocated to non-rejected endpoints. Implementation of this pre-defined ordered testing procedure included recycling, strongly controlled the Type I error at 2.5% (1-sided), amongst the primary (PFS) and the key secondary (OS and ORR) endpoints.

PFS and ORR were analysed at one time-point only. However, OS will be analysed on two occasions; at the time of the analysis of PFS and also at a later time-point when it is estimated that at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled (originally planned for 50%). The available alpha will be controlled amongst the two OS analyses by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the significance level applied at the interim (i.e., at the time of formal PFS and ORR analysis) is dependent upon the proportion of information available. This proportion of information was calculated at the interim using the data available at that time.

Using the allocated α=2% according to the MTP (ORR was not significant; one-sided p-value = 0.3645), the following was the case for the OS interim analysis:

- 142 deaths (out of the total of 462 patients recruited into the trial) occurred.
- The final OS analysis is planned for when it is estimated that at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled (originally planned for 50%).
- Therefore, at the time of the interim OS analysis, it was thought that 0.6147 of the full death information (142/231 deaths) was available and the 1-sided significance level applied for the OS interim analysis was 0.00301.
- The interim OS was not statistically significant, (one-sided p-value=0.2138), therefore none of the 2% of alpha was recycled to ORR (as ORR is analysed at one time-point only).

ORR was assessed using α=0.5%.

At the time of the final OS follow up analysis where at least 65% of patients have died and at least 8 years have passed since the last patient was enrolled, on the assumption that this will be conducted when 310 deaths have been observed, the one-sided significance level will be 1.845%.

4.2 Analysis methods

4.2.1 Disposition and anti-cancer therapy

The following outputs will be produced, including all data from baseline of the main study until DCO for the follow-up analysis

Shell reference	Reference from PFS analysis	Title	Notes
CCI		Patient disposition	All patients
		Important protocol deviations	Intention to treat analysis set
		Disallowed concomitant medication during study treatment	Intention to treat analysis set
		Disallowed bisphosphonate/Denosumab therapy during study treatment	Intention to treat analysis set
		All allowed concomitant medications during study treatment	Intention to treat analysis set

CCI	Post-discontinuation disease-related anticancer therapy	Intention to treat analysis set
	Discontinued subjects	All patients
	Subjects ongoing study at data cut-off	Intention to treat analysis set
	Subjects with important protocol deviations	Intention to treat analysis set
	Medication on entry and during the study	Intention to treat analysis set

4.2.2 Overall survival

The following OS tables, listings and figures (TLFs) will be produced, with amendments as noted below. All OS outputs will include the footnote:

Patients not known to have died are censored at the date they were last known to be alive, as recorded on the survival status CRF.

Shell reference	Reference from PFS analysis	Title	Notes
CCI		Survival status at the time of the OS analysis, secondary analysis at 65% OS maturity[1]	
		Median overall survival at the time of the OS analysis, secondary analysis at 65% OS maturity[1]	Quartiles (if reached) and median (50th percentile) OS will be summarised Percentage OS at 6 monthly intervals up to an appropriate time point will be summarised
		Overall survival, Stratified log-rank test, secondary analysis at 65% OS maturity[1]	

CCI	Sensitivity analysis of overall survival, Cox proportional hazards regression model, secondary analysis at 65% OS maturity[1]	
	Overall survival, Stratified log-rank test, subgroup analysis, secondary analysis at 65% OS maturity[1]	Subgroups are defined in section 4.2.1.2 of the main SAP
	Overall survival, Stratified log-rank test, geographical region subgroup analysis, secondary analysis at 65% OS maturity[1]	Geographical region subgroups are defined in section 4.2.1.2 of the main SAP
	Summary of total follow-up (months) for OS of all patients, secondary analysis at 65% OS maturity[1]	Follow-up is defined as the duration of follow-up is defined as the number of months from randomisation to death or last contact
	Patients censored for OS at more than 12 weeks before secondary analysis at 65% OS maturity[1]	A patient unknown to be alive or dead at the time of the DCO will be censored at the time they were last known to be alive (this differs to the programming notes in the shell)
	Overall survival at the time of secondary analysis at 65% OS maturity[1], Kaplan-Meier plot	
	Overall survival at the time of secondary analysis at 65% OS maturity[1], Kaplan-Meier plot (for subgroup: xxx)	Subgroups are defined in section 4.2.1.2 of the main SAP

CCI [redacted]	Overall survival at the time of secondary analysis after 65% of patients have died[1], Kaplan-Meier plot (for subgroup: Geographic region: xxx)	Geographical region subgroups are defined in section 4.2.1.2 of the main SAP
	Time to censoring for secondary analysis after 65% of patients have died[1], Kaplan Meier plot	
	Overall survival at the time of secondary analysis after 65% of patients have died[1], Forest plot, by subgroup	
	Overall survival at the time of secondary analysis after 65% of patients have died[1], Forest plot, by geographical region subgroup	
	Overall survival status at time of secondary analysis at 65% OS maturity[1]	

[1] At least 65% of patients have died and at least 8 years have passed since the last patient was enrolled

4.2.3 Best response to first subsequent breast cancer therapy

Best overall response subsequent to the first subsequent cancer therapy will be summarised as follows:

Shell reference	Reference from PFS analysis	Title	Notes
NA	NA	Summary of best overall tumour response to the first subsequent therapy	CCI [redacted]

NA	NA	Summary of best overall tumour response to the first subsequent therapy by subsequent therapy	CCI [redacted]
CCI [redacted]		Listing of systemic anticancer therapy post randomisation	

CCI [redacted]

CCI

4.2.4 Exposure to study drug

Total and actual treatment durations will be summarised by treatment group, from the baseline of the main study until DCO for the follow-up analysis.

Shell reference	Reference from PFS analysis	Title
CCI		Duration of exposure
		Study drug administration - fulvestrant and anastrozole
		Duration of exposure

4.2.5 Safety

Deaths and SAEs, from baseline of the main study until DCO for the follow-up analysis, will be listed for each patient and summarised by treatment received according to the system organ class (SOC) and preferred term (PT).

Shell reference	Reference from PFS analysis	Title
CCI		All Deaths

CCI	Serious Adverse Events with outcome of death by system organ class and preferred term
	Serious Adverse Events with outcome of death, causally related to study treatment
	Listing of deaths
	Serious Adverse Events with outcome of death - key patient information
	Serious adverse events, by system organ class and preferred term
	Serious adverse events, causing discontinuation from treatment, by system organ class and preferred term
	Serious adverse events, causally related to study treatment by system organ class and preferred term
	Serious adverse events, leading to study treatment discontinuation, causally related to study treatment
	Serious adverse events - Listing of key information for SAEs
	Listing of serious adverse events (1)
	Listing of serious adverse events (2)
	Listing of serious adverse events (3)

4.2.6 Quality of Life (QoL) questionnaires

4.2.6.1 FACT-B

All visits from the baseline of the main study until DCO for the follow-up analysis will be included in the summary of the FACT-B scores; specifically Trial Outcome Index (TOI), total FACT-B. Individual subscale scores will not be summarised in the follow-up analysis. The analysis of time to deterioration of TOI and FACT-B total score will be as outlined for the main SAP.

Shell reference	Reference from PFS analysis	Title	Notes
CCI		Compliance with FACT-B by time point.	CCI
		FACT-B total score over time	

CCI	Trial outcome index (TOI) score over time	
	FACT-B total score - change from baseline and categories of change from baseline	
	Trial outcome index (TOI) score over time - change from baseline and categories of change from baseline	
	FACT-B total score and TOI score time to deterioration (months)	
	Analysis of time to deterioration of FACT-B total score	Remove the p-value
	Analysis of time to deterioration of trial outcome index score	Remove the p-value
	Mean (+/- SD) FACT-B total score across timepoints, by treatment group	
	Mean (+/- SD) trial outcome index (TOI) score across timepoints, by treatment group	
	Mean (+/- SD) FACT-B total score change from baseline across timepoints, by treatment group	
	Mean (+/- SD) trial outcome index (TOI) change from baseline across timepoints, by treatment group	
	Kaplan-Meier plot for time to deterioration (months) - FACT-B total score	
	Kaplan-Meier plot for time to deterioration (months) of TOI	
	Review of patient reported outcomes questionnaire - FACT-B	
	Listing of total score by FACT-B domain	

4.2.6.2 EQ-5D

All visits from the baseline of the main study until DCO for the follow-up analysis will be included in the summary of EQ-5D individual questions and combined health score with be listed. VAS score and UK health state utility values and change from baseline will be listed and summarised. VAS score and health state combined score compliance rates will also be summarised similarly to FACT-B.

Shell reference	Reference from PFS analysis	Title
CCI		EQ-5D questionnaire - (VAS) score and health state combined score compliance rate by time point
		EQ-5D questionnaire - (VAS) score and UK health state utility value - summary scores
		EQ-5D questionnaire - (VAS) score and UK health state utility value - change from baseline
		Review of patient reported outcomes questionnaire - EQ-5D
		Listing of EQ-5D questionnaire - individual questions and health state combined score
		Listing of EQ-5D questionnaire - health scores
		Listing of EQ-5D questionnaire - health scores change from baseline

5. REFERENCES

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Notes: (1) CCI [redacted]