STATISTICAL ANALYSIS PLAN

A Phase III, randomized, two armed, parallel, triple-blind, active controlled, equivalency clinical trial to determine the therapeutic efficacy and safety between Pertuzumab® (Manufactured by CinnaGen Co.) compared with active control group treated by Perjeta® (Pertuzumab, the reference drug, Manufactured by Genentech) in neoadjuvant treatment of HER 2 positive Breast Cancer patients.

Name of Test Drug:	Pertuzumab
Phase:	III
Methodology:	Randomized, two-armed, triple-blind, parallel, active controlled, equivalency clinical trial
Sponsor:	CinnaGen Co No. 34, Sepehr Street, Farahzadi Blvd, Shahrak Gharb, Tehran, IRAN
Sponsor Representatives:	Dr. Araz Sabzevari Orchid Pharmed company CEO
NCT Number:	NCT04957212
Statistical Analysis Plan Date:	18 Jan 2020
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 Pertuzumab study (Phase III): A Phase III, randomized, two armed, parallel, triple-blind, active controlled, equivalency clinical trial to determine the therapeutic efficacy and safety between Pertuzumab® (Manufactured by CinnaGen Co.) compared with active control group treated by Perjeta® (Pertuzumab, the reference drug, Manufactured by Genentech) in neoadjuvant treatment of HER 2 positive Breast Cancer patients.

1.1.2. Trial registration number

IRCT20150303021315N11

1.2. SAP Version (SAP version number with dates)

Version: 1.0, Date: 18 Jan 2020

2. Section 2: Introduction

2.1. Objectives

To verify the equivalency of Pertuzumab® (Manufactured by CinnaGen Co.) vs. Perjeta® (Pertuzumab, the reference drug, Manufactured by Genentech), in neoadjuvant treatment of HER 2 positive Breast Cancer patients.

Primary objective(s):
Primary objective of this study is to evaluate equivalence of Pertuzumab® (Manufactured by CinnaGen Co.) compared to the Perjeta® (Reference drug, Genentech), when added to Carboplatin+Docetaxel+Trastuzumab regimen, based on the pathological complete response (pCR) in neoadjuvant treatment setting in HER2+ breast cancer patients.

Secondary objective(s):
The secondary purposes of this study are to establish the total pathological complete response (tpCR), overall response rate (ORR), breast-conserving surgery (BCS) and assess safety of Pertuzumab® (Manufactured by CinnaGen Co.) group in comparison with Perjeta® (Reference drug, Genentech) group.

3. Section 3: Trial Methods

3.1. Trial design – description of trial design

This is a, Phase III, multi-center, randomized, two-armed, triple-blind, parallel, active controlled, equivalency clinical trial with a 1:1 allocation.

3.2. Randomization

Patients will be dynamically randomized to different groups during the study using Minimization method (with a 90% random component). The two main variables on which the balance is performed will be as follows:

1-ER/PR: ER/PR+, ER/PR-

2-Type of breast cancer: operable, locally advanced, inflammatory

At the beginning of the study, each patient will receive a unique code in order to be recognized during the study. The assigned code consists of 4 letters (corresponding to the first two letters of the first name and the first two letters of the surname), three digits (center code), the first three letters of the generic drug name (which is PER-) and 3 digits (corresponding to randomization code). For example: ABCD001PER-001.

3.3. Sample size

Using an equivalence margin of 0.2, a sample size of 96 subjects in each one of both Pertuzumab® (CinnaGen Co.) and Perjeta® (Genentech Co.) groups achieve 80% power to detect bioequivalence for the difference between groups. The actual difference is considered zero. The PCR efficacy for Perjeta® group is 0.66 (22, 24, 25). Two-way independent T-test with 5% significance level will be used to analyze the results. Considering 10% dropout, final sample size is considered 107 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 case there is no final answer, the worst-case scenario “NO PCR” will be applied. Then, the results will be compared and if there was any significant differences, the reason will be evaluated. 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. Equivalence of Pertuzumab® (CinnaGen Co.) and Perjeta® will be concluded if the resulted 95% confidence interval for the difference will be within the predetermined range (-0.2, 0.2).

For the secondary endpoints total Pathological complete response (tpCR), 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.