STATISTICAL ANALYSIS PLAN

A Phase III, randomized, two-armed, double blinded, parallel, active controlled, non-Inferiority clinical trial study of AryoTrust (AryoGen Pharmed Trastuzumab) efficacy and safety in Human Epidermal Growth Factor Receptor 2–Positive breast cancer in comparison to Herceptin® (Genentech/Roche) control.

Name of Test Drug:	AryoTrust
Phase:	III
Methodology:	Randomized, two-armed, double-blind (patient and assessor blinded), parallel, active controlled, non-inferiority clinical trial
Sponsor:	AryoGen Pharmed No.140. Corner of Tajbakhsh Street 24th Kilometer of Tehran-Karaj Makhsous Road, Alborz, Iran.
Sponsor Representatives:	Dr. Araz Sabzevari Orchid Pharmed company CEO
NCT Number:	NCT03425656
Statistical Analysis Plan Date:	23 Dec 2017
Statistical Analysis Plan Version:	Version 1.0

1. Section 1: Administrative information

1.1. Title and Trial registration

1.1.1. Descriptive title that matches the protocol, with 'Statistical analysis plan' either as a fore runner or sub title, and trial acronym

Statistical analysis plan for AryoTrust study (Phase III): A Phase III, randomized, two-armed, double-blind (patient and assessor blinded), parallel, active controlled, non-inferiority clinical trial to evaluate the efficacy and safety of AryoTrust (AryoGen Pharmed Trastuzumab) in Human Epidermal Growth Factor Receptor 2–Positive breast cancer in comparison to Herceptin® (Genentech/Roche) control.

1.1.2. Trial registration number

IRCT201606226135N7

1.2. SAP Version (SAP version number with dates)

Version: 1.0, Date: 23 Dec 2017

2. Section 2: Introduction

2.1. Objectives

To verify the non-inferiority of AryoTrust (AryoGen Pharmed Trastuzumab) vs. Herceptin® (Genentech/Roche trastuzumab), both given concomitantly with docetaxel after Adriamycin plus cyclophosphamide in the neoadjuvant setting according to pathological clinical response and immunogenicity assay in patients with Human Epidermal Growth Factor Receptor 2–Positive breast cancer.

Primary objective(s):

The primary objective of this study is to verify the non-inferiority of AryoTrust vs. Herceptin®, given concomitantly with docetaxel after Adriamycin plus cyclophosphamide in the neoadjuvant setting according to pathological complete response (pCR) rate in patients with Human Epidermal Growth Factor Receptor 2–Positive breast cancer.

Secondary objective(s):

The secondary purposes of this study are to establish the overall response rate (ORR), breast-conserving surgery (BCS) and assess safety of AryoTrust (AryoGen Pharmed Trastuzumab) group in comparison with Trastuzumab (Herceptin®) group.

3. Section 3: Trial Methods

3.1. Trial design – description of trial design

This is a, Phase III, multi-center, randomized, two-armed, double blind (patient and assessor blinded), parallel, active controlled, non-inferiority clinical trial with a 1:1 allocation.

3.2. Randomization

The randomization is based on blocked randomization. Patient's allocation will be carried on 1:1 allocation ratio by 27 blocks (length of each block is 4). Randomization sequence will be generated using the random generation command in Microsoft Excel (RANDBETWEEN). Once the randomization has been made, a unique code will be assigned to each eligible patient, what she will be identified throughout the study by. The assigned code will be made up of four letters (corresponding to the first two letters of the patient's first name and the first two letters of the patient's family name), three digits (site code), two first letters of the drug's generic name which is followed by the study phase (e.g. TR3 for Trastuzumab phase 3 study) and four digits (corresponding to the randomization number).

3.3. Sample size

Using a non-inferiority margin of 0.25 for the primary end point, a sample size of 48 in each group achieves 82% power to detect a non-inferiority margin difference between the group proportions for the case the reference group proportion was considered as 0.60. The treatment group proportion was assumed to be 0.35 under the null hypothesis of inferiority. The test statistic used for sample size calculation is the one-sided Z test (unpooled) and the significance level of the test is targeted at 0.05. Considering 0.10 losses to follow up, final sample size is 54 in each group.

4. Section 4: Statistical Principles

4.1. Protocol Deviations

4.1.1. Description of which protocol deviations will be summarized

The number (and percentage) of patients with major and minor protocol deviations will be summarized by treatment group with details of type of deviation provided. No formal statistical testing will be undertaken.

4.2. Analysis populations

All tests of the effect of treatment on the primary outcome will be conducted on a per-protocol basis. The intent-to-treat (ITT) patient population includes all patients who signed the informed consent form and underwent random assignment. The per-protocol set (PPS) population will be defined as the ITT population excluding patients who violated protocols to a considerable extent, including major protocol inclusion/exclusion criteria or treatment protocols. Slight deviations may be acceptable. The primary outcome was first evaluated in the PP population and then in the ITT population (with and without imputation) as a sensitivity analysis. In the imputation for pCR, patients with no available data were considered as nonresponders. The safety will be assessed in the as-treated population, which includes all patients who received at least one dose of the assigned trial treatment.

5. Section 5: Trial Population

5.1. Recruitment (Information to be included in the CONSORT flow diagram)

In the "CONSORT" diagram, the number of people screened, eligible, randomized and receiving their allocated treatment will be provided.

5.1.1. Details of how baseline characteristics will be descriptively summarized

Categorical data will be summarized by numbers and percentages. Continuous data will be summarized by mean and SD. Tests of statistical significance will not be reported for the baseline characteristics.

6. Section 6: Analysis

6.1. Analysis methods

6.1.1. What analysis method will be used, and how the treatment effects will be presented

For the primary endpoint, comparison of pathologic complete response (pCR) rate, treatment differences in proportions will be calculated and p-value will be reported based on proportion test. A 95% two-sided confidence interval will be constructed and the upper bound to determine non-inferiority with a 2.5% significance level will be used.

For the secondary endpoints objective response rate (ORR) and breast conservation rate (BCS), frequency and proportions, and p-value will be reported based on proportion test.

Adverse events will be reported as incidence rate. Safety will assess on the basis of reports of adverse events, laboratory test results, and vital sign measurements. Moreover, the causality assessment of ADR will be reported in two groups.

6.1.2. List and describe each primary and secondary outcome including details of: methods used for assumptions to be checked for statistical methods

There is no assumption to check based on the proportion test.

6.2. Statistical Software

The analysis will be carried out using Stata version 14.