STATISTICAL ANALYSIS PLAN

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 bevacizumab (AryoGen Pharmed) plus FOLFIRI-3 in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 as a first line therapy in patients with metastatic colorectal cancer (mCRC).

Name of Test Drug:	Stivant
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
Statistical Analysis Plan Date:	03 July 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 Bevacizumab 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 bevacizumab (AryoGen Pharmed) plus FOLFIRI-3 in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 as a first line therapy in patients with metastatic colorectal cancer (mCRC).

1.1.2. Trial registration number

IRCT2015072517994N2

1.2. SAP Version (SAP version number with dates)

Version: 1.0, Date: 03 July 2017

2. Section 2: Introduction

2.1. Objectives

The evaluation of non-inferiority of efficacy and safety of bevacizumab (AryoGen) in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 (irinotecan plus leucovorin/5-fluorouracil as continuous infusion) and immunogenicity assay in patients with metastatic colorectal cancer (mCRC).

Primary objective(s):

To determine the non-inferiority of the efficacy of bevacizumab (AryoGen) versus bevacizumab (Avastin®) in progression free survival (PFS) when added to FOLFIRI- 3 (irinotecan plus leucovorin/ 5-fluorouracil as continuous infusion) in patients with metastatic colorectal cancer (MCRC).

Secondary objective(s):

The secondary purposes of this study are to establish the overall survival, objective response rate, time to treatment failure (TTF) and assess safety of bevacizumab (AryoGen) group in comparison with bevacizumab (Avastin®) group.

3. Section 3: Trial Methods

3.1. Trial design – description of trial design

This is a, Phase III, randomized, two arms, double blind (patient and assessor blinded), parallel active non inferiority controlled clinical trial with a 2:1 allocation.

3.2. Randomization

The randomization plan of the patients will be carried out using an on-line system (http://www.randomization.com). Using permuted block randomization (length of each block is 6) will be made, for a total of 126 patients (with 2:1 allocation ratio). Once the randomization has been made, each patient is given a code with which he will be identified throughout the study. The assigned code will be denoted by 4 initials (corresponding to the 2 first letter of the first name, the 2 first letter of the first surname) and 3 numbers (center code). Moreover, the code described is followed by study unique identification consisting of first two letters of the generic name and study phase, respectively (which is BE3-) and 4 numbers (corresponding to the randomization number), e.g. ABCD001BE3-0001. The randomization number will be assigned in a consecutive way.

3.3. Sample size

The primary endpoint (PFS) was assumed to be 10.7 months in both groups. By defining a 2 month shorter PFS with bevacizumab (AryoGen pharmed) than with bevacizumab (Avastin®) as the acceptance limit for non-inferiority, a non-inferiority margin of ($\delta = -2$ month) was selected. With 2:1 allocation, total sample sizes of 114, achieve 80% power to detect non-inferiority margin. The significance level of the test was targeted at 0.05 and standard deviation selected 4 months. Considering 10% losses to follow up, final sample size is 126 patients.

4. Section 4: Statistical Principles

4.1. Protocol Deviations

4.1.1. Description of which protocol deviations will be summarised

The number (and percentage) of patients with major and minor protocol deviations will be summarised 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 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, and 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. The slight deviations may be acceptable.

The safety will be assessed in the as-treated population, which included 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, 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 endpoint of PFS, the HR for Stivant to Avastin® and its 90 % CI will be calculated. Moreover PFS will be estimated using the Kaplan–Meier method. Furthermore log rank test will be applied to compare two treatments.

For the endpoints of Overall survival (OS) and time of treatment failures, the HR for Stivant to Avastin® and its 95 % CI will be calculated. Moreover these will be estimated using the Kaplan–Meier method. Furthermore log rank test will be applied to compare two treatments.

For Objective Response rate, proportion and p-value will be reported.

Adverse events will be reported as incidence. Safety will assess on the basis of reports of adverse events, laboratory-test results, and vital sign measurements. Moreover, 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

In survival analysis such as PFS, OS and TTF, proportional hazard (PH) assumption will be checked based on scaled Schoenfeld residuals test.

6.2. Statistical Software

The analysis will be carried out using Stata version 14.