STATISTICAL ANALYSIS PLAN

Version 2.0

RANDOMIZED, OPEN-LABEL, NON-INFERIORITY STUDY COMPARING THE SAFETY AND EFFICACY OF WAIT AND EXTENT REGIMEN WITH THE APPROVED TREATMENT REGIMEN OF LUCENTIS (RANIBIZUMAB) IN TURKISH PATIENTS WITH VISUAL IMPAIRMENT DUE TO DIABETIC MACULAR EDEMA

STUDY NUMBER: RFB002/Ranibizumab

STUDY NAME: SALUTE-D

Statistical Analysis Plan Signature Page

Version 2.0

Sponsor	:	NOVARTIS
Protocol	:	[CRFB002DTR01] / NCT02262260
Study title	:	Randomized, Open-Label, Non-Inferiority Study Comparing the Safety and Efficacy of Wait and Extent Regimen with the Approved Treatment Regimen of Lucentis (Ranibizumab) in Turkish Patients with Visual Impairment due to Diabetic Macular Edema

[redacted], Bio., M.Sc. — 12.02.2018

Author — Date

Reviewed by — Date

Approved by — Date

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1 ABBREVIATIONS

DME	Diabetic Macular Edema
BCVA	Best Corrected Visual Acuity
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundus Fluorescein Angiography
OCT	Optical Coherence Tomography
SAE	Serious Adverse Event
CRT	Central Retinal Thickness
VFQ-25	Visual Function Questionnaire

2 BACKGROUND

The purpose of this statistical plan is to define the tables, lists, data summaries and graphs to be prepared and to determine the statistical methods to be used for the analysis of the results of the study titled, "Randomized, Open-Label, Non-Inferiority Study Comparing the Safety and Efficacy of Wait and Extent Regimen with the Approved Treatment Regimen of Lucentis (Ranibizumab) in Turkish Patients with Visual Impairment due to Diabetic Macular Edema". This statistical analysis plan has been prepared in pursuant to and in line with ICH-GCP principles and protocol no. IMM – 11 – 0003.

3 OBJECTIVES OF THE STUDY

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate that the "wait and extend" regimen of ranibizumab is non-inferior to the posology described in the prescribing information regarding the mean change in BCVA from baseline at month 12 in Turkish patients with vision loss due to diabetic macular edema.

3.2. SECONDARY OBJECTIVES

- To compare the mean change in CRT from baseline at month 12 between the two groups using OCT
- To evaluate the number of injections required for a treatment period of 12 months with a "wait and extend" dosing regimen
- To evaluate the number of visits required for a treatment period of 12 months with a "wait and extend" dosing regimen
- To evaluate the number of patients with improvement in BCVA from baseline
- To evaluate the number of patients with improvement of 5 or more letters from baseline
- To evaluate the number of patients with improvement of 10 or more letters from baseline
- To evaluate the number of patients with improvement of 15 or more letters from baseline
- To evaluate the safety of intravitreal Lucentis (ranibizumab) injections in patients with DME
- To describe patient-reported change in functional ability in patients treated with Lucentis

4 STUDY DESIGN

Study Design for the Prescribing Information Regimen Arm

Phase	**Screening**		**Main Treatment**			
Visit	1	2	3	4	5	6 -14
Month	0		1	2	3	4 – 12
Day	–7 to –1	B	30	60	90	120 – 360

Study Design for the Wait and Extend Regimen Arm

Phase	**Screening**		**Main Treatment**			
Visit	1	2	3	4	5	Number of visits may vary by patient response
Month	0		1	2	3	4 – 12
Day	–7 to –1	B	30	60	90	120 – 360

This is a randomized, controlled, multicenter, 12-month study concerning Lucentis (ranibizumab). Patients who provide consents will enter a screening period and their eligibility for enrollment will be evaluated. Following the screening period and evaluation of patient eligibility, only one eye will be selected / treated as the study eye. Once eligibility is confirmed, patients will be randomized to one of the following treatment arms:

Arm 1: Prescribing information regimen arm: Treatment will be given monthly and maintained until maximum visual acuity is achieved (patient's visual acuity remaining stable for three consecutive monthly assessments performed during ranibizumab treatment). Thereafter, patients will be followed-up monthly for visual acuity.

Treatment will be reinitiated in case a loss in visual acuity due to DME is determined during follow-up. Thereafter, monthly injections are to be performed until stable visual acuity is achieved for three consecutive monthly assessments (refers to at least two injections). The period between two doses should not be shorter than 1 month.

Arm 2: Wait and extend regimen arm: Lucentis (ranibizumab) 0.5 mg will be injected at baseline, and at months 1 and 2. Following the three loading doses at baseline, patients will be invited for a follow-up visit one month later. Once visual acuity becomes stable and OCT demonstrates no evidence of edema, patients will no longer be given intravitreal injections and they will be invited to return 6 weeks later. The interval will be extended by 2 weeks for a maximum of 8 weeks for as long as the patient exhibits stable visual acuity, central retinal thickness and clinical findings. In the event of a negative change, the interval will be reduced back to 4 weeks.

5 ANALYZED POPULATIONS

The study population will include male and female patients (above 18 years of age) who were admitted with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c values not exceeding 12.0% at screening (Visit 1). Patients should be following a diet, exercise and/or pharmacologic therapy for diabetes mellitus and should have vision loss for focal or diffuse macular edema with central involvement in at least one eye as demonstrated by color fundus photography, fluorescein angiography and OCT over a period of 28 days prior to initial treatment. A total of 86 patients from 12 centers in Turkey are expected to be randomized. Because a screening failure rate of 20% is anticipated, 104 patients will be needed to be screened.

5.1. SAMPLE SIZE CALCULATION

A sample size of 86 patients (43 patients in each treatment arm) will provide 90% power to determine a non-inferiority margin of 5 letters between the treatment arms with a significance level of 0.025 for the test, and the mean (standard deviation) letter change of the prescribing information regimen arm will be approximately 7 (7). A 20% discontinuation rate is initially assumed in order to account for the missing data expected for a follow-up period of 1 year; thus, at least 104 patients (52 patients in each treatment arm) will be included in the study.

6 ANALYSIS PLAN

The number of attendance of the patients in each treatment group to visits and the total number of patients will be expressed as n and % in the table that should be available in the very beginning of the analysis.

6.1 DEMOGRAPHICS

- **Patients gender data**: Patients, male and female, in both treatment regimens will be expressed separately as n and %.
- **Patients age**: Patient age data for patients in the "Approved treatment regimen" and in the "Wait and extend treatment regimen" arms will be tabulated by calculating n, mean, standard deviation, minimum, maximum, median and 95% confidence interval.

  Patients will be grouped by age as 18-64 years, 65-84 years and ≥85 years, and patients in each age group will be listed as n and %.

6.2 STUDY EYE

Study eyes (Right Eye or Left Eye) of the patients randomized to either of the two treatment regimens will be listed as n and %.

6.3 MEDICAL HISTORY

Medical history before the written informed consent date and current medical conditions not related with the studied indication will be listed together with as n and % values.

6.4 VITAL FINDINGS

Patients' height (cm) and weight (kg) measurements will be tabulated providing descriptive statistics (n, mean, standard deviation, minimum, median, maximum and 95% confidence interval). Body Mass Index will also be calculated from height and weight variables using the Height /(Weight)^2 formula, and will be described again using descriptive statistics.

Systolic and Diastolic Blood Pressure (mm/Hg) measurements taken in the sitting position will be listed together with descriptive statistics.

These evaluations will be performed for 14 visits for the patient group receiving the "Approved Treatment Regimen" and for all visits to which the patients attend for the group receiving the "Wait and Extend" treatment regimen.

6.5 LABORATORY TESTS

Patients' HbA1C and Fasting Blood Glucose values will be listed for 14 visits for the patient group receiving the "Approved Treatment Regimen" and for all visits to which the patients attend for the group receiving the "Wait and Extend" treatment regimen, together with the descriptive statistics (n, mean, standard deviation, minimum, median, maximum and 95% confidence interval).

6.6 ASSESSMENT OF RENAL FUNCTION

Patients' Urea, Creatinine, Albumin, Total Protein and Uric Acid values will be collected at the first and fifth visits for patient groups receiving the "Approved Treatment Regimen" and "Wait and Extend" treatment regimen, and will be listed together with the descriptive statistics (n, mean, standard deviation, minimum, median, maximum and 95% confidence interval) for both visits for both treatment regimens.

6.7 ECG RESULTS

For both treatment groups, the number and percentage (n and %) of patients with normal and abnormal ECG results will be tabulated.

6.8 GENERAL OPHTHALMOLOGIC EXAMINATION

6.8.1 Biomicroscopic Evaluation

Frequency and percentage values for the right and left eyes evaluated using biomicroscopy will be listed for 14 visits for the patient group receiving the "Approved Treatment Regimen" and for all available visits for the patient group receiving the "Wait and Extend" treatment regimen. Lids, conjunctiva, cornea, iris, lens, anterior chamber and other assessments will be presented as percentage and frequency values for normal and abnormal assessments for both treatment arms and for both visits.

Frequency and percentage values for the right and left eyes evaluated using ophthalmoscopy will be listed for 14 visits for the patient group receiving the "Approved Treatment Regimen" and for all available visits for the patient group receiving the "Wait and Extend" treatment regimen.

The list of abnormalities identified with color fundus photography will be provided.

6.9 BCVA (BEST CORRECTED VISUAL ACUITY) – FROM 4 METERS WITH ETDRS

Descriptive statistics (n, mean, standard deviation, minimum, median, maximum and 95% confidence interval) for BCVA Test scores applied to both eyes will be tabulated for all 14 visits for the patient group receiving the "Approved Treatment Regimen" and until the last available visit for the patient group receiving the "Wait and Extend" treatment regimen. For both treatment groups, the change between the first and final visits will be compared using the t-test for paired sequences or Wilcoxon Signed Rank Test based on the fit of the data to normal distribution.

6.10 INTRAOCULAR PRESSURE (IOP) EXAMINATIONS

Descriptive statistics (n, mean, standard deviation, minimum, median, maximum and 95% confidence interval) for Intraocular Pressure values will be collected for all 14 visits for the patient group receiving the "Approved Treatment Regimen" and until the last available visit for the patient group receiving the "Wait and Extend" treatment regimen.

6.11 OPTICAL COHERENCE TOMOGRAPHY

The device used for OCT will be listed together with n and % values for both treatment arms. Frequency (n) and percentage (%) values for the options describing the results of intraretinal edema involving the macula (Yes, No, Not evaluated) will be tabulated for both groups. Type of the edema, if applicable, will also be tabulated using frequency and % values.

Descriptive statistics (n, mean, standard deviation, minimum, median, maximum and 95% confidence interval) for central thickness values for both eyes will be listed separately for each of the treatment arms.

Frequency (n) and percentage (%) values for the options describing subretinal fluid results (Yes, No, Suspected, Not evaluated) and the options describing results of vitreoretinal interface changes (Yes, No) will be tabulated for both eyes. Frequency (n) and percentage (%) values for the options, i.e. vitreoretinal traction, epiretinal membrane and macular hole will also be listed for patients with vitreoretinal interface changes.

6.12 FLUORESCEIN FUNDUS ANGIOGRAPHY (FFA)

For the results of FFA performed compulsorily at the first and month 12 visits and at investigator discretion during other visits, answers describing presence of diabetic macular edema (Yes, No) will be individually listed as frequency (n) and percentage (%) values for the right and left eyes in each of the treatment arms, and frequency (n) and percentage (%) values for the specified "Focal" and "Diffuse" options will be listed for those with the "Yes" answer.
Yes and No answers to macular ischemia and peripheral ischemia questions will be individually listed as frequency (n) and percentage (%) values for the right and left eyes in each of the treatment arms. For Yes, No and Suspected answers to another condition identified with FFA, frequency (n) and percentage (%) values will be tabulated, and the details provided for the Yes answers will be provided.
The rates of diabetic macular edema, macular ischemia, peripheral ischemia and other conditions identified with FFA will be compared during the first and month 12 visits using the Mc Nemar test.

6.13 CONCOMITANT MEDICATIONS / TREATMENTS

Yes or No answers to whether patients were receiving concomitant medications / treatments will be listed as frequency (n) and percentage (%) values for both treatment groups.
The medications used by the patients receiving concomitant medications / treatments will be grouped and listed.

6.14 EFFICACY EVALUATION

6.14.1 Visual Acuity

In order to demonstrate that the "wait and extend" regimen of ranibizumab is non-inferior to the posology described in the prescribing information, mean change in BCVA at month 12 from the baseline visit will be determined for both treatment groups, and a comparison will be made between the two groups using the Mann Whitney u test.
The number of patients with improvement in BCVA from baseline will be compared for the two treatment groups using the Chi-Square test (with Fisher's Exact Test where appropriate).
The number of patients with improvement of 5 or more letters from baseline will be compared for the two treatment groups using the Chi-Square test (with Fisher's Exact Test where appropriate).

The number of patients with improvement of 10 or more letters from baseline will be compared for the two treatment groups using the Chi-Square test (with Fisher's Exact Test where appropriate).

The number of patients with improvement of 15 or more letters from baseline will be compared for the two treatment groups using the Chi-Square test (with Fisher's Exact Test where appropriate).

6.14.2 Optical Coherence Tomography

The mean change from baseline to month 12 in Central Retinal Thickness determined with Optical Coherence Tomography for both eyes will be calculated for both groups and will be compared using the Mann Whitney u test.

6.14.3 Injection and Visits

The number of injections and visits required for a treatment period of 12 months with a "wait and extend" dosing regimen will be evaluated.

6.14.4 VFQ-25 Questionnaire Evaluation

Scores from the VFQ-25 questionnaire determined at the first and month 12 visits will be compared separately in the "Approved treatment regimen" and "Wait and extend" treatment regimen groups using the Wilcoxon Signed Rank Test.

6.15 SAFETY ASSESSMENT

6.15.1 Adverse / Serious Adverse Events

The list of the Adverse / Serious Adverse Events (SAE) reported in each visit will be provided. All adverse events will be examined regarding the visits they occurred, severity (mild, moderate, severe), relationship with the drug (suspected, not suspected), outcome (continuing, resolved), actions taken (no action taken, dose adjusted/dosing interrupted, additional treatment given, non-pharmacological treatment given, hospitalized), additional treatments if applicable, time between hospitalization and discharge dates, and length of hospital stay.