STATISTICAL ANALYSIS PLAN

SAP VERSION:	Final 1.0
SPONSOR:	Aurobindo Pharma Research Center-II Survey No -71 & 72, Indrakaran Village, Kandi Mandal, Sangareddy, Dt Telangana -502329, India, Tel. no: +91-40-8455223700 Ext-1516
STUDY TITLE:	A randomized, multiple -dose, double blind, placebo controlled, parallel group, multicentric study to evaluate Efficacy and Safety of Beclomethasone Dipropionate Metered Dose Inhaler (Inhalation aerosol) (0.04mg/INH) in male and /or female subjects with Asthma • Group I (Test): Beclomethasone Dipropionate 0.04 mg/INH; • Group II (Reference): QVAR® 40 mcg (Beclomethasone dipropionate HFA); and • Group III: Placebo
Investigational Product:	Beclomethasone Dipropionate Metered Dose Inhaler (Inhalation Aerosol) (0.04 mg/ INH); Manufactured by: Aurolife, a subsidiary of Aurobindo Pharma, USA, Inc., 2929 Weck Dr., Durham, NC 27709.
Reference Product:	QVAR® 40 mcg (Beclomethasone dipropionate HFA), Inhalation Aerosol; Marketed by: Teva Pharmaceuticals LLC Frazer, PA 19355. NDC code: 59310-202-12
Placebo Product:	Placebo Metered Dose Inhaler; Manufactured by: Aurolife, a subsidiary of Aurobindo Pharma, USA, Inc., 2929 Weck Dr., Durham, NC 27709.
Study Phase:	Clinical Pharmacodynamic BE Study
PROTOCOL NUMBER:	CR176-17
PROTOCOL VERSION/DATE:	Version 1.0 Amendment 02 Dated 07.08.2019

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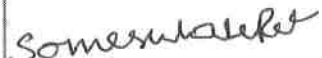
Reviewed By: Dr.Someswara Rao.K Sr. General Manager, Pharmacokinetics and Biostatistics AXIS Clinicals Ltd, 1-121/1, Miyapur, Hyderabad, 500049, India Telephone: +91 40 4040 8064 FAX – 91-40-4040 8060		23/10/19.
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1. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDP	Beclomethasone dipropionate
BMI	Basal Metabolic Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
EOS	End of Study
ECRF	Electronic Case Report Form
FDA	Food and Drug Administration
FeNO	Exhaled Nitric Oxide
FEV1	Forced expiratory volume in 1 second
HBsAg	Hepatitis B Surface Antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS'S	Inhaled corticosteroids
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
LOCF	Last Observation Carried Forward
MDI	Metered-Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	modified Intent-to-Treat
mL	Milliliter
PEF	Peak expiratory flow
PFT	Pulmonary Function Test
PI	Principal Investigator
PP	Per Protocol
RBC	Red blood cell count
RLD	Reference listed drug

SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
US/USA	United States of America
UAE	Unexpected Adverse Events
WBC	White blood cell count

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to outline in detail the statistical methods, data derivations, and presentations of data so that valid conclusions can be reached to address the study objectives outlined in the CR176-17 Protocol Amendment 02 Dated 07.08.2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the protocol. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

2.1. Responsibilities

Inductive Quotient will perform the statistical analyses for all clinical data collected.

Inductive Quotient is responsible for production and quality control of all datasets, tables, figures, and listings.

2.2.Timing of Analyses

Final analysis will be done by Inductive Quotient after receipt of the final data from AXIS. Any additional tables required by the regulatory or sponsor also will be undertaken in this SAP.

3. STUDY RATIONALE

Aurobindo Pharma, India, is seeking marketing approval for Beclomethasone Dipropionate Metered Dose Inhaler (0.04 mg/INH) in USA, for which demonstration of equivalence in efficacy to a reference QVAR® 40 mcg (Beclomethasone dipropionate hydrofluoroalkane) is required; therefore an appropriate comparability exercise is required to demonstrate that the similar therapeutic benefit with that of reference medicinal products in terms of quality, safety and efficacy is achieved and superiority in efficacy to that of placebo.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Primary Objective

- To compare the therapeutic equivalence of Beclomethasone Dipropionate MDI (Inhalation Aerosol) 0.04 mg/ INH, with the marketed QVAR® 40 mcg (Beclomethasone dipropionate hydrofluoroalkane (HFA) and to demonstrate the superiority of both active treatments compared to placebo.

4.2. Secondary Objective

- To assess the safety and tolerability of Beclomethasone Dipropionate Metered Dose Inhaler (Inhalation Aerosol) (0.04 mg/ INH).

4.3. End points

4.3.1. Efficacy

- **Primary Endpoint**: Mean change in Forced Expiratory volume in 1 second (FEV 1) from baseline (visit 3) to end of study visit (visit 5).
- **Secondary Endpoints:**
  - Mean change in FeNO value from baseline (visit 1 and visit 3) to end of study visit (visit 5)
  - Percentage of subjects with reduction of FeNO from Baseline (visit 1 and visit 3) to End of Study (Visit 5)

4.3.2. Safety

- Safety will be assessed on the basis of reported adverse events, serious adverse events and laboratory assessments.

5. STUDY DESIGN

This is a randomized, multiple dose, double blind, placebo-controlled, parallel group, multicentric study to evaluate the Efficacy and Safety of Beclomethasone Dipropionate (0.04 mg/ INH) Metered Dose Inhaler in male and/ or female subjects with Asthma [Group I (Test): Beclomethasone Dipropionate 0.04 mg/ INH; Group II (Reference): QVAR® 40 mcg (Beclomethasone dipropionate HFA), Inhalation Aerosol; and Group III: Placebo].

A total of five visits are scheduled in this study.

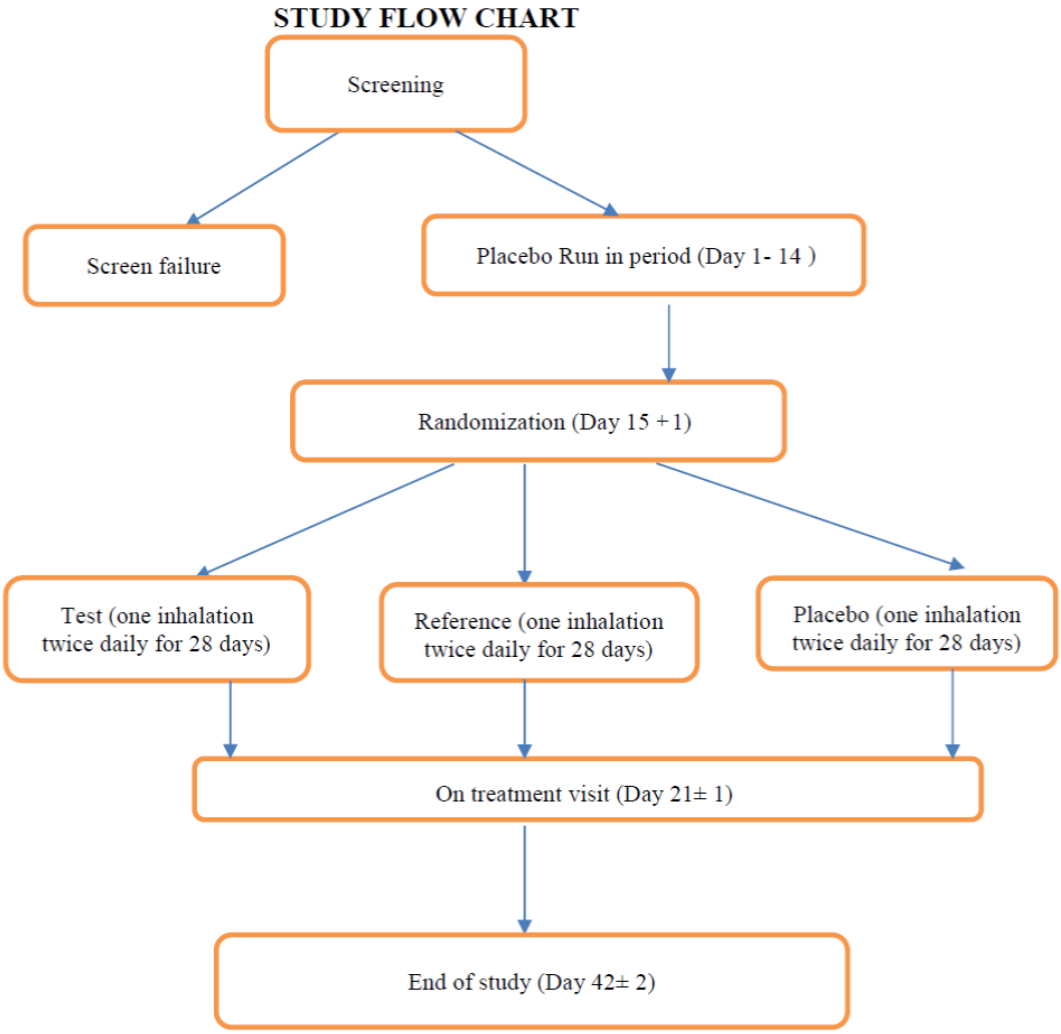
- Visit 1 Screening (Day -7 to Day -1),
- Visit 2**.** Day 0
- Visit 3. Randomization (Day 15 + 1),
- Visit 4. On-treatment visit (Day 21 ± 1)
- Visit 5. End of Study visit (Day 42 ± 2).

All subjects will be reported to the study site for screening. Subjects with asthma diagnosed as per National Asthma Education and Prevention Program at least 12 months prior will be briefed about the study and Informed Consent Form will be obtained. An exhaled nitric oxide (FeNO) test will be performed. If FeNO is < 25 ppb, those subjects will not be screened further. Pulmonary function test (PFT) by spirometer will be performed. After completion of the required screening tests and procedures, subjects meeting all the inclusion criteria and none of the exclusion criteria will be asked to visit the study site for run-in period. Subjects will be provided with placebo metered dose inhaler in the run-in period and will be advised to take one inhalation twice daily for two weeks. Subjects will be provided with subject diary and rescue medication (Salbutamol) with detail instructions regarding filling of subject diary and usage of rescue medication (Salbutamol).

Subjects will be required to visit on Day 15 + 1 and those subjects who completed the placebo run period and met the applicable eligible criteria will be randomized. An exhaled nitric oxide (FeNO) test will be performed on day 15 + 1. Pulmonary function test (PFT) by spirometer will be performed. Airway reversibility will be checked. According to the randomization scheme, subjects will be supplied with the study medication (either Test or Reference or Placebo in 2:2:1 ratio as per the randomization schedule) along with diary card with instructions regarding filling of subject diary.

Subjects will be advised to take one inhalation twice daily for 4 weeks in the morning and evening, preferably on the same time period during the entire treatment period. Subjects need to report to the Investigator site on day 21 ± 1 and 42 ± 2. At these visits (Visit 4 and Visit 5), efficacy and safety evaluation will be done. At the EOS visit (Visit 5), subjects will go through all the end of study evaluation procedures, as outlined in the Table of Events (**Table I**). They will be clinically evaluated for the assessment of the efficacy parameters and Investigator's Global Evaluation Score.

At every study visit, all the procedures mentioned in the Table of events (Table I) will be carried out. Safety assessments (reporting of adverse events and serious adverse events if any, clinical laboratory measures and vital sign parameters) will be performed and any change in concomitant medications will be noted at all the scheduled visits.



Note: After Placebo Run-in Period, subjects will be randomized either to test/ reference/ placebo if they fulfil the eligibility.

5.1. Schedule of Assessments (Table I)

Procedure	Screening Period		Run-in Period	Treatment Period		End of Study
	-7 days	Day 0	Day 1 to Day 14	Day 15 + 1	Day 21±1	Day 42±2
Visit	**1**	**2**	**--**	**3**	**4**	**5**
Informed consent	X	--	--	--	--	--
Eligibility criteria	X	--	--	X	--	--
Demography	X	--	--	--	--	--
Medical and Medication History[1]	X	--	--	--	--	--
General & Systemic Examination[2]	X	X	--	X	X	X
Vital signs[3]	X	X	--	X	X	X
Serum Pregnancy Test (for females of child bearing potential)	X	--	--	--	--	--
Urine Pregnancy Test (for females of child bearing potential)	--	--	--	X	--	X
Clinical Laboratory Test[4]	X	--	--	--	--	X
12 lead ECG	X	--	--	--	--	--
Chest X-Ray (PA view)	X	--	--	--	--	--
FeNO Estimation	X	--	--	X	--	X
FEV1 value recording (through Spirometry)	X	X	--	X	X	X
Bronchodilator/ Reversibility test	--	--	--	X	--	--
Placebo Canister Dispensing (for Run-in period)	--	X	--	--	--	--
Collection of Placebo Canister given in run-in Period	--	--	--	X	--	--
Rescue Medication Dispensing	--	X	--	X	--	--
Collection of rescue medication canister	--	--	--	X	--	X
Subject Diary Card Dispensing	--	X	--	--	--	--
Placebo Administration (in Run-in Period)	--	--	One inhalation two times daily from Day 1 to Day 14	--	--	--
Subject Diary Card Compliance	--	--	--	X	X	X
Placebo administration compliance (Run-in- Period)	--	--	--	X	--	--
Randomization	--	--	--	X	--	--
Study Drug Dispensing (for Treatment period)	--	--	--	X	--	--
Study Drug Administration	--	--	--	One inhalation two times daily from Day 15 to Day 42		

Procedure	Screening Period		Run-in Period	Treatment Period		End of Study
	-7 days	Day 0	Day 1 to Day 14	Day 15 + 1	Day 21±1	Day 42±2
Visit	**1**	**2**	**--**	**3**	**4**	**5**
Collection of Study Drug Canister	--	--	--	--	--	X
Collection of Subject Diary	--	--	--	--	--	X
Concomitant Medication Check	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X
Asthma Control Test Questionnaire	--	--	--	X	--	X
Investigator's Global Evaluation	--	--	--	X	--	X

[1]Medical and medication history will be performed at screening visit only.
[2]General and Systemic examination includes head, neck, eye, ear, nose, throat, skin & appendages, renal, cardiovascular, pulmonary, reproductive, endocrine, gastrointestinal, nervous system, musculo-skeletal, peripheral vascular and psychiatric.
[3]Vital signs include: blood pressure (supine), respiration rate, pulse rate and body temperature in $^0F/^0C$.
[4] Haematology panel includes haemoglobin, haematocrit, white blood cell count with differential cell count, red blood cell count and platelets. Serum chemistry panel will include blood urea nitrogen, creatinine, albumin, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase random blood sugar, sodium, potassium, and chloride. Serum pregnancy test (for females of child bearing potential) will be done at screening only.

6. INCLUSION & EXCLUSION CRITERIA

Inclusion criteria

1. Adult male or female subjects of aged ≥18 to ≤ 65 years inclusive.
2. Diagnosis of asthma as defined by the National Asthma Education and Prevention Program at least 12 months prior to screening.
3. Pre-bronchodilator FEV1 of ≥ 45% and ≤ 85% of predicted value during the screening visit and on the first day of treatment visit.
4. ≥15% and > 0.20 L reversibility of FEV1 within 30 minutes following 360 mcg of Salbutamol inhalation (pMDI) on the first day of treatment visit.
5. Subjects with FeNO > 25 ppb at screening and on the first day of treatment visit.
6. Subjects stable on their chronic asthma treatment regimen for at least four weeks prior to enrollment.
7. Subject should able to replace current SABAs with Salbutamol inhaler for use as needed for the duration of the study.
8. Subject should be able to withhold all inhaled SABAs for at least six hours prior to lung function assessments on study visits.

9. Ability to discontinue their asthma medications (inhaled corticosteroids and long-acting β agonists) during the run-in period and for remainder of the study.
10. Asthma patients who are stable on low dose ICS or low dose ICS+LABA or who would be stable with low dose ICS as per Investigator's clinical judgement.
11. Currently non-smoking; had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having had ≤ 10 pack-years of historical use.
12. Willingness to give their written informed consent to participate in the study.
13. Subjects willing to perform all study related procedures including the use of study inhalers, Spirometry and willing to complete the Subject diary.
14. Female of child-bearing potential, agreed to use a reliable method of contraception during study (e.g., condom + spermicide, IUD, oral, transdermal, injected or implanted hormonal contraceptives).

Exclusion criteria

1. Life-threatening asthma, a history of asthma episodes(s) requiring intubation, and/or associated with hypercapnia, respiratory arrest or hypoxic seizures, asthma related syncopal episode(s).
2. Hospitalizations within the past year prior to the screening for the conditions mentioned in exclusion criteria No.01 or during the run-in period.
3. Significant respiratory disease other than asthma (COPD, interstitial lung disease, etc.)
4. Evidence or history of clinically significant disease or abnormality including congestive heart failure, uncontrolled hypertension
5. Evidence or history of clinically significant disease or abnormality including uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia.
6. Historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, or other diseases that, in the opinion of the investigator, would put the subject at risk through study participation, or would affect the study analyses if the disease exacerbates during the study.
7. Viral or bacterial, upper or lower respiratory tract infection, or sinus, or middle ear infection within four weeks prior to the screening, during the run-in period, or on the day of treatment.
8. Hypersensitivity to Beclomethasone or any of the ingredients of the formulation and any sympathomimetic drug (e.g., Salbutamol) or any inhaled, intranasal, or systemic corticosteroid therapy.
9. Subjects receiving β2-blockers, anti-arrhythmics, anti-depressants, and monoamine oxidase inhibitors within 4 weeks prior to the screening.
10. Subjects who required systemic corticosteroids (for any reason) within the past 2 months.
11. Clinically significant abnormalities in ECG at screening as per investigators discretion.
12. Female subjects who are pregnant, nursing or planning a pregnancy during the study.
13. Subjects who have participated in another investigational drug or device research study within 30 days of screening.

14. Subjects who are using any medication or has any disease which in the judgment of the Investigator will interfere with the conduct or interpretation of the study.

7. STUDY TREATMENTS

- **Group I: Investigational Product:** Beclomethasone Dipropionate Metered Dose Inhaler (Inhalation Aerosol) (0.04 mg/ INH); Manufactured by: Aurolife, a subsidiary of Aurobindo Pharma, USA, Inc., 2929 Weck Dr., Durham, NC 27709.

- **Group II: Reference Product:** QVAR® 40 mcg (Beclomethasone dipropionate HFA), Inhalation Aerosol; Marketed by: Teva Pharmaceuticals LLC Frazer, PA 19355. NDC code: 59310-202-12

- **GROUP III: PLACEBO –** Manufactured by: Aurolife, a subsidiary of Aurobindo Pharma, USA, Inc.2929 Weck Dr., Durham, NC 27709

  Subjects will receive one inhalation of Study medication (either Test/ Reference/ Placebo) twice daily.

7.1. Method of Assigning Subjects to Treatment Groups

This study will be double blind randomized parallel group study with three arms: Reference Formulation, Test Formulation, Placebo formulation. Randomization will be in 2:2:1 proportion. The potential total enrolled sample size will be 1550 subjects [(620 (Test): 620 (Reference): 310 (Placebo)]. The subjects will be assigned to the placebo or active groups as per a predetermined randomization schedule. The actual treatment given to individual subject will be determined by a randomization scheme prepared by third party. Randomization will be done after completion of placebo run in period.

An IWRS (Interactive Web Response System) will be used to administer the randomization schedule. The programming, validation and monitoring of the randomization process by IWRS will be guided by the applicable SOPs of the IWRS vendor. In practice, the investigator or designee will use the IWRS system to receive the dosing formulation (test/reference/ placebo) for the subject.

7.2. Blinding

This study is double-blinded. The treatment allocation information was concealed from the study personnel (Principal Investigator, sponsor, and laboratory staff) and the subjects.

8. Sample Size Justification

Computer simulations (100,000 trials/subject number evaluated) were performed using Statistics101: Resampling Simulator Version 4.6 (John Grosberg, stats101@statistics101.net) assuming that approximately 80% of ITT subjects would also qualify as PP. The proportion of the trials where the 90% confidence interval on the Test-to-Reference ratio was within the interval 0.80 to 1.25 in the PP population was considered the power for Bioequivalence for the subject number evaluated. Likewise, the proportion of trials where both the Test and Reference means were greater than, and statistically different from ($p < 0.05$, 2-sided), that of the placebo in the mITT population was considered the power for Superiority for the subject number. The proportion of the trials that demonstrated both Bioequivalence in the PP population and Superiority in the mITT population was considered the power for study success. The results of these simulations are provided in the following table. Change from baseline in FEV1 for Test, Reference and Placebo was considered to be 0.24 L, 0.24 L and 0.05 L respectively. These considerations are based upon results of study 1081 mentioned in the Summary Basis of Approvals for QVAR®. Coefficient of Variation for Mean change from baseline in FEV1 value was assumed to be 115.5% of the Reference Mean.

mITT subjects (Test: RLD: Placebo)	**PP Subjects** (Test: RLD: Placebo)**	**Power Bioequivalence**	**Power Superiority**	**Power Study Success**
588:588:294 (1470)	470:470:235 (1175)	0.80	>0.99	0.80

Based upon calculations shown in table above, a sample size of 1470 subjects in mITT population (588:588:294 subjects in Test: RLD: Placebo respectively) with 1175 in the PP population (470:470:235) will have 80 % power to demonstrate both bioequivalence between the two active treatments and to show that each of these are superior to placebo.
Randomization schedule will be generated using appropriate software package.

9. DATA COLLECTION

All subject data will be captured in the subject source documents which will be transcribed to the eCRFs. The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials.

10. ANALYSIS POPULATIONS

10.1. Safety

The Safety population will include all randomized subjects who received at least one dose of investigational study treatment during the double blind treatment period.

10.2. ITT Population

All the randomized patients will be included in intent to treat population (ITT).

10.3. mITT Population

The mITT population will include all randomized subjects who met all inclusion/exclusion criteria, and received study treatment, and having at least one post baseline efficacy assessment. Missing efficacy results in the mITT population will be imputed using last observation carried forward (LOCF). The mITT population will be used to compare both test and reference products for superiority over placebo.

10.4. Per Protocol Population

The PP population will include all randomized subjects who meet all inclusion/exclusion criteria and are found to be compliant with the assigned study treatment, who return to the study site for the primary endpoint visit at 4 weeks (+/- 7 days) OR discontinue from the study as a treatment failure, or no clinical benefit and do not have any major protocol deviation impacting efficacy outcome. The PP population will be used for the bioequivalence evaluation of test vs. reference. Subjects who used at least 75% and no more than 125% of study treatment doses will be considered be compliant to study medication. Compliance will be assessed based upon diary data for study drug administration. Protocol deviations will be classified as major (impacting efficacy assessment) or minor, prior to database lock using blinded study data by study personnel who are not aware of treatment assignments.
Protocol deviation classification and individual subject's assignment to analysis population will be finalized before un-blinding of data. Summary of subjects with Major vs minor Protocol deviations will be provided along with listing.

10.5. Procedure for Accounting for Missing Data

Missing efficacy results in the mITT population will be imputed using last observation carried forward (LOCF). The mITT population will be used to compare both test and reference products for superiority over placebo.

If subject discontinued due to lack of efficacy and does not have a post baseline value, then subject will be included in mITT population with baseline value carried forward.

Subjects discontinued early for reasons other than lack of efficacy will be excluded from the PP population but included in the mITT population. Subjects discontinued early for lack of efficacy will be included in the PP population, using LOCF imputation for missing efficacy results. The PP population will be used to compare test and reference products for equivalence.

11. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

The following general rules will be followed for the analysis specified in this SAP.

Quantitative variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max) and coefficient of variation (CV).

Qualitative variables will be summarized using counts and percentages.
Baseline value will be defined as the last non-missing measurement (scheduled or unscheduled) prior to the initiation of randomized study treatment. In most cases, this will be data from Visit 1.

Unscheduled visits: Subject data obtained during unscheduled visits/assessments will not be summarized but will be included in subject data listings only; except for the analysis of maximum values and maximum changes from baseline. Unscheduled visit values will not be used to impute missing scheduled visit values, except for baseline calculation.

Coding: For summarization, medical history, concurrent therapies, and AEs will be coded to the latest versions of MedDRA and WHO Drug dictionaries, as appropriate.

12. STATISTICAL ANALYSIS

12.1. Subject Disposition

The total number of randomized subjects, subjects who completed the study, subjects who discontinued from the study with reason of discontinuation will be summarized by treatments and overall.
Inclusion and Exclusion criteria will be presented in listing format for all subjects.

12.2. Demographic and Baseline Characteristics

Demographic information collected at screening will be summarized descriptively for the randomized population, including Box plots and frequency distributions.

Variables summaries (for all data collected) will be presented. Demographic and baseline characteristics will also be presented by site.

12.3. Protocol Deviations and Protocol Waivers

Investigator will conduct this study in accordance with protocol approved by IEC and DCGI.

In case of all deviations, investigator shall document all the deviations and notify same to EC which accorded approval for the study.

The Protocol violations list will be finalized.

12.4. Analysis of Efficacy Data

12.4.1. Primary Efficacy

Analysis will be carried out with FEV1 original values as given below

1. FEV1 values at baseline, and FEV1 EOS values will be used in the analysis

Mean change in Forced Expiratory volume in 1 second (FEV 1) from baseline (visit 3) to end of study visit (visit 5), will be analyzed as primary end value point.

Note: “Baseline morning FEV1 readings at visit 3 will be the average of pre dose highest FEV1 values at two time points (i.e., Patient needs to perform one baseline Spirometry session with minimum of 3 acceptable readings and then after a gap of minimum 30 minutes, one more baseline session will be performed with minimum of 3 acceptable readings. Highest value from both the sessions will be noted. Average of both the highest readings will be considered as baseline FEV1 value). Sampling need to be taken on the same time (with a window period of

± 30 min) of day as used for first day of a 4 week treatment on the last day of a 4-week treatment.

First 76 patients who enrolled into the study prior to protocol waiver dated 17/04/19 will not be considered for efficacy conclusion. Data with inclusion of 76 subjects will be provided as an additional information. This data will not be considered for PP population and will be considered in mITT population.

Primary Analysis

The primary endpoint is the change from baseline to week 4 for FEV1. The statistical evaluations for this endpoint are described below.

Equivalence

Compound Hypothesis to be tested is H0: $\mu T / \mu R \leq 0.80$ or $\mu T / \mu R \geq 1.25$ versus
HA: $0.80 < \mu T / \mu R < 1.25$

(or)

H01: $\mu T - \mu R < -0.20$ Versus HA1: $-0.20 \leq \mu T - \mu R$ (The lower tail)
H02: $\mu T - \mu R > 0.20$ Versus HA2: $\mu T - \mu R \leq 0.20$ (The upper tail)

Where μT = mean of test treatment, and μR = mean of reference treatment

Analysis of covariance (ANCOVA) will be used to evaluate the mean change in FEV1 at week 4, for the test and reference treatments using baseline FEV1 as a covariate and treatment and clinical site as factors. The 90% confidence interval will be computed based on the results from the ANCOVA. The 90 % confidence interval on the test-to-reference ratio must contain within the interval 80.00% to 125.00% for the test product to be considered equivalent to the reference product.

1. When the null hypothesis H0 is rejected at 5 % level of significance bioequivalence will be claimed by the 90% C.I lies between 0.8 to 1.25 (for ratio)
2.When the null Hypothesis H01 and H02 are rejected at 5% level of significance, bioequivalence will be claimed by the 90% C.I lies between -0.2 to 0.20 (Change Mean difference).

Superiority

Hypothesis is to be tested is

$H0: \mu_T - \mu_P \leq 0$
$HA: \mu_T - \mu_P > 0$

and

$H0: \mu_R - \mu_P \leq 0$
$HA: \mu_R - \mu_P > 0$

where
μ_T = mean of test treatment
μ_R = mean of reference treatment
μP = mean of placebo treatment.

Analysis of Covariance will be used to compare each active(test/reference) treatment with placebo using Baseline FEV1 as covariate and clinical site and treatment as factor. If the active treatment shows a greater increase in FEV1 from baseline than that for the placebo, and the difference between it and the placebo is statistically significant ($p<0.05$), and the lower limit of the difference should be greater than 0, then the active treatment will be considered superior to placebo. Superiority must be shown for both active treatments over placebo for the equivalence evaluation between the test and reference treatments to be considered valid.

12.4.2. Secondary Efficacy Variables

- Mean change in FeNO value from baseline (visit 1 and visit 3) to end of study visit (visit 5)
- Percentage of subjects with reduction of FeNO from Baseline (visit 1 and visit 3) to End of Study (Visit 5)
  Descriptive Summary statistics will be presented for all secondary endpoints for active treatment groups. Number and percentage of subjects meeting the criteria for reduction (at least 20 % for FeNO ≥ 50 ppb values and at least 10 % for FeNO < 50 ppb) in FeNO will be presented.

12.5. Safety Analysis

All safety analysis will be run on the safety population as described in section 10.1(Safety).

12.5.1. Adverse Events

Number of events and numbers and proportions of study subjects experiencing AEs will be tabulated by treatment arm received and overall. AEs and SAEs will be classified according to the MedDRA [22.0] or upgraded version (Medical Dictionary for Regulatory Activities) system and summarized by system organ class and preferred term. SAEs and drug related AEs will also be tabulated separately by treatment arm.

The proportions of subjects experiencing at least one adverse event will be compared between treatment arms using a Chi-square or Fisher exact test.
AEs will be summarized for different time period: Immediate AEs

- AEs will also be summarized by site. Inferential statistics will be used to compare proportions between treatment arms only for treatment period but not for baseline day 0 and run in period.

12.6. General and Systemic Examination

A subject wise listing displaying abnormal results of general and systemic examination will be provided, displaying body system, the abnormality for the safety population.

12.7. Medical History

Medical history will be classified by System Organ Class (SOC) and Preferred Term (PT) for the mITT population and will be summarized using counts and percentages. A subject-wise listing of medical history will be presented.

12.8. Vital Signs

Descriptive statistics will be displayed for all the vital signs for the respective visits. Vital signs data will be summarized by presenting summary statistics of actual values and change from baseline values by visit. A subject-wise listing displaying results of vital signs assessments will also be provided.

12.9. Prior and Concomitant Medication

Subject wise Listings will be provided for Prior and concomitant medications.

12.10. 12 Lead electrocardiogram & Chest X-Ray (PA View)

A subject wise listing will be provided for abnormal 12 Lead ECG and Chest X Ray results.

12.11. Laboratory Investigations: Hematology and Serum Chemistry Panel

Descriptive statistics will be displayed for all the laboratory parameters for the respective visits. A subject wise listing will be provided for normal and abnormal laboratory parameters.

12.12. Treatment Compliance

Compliance will be assessed by the data obtained from subject diary. This will be recorded in the eCRF.

Treatment compliance will be assessed on the basis of diary cards with following formula

$$\frac{\text{(Number of doses administered) x 100}}{\text{Number of expected doses}}$$

Compliance will be presented as subjects who have taken approximately 75% to 125% of the doses of the assigned study drug.

13. DEFINITIONS

For this study, the following definitions are used:

1.Screen Failures: Patients entered into the study are those from whom informed consent for the study has been obtained. Patients entered into the study but not assigned to a treatment group are considered to be screen failures.

2.Randomized: Patients who are enrolled in the study are those who have been assigned to a treatment group.

3.Multiple Comparisons and Multiplicity:

There is one primary efficacy endpoint in this study, will be tested at a significance level of 0.05. Covariate adjustments for primary endpoints will be made.
Nominal 2-sided p-values will be reported for primary efficacy endpoint.

4. Data Handling Conventions

"End of treatment" will refer to the subject's last dose visit or early termination visit.
"End of study" will refer to the subject's visit 5 or early termination visit.

4.1. Early Termination and Missing Data:

If possible, data for subjects who terminated the study early will be collected at the scheduled visit.

Missing post baseline efficacy values will be imputed using last observation carried forward (LOCF). Missing baseline values and missing safety data will not be imputed

14. TITLES OF MOCK SHELLS

Attached document **PDF:** Beclomethasone_ Mock TLFs v1 1 23-10-2019.pdf
WORD: Beclomethasone_ Mock TLFs v1 1 23-10-2019.docx

15. APPENDIX: ANALYSIS PRESENTATION CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS® program name, including the path that generates the output;
3. Any other output specific details that require further elaboration.

In general, row entries in tables are made only if data exists for at least one subject (i.e., a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.
The treatment and subject number will be included in all data listings. All listings will be sorted by study treatment, subject number, and visit date, as applicable. Subject listings will also include the number of days relative to the initial exposure to the study drug, if applicable.
This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

• The number and percentage of responses will be presented in the form XX (XX.X%).
• All summary tables will include the analysis population sample size (ie, number of subjects).
• Date variables will be formatted as DDMMMYYYY for presentation.
• SAS® Version 9.4 or higher will be the statistical software package used for all data analyses, except for the interim analysis where SAS Version 9.1.3 or higher will be used.

16. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.
2. Protocol: CR176-17 Version 1.0, Version 1.0 Amendment 02 Dated 07.08.2019