CLINICAL TRIAL PROTOCOL

Protocol 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]
Protocol Number:	CR176-17
Version & Date of Protocol:	Version 1.0, Amendment 02 Dated 07.08.2019
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
Study Phase:	Clinical Pharmacodynamic BE Study
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,
CRO:	AXIS Clinicals Ltd 1-121/1, Miyapur Hyderabad 500049, India Telephone: +91 40 4040 8064 FAX – 91-40-4040 8060

PROTOCOL SYNOPSIS

Name of Sponsor/ Company:	Aurobindo Pharma, India	**For National Authority Use Only**
Name of Finished Product:	Beclomethasone Dipropionate MDI 0.04 mg/ INH	
Name of Active Ingredient:	Beclomethasone	
Protocol No and version:	CR176-17 and Version 1.0, Amendment 02	
Study centers:	Approximately 40 centers across India	
Study duration: 52 Days	Clinical Pharmacodynamic BE Study	
Objectives:	**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 superiority of both active treatments over placebo. **Secondary Objective:** The secondary objective is to assess the safety and tolerability of Beclomethasone Dipropionate Metered Dose Inhaler (Inhalation Aerosol) (0.04 mg/ INH)	
Study Population	Male and female subjects aged ≥ 18 years and ≤ 65 years diagnosed with Asthma for at least 12 months prior to screening.	
Methodology:	1. 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 (Inhalation Aerosol) in male and/ or female subjects with Asthma. 2. The study is divided into 3 periods: Screening period (7 days), Run-in period (up to 14 days) and Treatment period (28 days). 3. A total of five visits to the Investigator site are scheduled; Screening Visit (Day -7 to Day -1), visit 2 on Day 0 for start of run in period, Randomization visit (Day 15 + 1), On-treatment visit (Day 21 ± 1) and End of Study/ EOS Visit (Day 42 ± 2). 4. The total duration for a study subject will be approximately 52 Days including 7 days of screening, 14 days of run-in period with one day of window period, 28 days of treatment period and two days of window period. 5. On Visit 1 (Screening visit), subjects with asthma diagnosed as per National Asthma Education and Prevention Program at least 12 months	

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prior will be briefed about the study and Informed Consent Form will be obtained from the subjects. After signing of the ICF, an exhaled nitric oxide (FeNO) test will be performed. Subjects will not be considered for further screening procedures, if FeNO is < 25 ppb.

6. Subjects will undergo pulmonary function test (PFT) through spirometer and those subjects with FEV1 of ≥ 45% and ≤ 85% of predicted value will undergo further screening procedures.

7. On Visit 2 (Day 0), after completion of screening procedures, eligible subjects will be advised to start the placebo run-in period of 14 days with one day of window period. Subjects will be provided with placebo metered dose inhaler and advised to take one inhalation twice daily during entire course of run in period.

8. Subject diary and rescue medication (Salbutamol) will also be dispensed to the subjects and detailed instructions will be provided regarding filling of subject diary and usage of rescue medication and placebo. FEV1 will be measured by Spirometry on this visit. Highest FEV1 will be considered from the 3 acceptable readings in this session for inclusion into study.

9. On Visit 3 (Day 15+1), subjects will be instructed to bring subject diaries and study medication (placebo and rescue medication) for reconciliation by the study team. The subject diary entries will be checked to ensure compliance. Usage of the placebo medication will be cross verified through the subject diary entries.

10. An exhaled nitric oxide (FeNO) test will be performed followed by Asthma Control Test (ACT) questionnaire evaluation in this visit.

11. Subjects' baseline FEV1 readings by performing Spirometry (average of pre dose highest FEV1 values at two time points- 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.

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Highest value from both the sessions will be noted. Average of both the highest readings will be considered as baseline FEV1 value) will be noted. The baseline score for the Investigator's Global Evaluation will be recorded.

12. Subjects airway reversibility will be checked by performing a bronchodilator test wherein the initial baseline lung volume is measured by spirometer followed by administration of 360 mcg (90 mcg X 4 puffs at intervals approx.10 sec to 15 sec between each puff) of Salbutamol inhalation and then a repeat lung volume measurement by spirometer within 30 minutes of Inhalation of Salbutamol.

13. Only subjects with ≥ 15 % and > 0.20 L reversibility of FEV1 at the time of first day of treatment visit will be considered for treatment period.

14. Subjects who meet the applicable Inclusion and Exclusion criteria will be randomized to either of the Test/ Reference/ Placebo groups in a 2:2:1 as per the pre-specified randomization schedule. Subjects will receive their assigned study medication, along with instructions regarding method of administration. All subjects are required to take one inhalation of the assigned study medication two times daily for 4 weeks.

15. The first dose of study medication will be administered to the subject at the site in the morning and the second dose will be self-administered by the subject in the evening at his/ her home and the subject will be advised to take one inhalation twice daily during the 4 weeks treatment period. Study medication, rescue medication (Salbutamol) and subject diary will be dispensed to the subject.

16. Subjects need to return for Visit 4 (Day 21 ± 1). The predose FEV1 readings will be taken. Highest FEV1 will be considered from the 3 acceptable readings in this session.

17. Also, measurement of vital signs, general and systemic examination and AE monitoring will be done. Compliance of subject dairy and concomitant medication will be checked.

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	18. Subjects need to return for Visit 5 (Day 42 ± 2: End of Study/EOS). FEV1 will be measured in the morning prior to the dosing of inhaled medications on this day at the same time (with a window period of ± 30 min) as that of the baseline reading on Visit 3. Two sessions with at least 3 acceptable readings each will be performed. Highest value from both the sessions will be noted. Average of both the highest readings will be considered as EOS FEV1 value. 19. An exhaled nitric oxide (FeNO) test will be performed. The Asthma Control Test (ACT) questionnaire will be evaluated and the Investigator's Global Evaluation will be performed. Also, measurement of vital signs, general and systemic examination, concomitant medication recording and AE monitoring will be done. Urine Pregnancy Test (for females of child bearing potential) will be done. Clinical laboratory tests will be repeated to check safety of subjects before they are discharged from the study. 20. The subjects are required to submit their issued study drug container, rescue medication and subject diaries for compliance checking.
Number of subjects	Assuming 5% loss from enrolled population to mITT population, 1550 subjects will be enrolled in this study. Subjects will be enrolled in 2:2:1 proportion as 620:620:310 (Test: RLD: Placebo respectively).
Diagnosis and main criteria for inclusion and Exclusion:	**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.

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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

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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

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	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.
Investigational and Reference Product, dose and mode of administration:	**Group-I (Test):** Beclomethasone Dipropionate Metered Dose Inhaler (0.04 mg/ INH) Manufactured by: Aurolife, a subsidiary of Aurobindo Pharma, USA, Inc. 2929 Weck Dr., Durham, NC 27709. **Group-II (Reference):** 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 (0.04 mg/ INH) of Study medication (either Test/Reference/Placebo) twice daily.
Concomitant Medication	No other asthma medication will be allowed in the study, except for the use of inhaled short-acting ß2- agonist Salbutamol pMDI as rescue medication throughout the study duration. Subjects will be allowed to use Salbutamol, maximum of 6 puffs/ day, if required.
Efficacy Endpoints	**Primary Endpoint** • Mean change in Forced Expiratory volume in 1 second (FEV 1) from baseline (visit 3) to end of study visit (visit 5).

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	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. **Secondary Endpoints** • Mean change in FeNO value from base line (visit 1 & 3) to end of study visit (visit 5) • Percentage of subjects with reduction of FeNO from Baseline (Visit 1 & 3) to End of Study (Visit 5)	
Safety Endpoints	Safety will be assessed on the basis of reported adverse events, serious adverse events and laboratory assessments.	
Statistical Analysis	1. Primary endpoint will be analyzed by comparing between Test and Reference groups for Equivalence and further comparing between Test group versus Placebo and Reference group versus Placebo for Superiority. 2. Test group will be declared equivalent to Reference group, if the 90 % CI of the ratio between the Test product and Reference product for the primary endpoint is within the limits of 80.00% - 125.00% at the end of study (Day 42 ± 2). 3. At study conclusion, Test and Reference groups will each be evaluated for Superiority over Placebo ($p < 0.05$) at Visit 5/ EOS (Day 42 ± 2). For this the mITT analysis population and Last Observation Carried Forward (LOCF) will be used.	

Table – I: TABLE OF EVENTS

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	--	--	--

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**
			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		
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 $^{0}F/^{0}C$.

[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.

SIGNATURE PAGE

The final protocol has been reviewed for completeness, accuracy, and compliance with applicable regulatory expectations.

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LIST OF ABBREVIATIONS

ACT	American Thoracic Society
ADR	Adverse Drug Reaction
17-BMP	Beclomethasone-17-monopropionate
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDP	Beclomethasone dipropionate
BMD	Bone Mineral Density
BMI	Basal Metabolic Index
BOH	Beclomethasone
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDSCO	Central Drugs Standard Control Organization
COPD	Chronic obstructive pulmonary disease
CQA	Clinical Quality Assurance
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DCGI	Drugs Controller General of India
EC	Ethics Committee
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
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HPA	Hypothalamic-pituitary-adrenal
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMR	Indian Council for Medical Research

ICSs	Inhaled corticosteroids
IG	Immunoglobulin
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LAR	Legally Acceptable Representative
LABA	Long Acting Beta Agonists
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
NABL	National Accreditation Board for Testing and Calibration Laboratories
OTC	Over-the-counter
PEF	Peak expiratory flow
PFT	Pulmonary Function Test
PI	Principal Investigator
PP	Per Protocol
ppb	Parts Per Billion
RBC	Red blood cell count
RLD	reference listed drug
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
US/USA	United States of America
UAE	Unexpected Adverse Events
VZIG	Varicella-zoster immune globulin
WBC	White blood cell count

1.0 INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment[1]. The incidence and prevalence of asthma have increased during the past 20 years, affecting 5-10% of the global population[2].

The administration of corticosteroids via inhalation is considered the optimal route for appropriate drug delivery for treatment of bronchial asthma and could reduce asthma hospitalizations by as much as 80%[3]. The inflammatory process in asthma involves the increased expression of a wide variety of pro-inflammatory chemokines, cytokines, growth factors, lipid mediators, adhesion molecules, enzymes, and increased numbers of resident and invading inflammatory cells[4].

Inhaled corticosteroids (ICSs) are believed to exert their effects after translocation into the nucleus of the respiratory epithelial cell and other cells in the airway, via the glucocorticoid receptor. The steroid-receptor complex within the nucleus promotes transcription of genes that decrease inflammation and inhibit transcription of genes that encode proteins that increase inflammation. There is also evidence that ICSs may facilitate the action of β_2 adrenergic agonists by increasing the concentrations of β_2 adrenergic receptors on smooth muscle cells and decreasing airway smooth-muscle cell hypo responsiveness to β_2 agonist[5].

Regardless of the structure differences of the various ICSs, they all work through the same mechanism of action. Differences in the chemical structure of the various ICSs cause differences in their pharmacokinetic properties, which can be advantageous for clinical efficacy and safety.

Pharmacokinetic and Pharmacodynamic Features of different Inhaled Corticosteroids[6]

	Beclomethasone Dipropionate	Beclomethasone Monopropionate	Budesonide	Fluticasone Propionate	Ciclesonide	Des-ciclesonide	Mometasone Furoate
Oral bioavailability (%)	< 1	26	11	< 1	< 1	< 1	< 1
Pulmonary deposition (%)	51	*	28	16	52	*	14
On-site activation	Somewhat	Somewhat	No	No	Yes	Yes	No
Receptor binding affinity†	53	1,345	935	1,800	12	1,200	2,200
Protein binding (%): free fraction (%)	87:13	87:13	88:12	90:10	99:1	99:1	98–99: approx 1
Half-life (h)	0.5	2.7	2.8	7.8	0.36	3.4	4.5
Volume of distribution (L)	20	424	183	318	207	897	152
Clearance (L/h)	15	120	84	69	152	228	53.5

*Beclomethasone monopropionate and des-ciclesonide are the active metabolites of beclomethasone dipropionate and ciclesonide; they only exist in the airways and are the products of enzymatic conversion from the inhaled parent compounds, so only beclomethasone dipropionate and ciclesonide are inhaled and therefore have deposition data.
†Receptor binding affinities values are relative to 100, which is the affinity of dexamethasone.
(Adapted from Reference 7)

Pathophysiology and pathogenesis of bronchial asthma[7]

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

Bronchoconstriction: In bronchial asthma, the main physiological event leading to clinical symptoms is airway narrowing. In acute exacerbations of asthma bronchoconstriction occurs quickly to constrict the airways as a response to exposure to a different stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells which includes histamine, tryptase, leukotrienes, and prostaglandins. Aspirin and other nonsteroidal anti-inflammatory drugs can also cause acute airflow obstruction and this non-IgE-dependent response also involves mediator release from airway cells.

Airway edema: This results from persistent and progressive inflammation.

Airway hyperresponsiveness: It is an exaggerated bronchoconstrictor response to a wide variety of stimuli and it is a major, but not necessarily unique, feature of asthma. The cause for this hyperresponsiveness is inflammation, dysfunctional neuroregulation, and structural changes; inflammation is the major factor in determining the degree of airway hyperresponsiveness. Treatment directed toward reducing inflammation can reduce airway hyperresponsiveness and improve asthma control.

Airway remodeling: Airflow limitation may be only partially reversible in few patients. Permanent structural changes in the form of progressive loss of lung function can occur and it is not prevented by or fully reversible by current therapies. Airway remodeling involves many of the structural changes like thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion.

Diagnosis of asthma[7]:

To establish a diagnosis of asthma, the clinician should determine that

— Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present.

— Airflow obstruction is at least partially reversible.

— Alternative diagnoses are excluded.

Recommended methods to establish the diagnosis are

— Detailed medical history.

— Physical exam focusing on the upper respiratory tract, chest, and skin.

— Spirometry to demonstrate obstruction and assess reversibility.

Reversibility is determined either by an increase in FEV1 of ≥12 percent from baseline or by an increase ≥10 percent of predicted FEV1 after inhalation of a short-acting bronchodilator.

— Alternative diagnoses should be excluded.

Classification of Asthma Severity[7]

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20 –39 yr 80% 40 –59 yr 75% 60 –80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

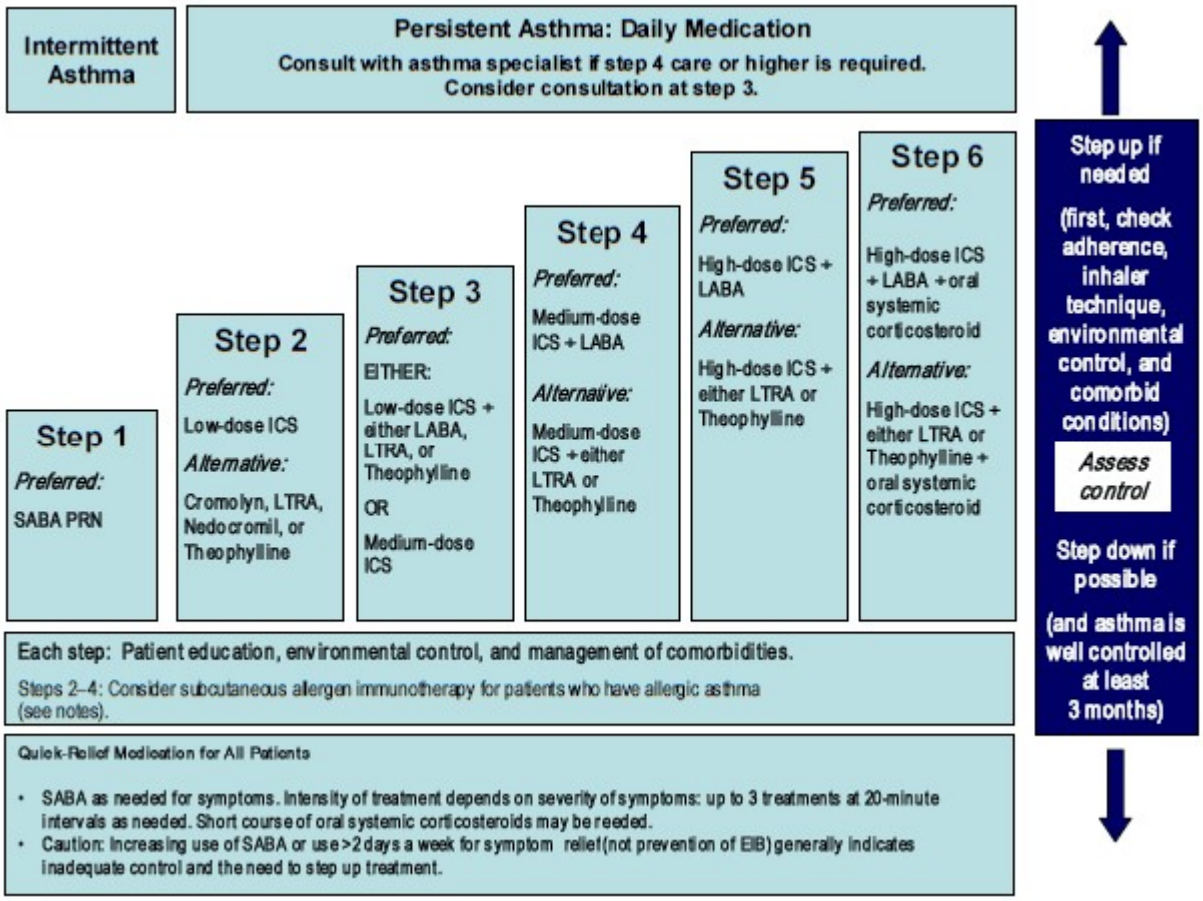
[7]National Institutes of Health, author. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007.

Treatment of asthma[7]:

Asthma drugs are classified as either relievers or controllers or more broadly as either bronchodilator or anti-inflammatory drugs.

Reliever asthma drugs are bronchodilators that act fast usually within the first few minutes. Controller medications are the main stay of asthma management because they target the underlying inflammatory process. Controller drugs include corticosteroids, Leukotriene modifiers and anti- Immunoglobulin E therapy.

Step wise approach for managing asthma in youth's ≥ 12 years age and adults



[7]National Institutes of Health, author. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007.

QVAR® 40 mcg (Beclomethasone dipropionate HFA 40 mcg), Inhalation Aerosol

The active component of QVAR 40 mcg Inhalation Aerosol and QVAR 80 mcg Inhalation Aerosol is beclomethasone dipropionate, USP, a corticosteroid having the chemical name 9-chloro-11ß,17,21-trihydroxy-16ß-methylpregna-1,4-diene-3, 20-dione 17, 21-dipropionate. Beclomethasone dipropionate (BDP) is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone[9].

INDICATIONS AND USAGE

QVAR is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. QVAR is also indicated for asthma patients who require systemic corticosteroid administration, where adding QVAR may reduce or eliminate the need for the systemic corticosteroids.

Important Limitations of Use:

• Beclomethasone is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Status Asthmaticus

QVAR is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity

QVAR is contraindicated in patients with known hypersensitivity to beclomethasone dipropionate or any of the ingredients in QVAR.

WARNINGS AND PRECAUTIONS

Local Effects

Localized infections with Candida albicans have occurred in the mouth and pharynx in some patients receiving QVAR. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with QVAR therapy, but at times therapy with QVAR may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Deterioration of Asthma and Acute Episodes

QVAR is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta-2 agonist, not QVAR, should be used to relieve acute symptoms such as shortness of breath. Instruct patients to contact their physician immediately if episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with QVAR. During such episodes, patients may require therapy with oral corticosteroids.

Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed in patients who are transferred from systemically active corticosteroids to QVAR because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections (particularly gastroenteritis) or other conditions with severe electrolyte loss. Although QVAR may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Patients requiring oral or other systemic corticosteroids should be weaned slowly from oral or other systemic corticosteroid use after transferring to QVAR. Lung function (FEV1 or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral or other systemic corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to QVAR may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Immunosuppression

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection. Nor is the contribution of the underlying disease and/or prior corticosteroid treatment known. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis

with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

Paradoxical Bronchospasm

Inhaled corticosteroids may produce inhalation induced bronchospasm with an immediate increase in wheezing after dosing that may be life-threatening. If inhalation induced bronchospasm occurs following dosing with QVAR, it should be treated immediately with an inhaled, short-acting bronchodilator. Treatment with QVAR should be discontinued and alternate therapy instituted.

Immediate Hypersensitivity Reactions

Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm, may occur after administration of QVAR. Discontinue QVAR if such reactions occur.

Hypercorticism and Adrenal Suppression

QVAR will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since beclomethasone dipropionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of QVAR in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with QVAR should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when beclomethasone dipropionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of QVAR should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Effects on Growth

Orally inhaled corticosteroids, including QVAR, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving QVAR

routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including QVAR, titrate each patient's dose to the lowest dosage that effectively controls his/ her symptom.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

Eye Disorders

Glaucoma, increased intraocular pressure, blurred vision and cataracts have been reported following the use of long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma and/or cataracts while using QVAR.

ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Candida albicans infection
- Immunosuppression
- Hypercorticism and adrenal suppression
- Growth effects and Use in Specific Populations
- Eye Disorders

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following reporting rates of common adverse experiences are based upon 4 clinical trials in which 1196 patients (671 female and 525 male adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with QVAR (doses of 40, 80, 160, or 320 mcg twice daily) or CFC-BDP (doses of 42, 168, or 336 mcg twice daily) or placebo. Below table includes all events reported by patients taking QVAR (whether considered drug

related or not) that occurred at a rate over 3% for QVAR. In considering these data, difference in average duration of exposure and clinical trial design should be taken into account.

Adverse Events Reported by at Least 3% of the Patients for QVAR by Treatment and Daily Dose

Adverse Events	Placebo (N=289) %	QVAR			
		Total (N=624) %	80-160 mcg (N=233) %	320 mcg (N=335) %	640 mcg (N=56) %
Headache	9	12	15	8	25
Pharyngitis	4	8	6	5	27
Upper resp tract infection	11	9	7	11	5
Rhinitis	9	6	8	3	7
Increased asthma symptoms	18	3	2	4	0
Oral symptoms inhalation route	2	3	3	3	2
Sinusitis	2	3	3	3	0
Pain	<1	2	1	2	5
Back pain	1	1	2	<1	4
Dysphonia	2	<1	1	0	4

Other adverse events that occurred in these clinical trials using QVAR with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were nausea, dysmenorrhea, and coughing. Oropharyngeal candidiasis occurred in < 1% of patients in both QVAR and placebo treatment groups.

CLINICAL PHARMACOLOGY

Mechanism of Action

Beclomethasone dipropionate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines). These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monoester, 17 monopropionate (17-BMP). Beclomethasone 17 monopropionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. The clinical significance of these findings is unknown. Studies in patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of QVAR.

Pharmacodynamics

HPA Axis Effects

The effects of QVAR on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 40 corticosteroid-naive patients. QVAR, at doses of 80, 160 or 320 mcg twice daily was compared with placebo and 336 mcg twice daily of beclomethasone dipropionate in a CFC propellant based formulation (CFC-BDP). Active treatment groups showed an expected dose-related reduction in 24-hour urinary-free cortisol (a sensitive marker of adrenal production of cortisol). Patients treated with the highest dose recommended of QVAR (320 mcg twice daily) had a 37.3% reduction in 24-hour urinary-free cortisol compared to a reduction of 47.3% produced by treatment with 336 mcg twice daily of CFC-BDP. There was a 12.2% reduction in 24-hour urinary-free cortisol seen in the group of patients that received 80 mcg twice daily of QVAR and a 24.6% reduction in the group of patients that received 160 mcg twice daily. An open label study of 354 asthma patients given QVAR at recommended doses for one year assessed the effect of QVAR treatment on the HPA axis (as measured by both morning and stimulated plasma cortisol). Less than 1% of patients treated for one year with QVAR had an abnormal response (peak less than 18 mcg/dL) to short-cosyntropin test.

Pharmacokinetics

Beclomethasone dipropionate (BDP) undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption. The pharmacokinetics of 17 BMP has been studied in asthmatics given single doses.

Absorption: The mean peak plasma concentration (Cmax) of BDP was 88 pg/ml at 0.5 hour after inhalation of 320 mcg using QVAR (4 actuations of the 80 mcg/actuation strength). The mean peak plasma concentration of the major and most active metabolite, 17-BMP, was 1419 pg/ml at 0.7 hour after inhalation of 320 mcg of QVAR. When the same nominal dose is provided by the two QVAR strengths (40 and 80 mcg/actuation), equivalent systemic pharmacokinetics can be expected. The Cmax of 17-BMP increased dose proportionally in the dose range of 80 and 320 mcg.

Metabolism: Three major metabolites are formed via cytochrome P450-3A catalyzed biotransformation: beclomethasone-17-monopropionate (17-BMP), beclomethasone-21 monopropionate (21-BMP) and beclomethasone (BOH). Lung slices metabolize BDP rapidly to 17-BMP and more slowly to BOH. 17-BMP is the most active metabolite.

Distribution: The in vitro protein binding for 17-BMP was reported to be 94-96% over the concentration range of 1000 to 5000 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of BDP or its metabolites.

Elimination: The major route of elimination of inhaled BDP appears to be via hydrolysis. More than 90% of inhaled BDP is found as 17-BMP in the systemic circulation. The mean elimination half-life of 17-BMP is 2.8 hours. Irrespective of the route of administration (injection, oral or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine.

CLINICAL STUDIES

Blinded, randomized, parallel, placebo-controlled and active-controlled clinical studies were conducted in 940 adult asthma patients to assess the efficacy and safety of QVAR in the treatment of asthma. Fixed doses ranging from 40 mcg to 160 mcg twice daily were compared to placebo, and doses ranging from 40 mcg to 320 mcg twice daily were compared with doses of 42 mcg to 336 mcg twice daily of an active CFC-BDP comparator. These studies provided information about appropriate dosing through a range of asthma severity. A blinded, randomized, parallel, placebo-controlled study was conducted in 353 pediatric patients (age 5 to 12 years) to assess the efficacy and safety of HFA beclomethasone dipropionate in the treatment of asthma. Fixed doses of 40 mcg and 80 mcg twice daily were compared with placebo in this study. In these adult and pediatric efficacy trials, at the doses studied, measures of pulmonary

function [forced expiratory volume in 1 second (FEV1) and morning peak expiratory flow (AM PEF)] and asthma symptoms were significantly improved with QVAR treatment when compared to placebo.

In controlled clinical trials with adult patients not adequately controlled with beta-agonist alone, QVAR was effective at improving asthma control at doses as low as 40 mcg twice daily (80 mcg/day). Comparable asthma control was achieved at lower daily doses of QVAR than with CFC-BDP. Treatment with increasing doses of both QVAR and CFC-BDP generally resulted in increased improvement in FEV1. In this trial the improvement in FEV1 across doses was greater for QVAR than for CFC-BDP, indicating a shift in the dose response curve for QVAR.

Proper Use and Care of the Inhaler

Priming: Priming is essential to ensure appropriate beclomethasone dipropionate content in each actuation. Instruct patients to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 10 days by releasing two sprays into the air, away from the face.

Cleaning: For normal hygiene, the mouthpiece of the inhaler should be cleaned weekly with a clean, dry tissue or cloth. DO NOT WASH OR PUT ANY PART OF THE INHALER IN WATER.

Dose Counter: Inform patients that QVAR has a dose counter attached to the actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 2 times, at which point the total number of actuations will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of two (e.g., 120, 118, 116, etc). When the counter displays 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Inform patients to discard the QVAR inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

1.1. 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.

2.0 STUDY OBJECTIVES

2.1. 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 hydro fluoroalkane (HFA)) and to demonstrate superiority of both active treatments over placebo.

2.2. Secondary Objective

The secondary objective is to assess the safety and tolerability of Beclomethasone Dipropionate MDI (Inhalation Aerosol) 0.04 mg/ INH.

3.0 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 will be scheduled to the investigator site [i.e., Screening Visit (Day -7 to Day -1), Run in period (visit 2) on Day 0, Randomization visit (visit 3- Day 15 + 1), On-treatment visit (visit 4- Day 21 ± 1) and the End of Study visit (visit 5- Day 42 ± 2)].

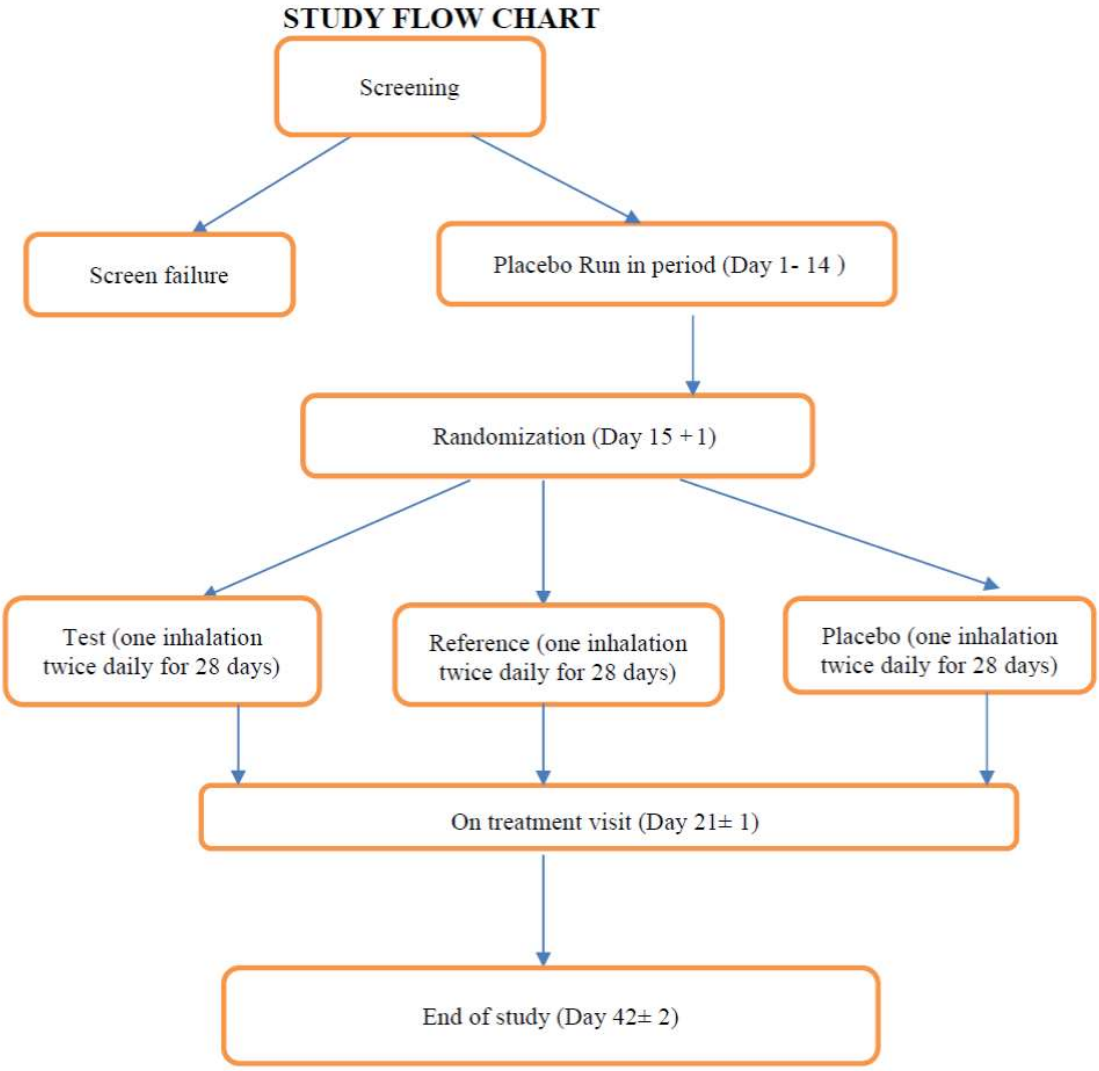
All subjects will be reported to the study site for screening. Subjects with asthma diagnosed as per National Asthma Education and Prevention Program at least 12 months prior will be briefed about the study and Informed Consent Form will be obtained. An exhaled nitric oxide (FeNO) test will be performed. 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 fulfill the eligibility criteria.

4.0 STUDY VISITS

There will be a total of five visits in this study:

- Screening (Day -7 to Day -1);
- Run in period (Visit 2: Day 0);
- Randomization visit (Visit 3: Day 15 + 1)
- On-treatment Visit (Visits 4: Day 21 ± 1) and
- End of study visit (Visit 5: Day 42 ± 2)

Total expected duration for a subject in the study is 52 days.

4.1. Visit 1: Screening (Day -7 to Day -1)

All subjects should be screened within 7 days prior to start of Placebo run-in period. Voluntarily given informed consent will be obtained from each subject and or/ Legally Acceptable Representative (LAR) and or/ Impartial Witness, prior to commencing any study specific procedures. Investigator at investigational site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

During the informed consent process, subjects shall also be made aware of the associated risks and other possible alternate medications for the same indication.

Subjects must be made aware that they are free to discontinue the study at any point of time during the study, and in case of trial related injury/death they will be provided free medical management and financial compensation as per the regulatory practice. Subject will be given opportunity to ask questions and adequate time will be given to consider the written information provided. Investigator at site must retain the original, signed ICF for the study file. A copy of the signed ICF shall be given to the subject.

Once informed consent has been obtained, the subject's eligibility to enter the study will be verified in accordance with the inclusion and exclusion criteria. The procedures that will be carried out during this visit are mentioned in **Table II**.

During the screening period from Day -7 to Day -1 (Visit 1), screening lab investigations and general & systemic examination will be conducted; the subjects' vital signs, concomitant medications as well as detailed medical and medication history will be noted. At the screening visit, all medications taken within 14 days prior to screening, including over-the-counter (OTC) products will be recorded. An exhaled nitric oxide (FeNO) test will be performed, if FeNO < 25 ppb, then subject will not be further screened. Spirometry test will be performed to evaluate

FEV1 value. Highest value of 3 acceptable readings in this session will be considered for inclusion into study.

Table II: Procedures on Screening Visit

Procedure	**Screening Visit** (Day -7 to Day -1)
Informed consent	X
Eligibility criteria	X
Demography*	X
Medical and Medication History	X
General & Systemic Examination	X
Vital signs	X
Laboratory Investigations	X
Serum pregnancy test (for females of child bearing potential)	X
12 Lead ECG	X
Chest X-Ray (PA view)	X
FeNO estimation	X
FEV1 value recording (through Spirometry)	X
Concomitant medication check	X
Adverse event recording	X

- General and Systemic examination includes head, neck, eye, ENT, skin & appendages, renal, cardiovascular, pulmonary, reproductive, endocrine, gastrointestinal, nervous system, musculoskeletal, peripheral vascular and psychiatric
- Vital signs include Blood Pressure (Supine), Respiration Rate, Pulse Rate and Body Temperature in ^{0}F/ ^{0}C.
- 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.
- *If a valid age certificate of subject is not available, the subject will give written confirmation of the age and will be authenticated by Investigator.

AE monitoring will be done at all stages of the study after signing of the ICF. The PI/ study staff shall instruct the subject to inform immediately in case of any emergency or untoward symptoms during any point of the study. Once all assessments and laboratory tests have been completed, the subject will be asked to visit the site on Day 0.

4.2. Visit 2: (Day 0)

Subjects fulfilling all inclusion and none of the exclusion criteria will be considered for Run-in period. Subjects vital signs, concomitant medication, adverse events, general and systemic evaluation will be done. FEV1 values will be recorded using spirometry. Highest value of 3

acceptable readings in this session will be considered. Subjects will be provided with placebo and will be advised to inhale the product twice daily for 2 weeks. Subjects will be provided with subject diary and rescue medication (Salbutamol) with the instructions to fill the diary and for the use of rescue medication (Salbutamol). This Run-in period is required to wash out any pre-study corticosteroids/long-acting bronchodilators, to establish FEV1 baseline values and to evaluate subject disease conditions, need of rescue medication and treatment compliance. **Table III** shows a list of all procedures to be completed on Visit 2.

Table III Procedures on Day 0

Procedure	**Day 0**
General & Systemic Examination	X
Vital signs	X
Spirometry	X
Dispensing of Placebo product (for Run-in period)	X
Rescue Medication Dispensing	X
Subject Diary Dispensing	X
Concomitant medication check	X
Adverse event recording	X

- General and Systemic examination includes head, neck, eye, ENT, skin & appendages, renal, cardiovascular, pulmonary, reproductive, endocrine, gastrointestinal, nervous system, musculoskeletal, peripheral vascular and psychiatric
- Vital signs includes Blood Pressure (Supine), Respiration Rate, Pulse Rate and Body Temperature in $^{0}F/^{0}C$.

4.3. Placebo Run in period (Day 1 to Day 14)

During the Run-in period, subjects will administer one inhalation of placebo twice daily for 2 weeks duration. Subjects will be requested to mention any concomitant medications used during this time in their subject diaries. During this period, pre-study corticosteroids/ long-acting bronchodilators will be washed out and FEV1 baseline values will be established.

Table IV Procedures from Day 1 to Day 14

Procedure	**Run-in Period**
	Day 1 to Day 14
Placebo administration	One inhalation two times daily from Day 1 to Day 14
Concomitant medication check	X
Adverse event recording	X

4.4. Randomization (Day 15 + 1)

Subjects who have completed Run in period will be advised to visit the Investigator site on day 15 + 1 for randomization. Subjects' compliance to the run in period will be assessed with respect to the placebo and rescue medication administration as per the details entered in subject diary.

Subjects who successfully completed the run-in period will undergo exhaled nitric oxide (FeNO) test. Airway reversibility will be checked by performing a bronchodilator test wherein the initial baseline lung volume is measured by spirometer followed by administration of 360 mcg of Salbutamol inhalation and then a repeat lung volume measurement by spirometer within 30 minutes of Inhalation of Salbutamol. Subject's baseline FEV1 readings will be noted before the morning dose. "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).

The subjects who met all the applicable eligible criteria will be randomized to either Test/ Reference/ Placebo groups in a 2:2:1 as per the pre-specified randomization schedule. Subjects will receive their assigned study medication, along with instructions regarding method of administrations. All subjects will be required to take one inhalation twice daily for 4 weeks. The Asthma Control Test (ACT) questionnaire will be evaluated in this visit. The baseline score for the Investigator's Global Evaluation will be recorded.

Study medication, rescue medication (Salbutamol) and subject diary will be dispensed to the subject with a detail instruction regarding how study medication and rescue medication need to be taken and filling instructions of the subject diary.

The first dose of study medication will be administered at the site in the morning to the subject and the subject will self-administer the second dose in the evening at his/ her home.

Table V Procedures from Day 15 +1

Procedure	**Treatment Period**
	Day 15 +1
Placebo administration compliance (Run in period)	X
Collection of Placebo Canister given in run-in period	X
Eligibility criteria (applicable)	X
General & Systemic Examination	X

Procedure	Treatment Period
Vital signs	X
Urine Pregnancy Test (for females of child bearing potential)	X
Collection of rescue medication canister	X
FeNO estimation	X
Reversibility/Bronchodilator test	X
FEV1 baseline value recording (through Spirometry)	X
Randomization	X
Study Drug Dispensing (for Treatment period)	X
Rescue Medication Dispensing	X
Study Drug Administration	One inhalation two times daily from Day 15 to Day 42
Subject Diary Card Compliance	X
Concomitant Medication check	X
Adverse event recording	X
Asthma Control Test Questionnaire	X
Investigator's Global Evaluation	X

- General and Systemic examination includes head, neck, eye, ENT, skin & appendages, renal, cardiovascular, pulmonary, reproductive, endocrine, gastrointestinal, nervous system, musculoskeletal, peripheral vascular and psychiatric
- Vital signs include Blood Pressure (Supine), Respiration Rate, Pulse Rate and Body Temperature in ^{0}F/ ^{0}C.

4.5. Visit 4 (Day 21 ± 1)

Subjects will be asked to visit the site on Day 21 ± 1 (Visit 4). The predose FEV1 readings will be taken in the morning. Highest value from three acceptable readings will be considered. Measurement of vital signs, general and systemic examination,
andAE monitoring will also be done. Compliance of subject dairy, study medication and concomitant medication will be checked.

Table VI Procedures from Day 21 ± 1

Procedure	Treatment Period
	Day 21 ± 1
General & Systemic Examination	X
Vital signs	X
Spirometry	X
Study Drug Administration	One inhalation two times daily

	from Day 15 to Day 42
Subject Diary Card Compliance	X
Concomitant Medication check	X
Adverse event recording	X

- General and Systemic examination includes head, neck, eye, ENT, skin & appendages, renal, cardiovascular, pulmonary, reproductive, endocrine, gastrointestinal, nervous system, musculoskeletal, peripheral vascular and psychiatric
- Vital signs include Blood Pressure (Supine), Respiration Rate, Pulse Rate and Body Temperature in ^{0}F/ ^{0}C.

4.6. End of Study (Day 42 ± 2)

Subjects will be asked to visit the site on Day 42 ± 2, End of Study/EOS (Visit 5). The FEV1 readings will be taken before morning dosing of inhaled medication corresponding to the time (with a window period of ± 30 min) of predose FEV1 taken on the 1st day of the start of the treatment. Two spirometry sessions with at least 3 acceptable readings each will be performed. Highest value from both the sessions will be noted. Average of both the highest readings will be considered as EOS FEV1 value. An exhaled nitric oxide (FeNO) test will be performed. The Asthma Control Test (ACT) questionnaire will be evaluated and the Investigator's Global Evaluation will be performed. Measurement of vital signs, general and systemic examination, concomitant medication recording and AE monitoring will also be done. Subject diary, study medication and rescue medication will be collected from the subjects and efficacy evaluation will be done. Clinical laboratory tests will be repeated to check safety of subjects. Urine Pregnancy Test will be done for females of child bearing potential.

Table VII shows a list of all procedures to be completed on End of Study.

Table VII: End of Study

Procedure	**End of Study**
	Day 42 ± 2
General & Systemic Examination	X
Vital signs	X
Urine Pregnancy Test (for females of child bearing potential)	X
Laboratory Investigations	X
FeNO estimation	X
Spirometry	X
Subject Diary Card Compliance	X
Concomitant Medication check	X
Adverse event recording	X
Asthma Control Test Questionnaire	X

Procedure	End of Study
	Day 42 ± 2
Investigator's Global Evaluation	X
Collection of subject diary, study drug and rescue medication canister	X

- General and Systemic examination includes head, neck, eye, ENT, skin & appendages, renal, cardiovascular, pulmonary, reproductive, endocrine, gastrointestinal, nervous system, musculoskeletal, peripheral vascular and psychiatric
- Vital signs include Blood Pressure (Supine), Respiration Rate, Pulse Rate and Body Temperature in ^{0}F/ ^{0}C.
- 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.

On Visit 5, subjects will be asked to complete all other end of study procedures. The subjects are required to submit their issued study drug and subject diaries for compliance checking.

4.7. Withdrawal Visit

A subject must be prematurely withdrawn from the study if the subject fulfills any of the withdrawal criteria specified in **Section 5.4**. In addition to the withdrawal procedures including General and Systemic Examination, Vital Signs, Urine Pregnancy Test and Clinical Laboratory Tests, the details of concomitant therapies will also be recorded.

5.0 STUDY POPULATION

5.1. Number of subjects

Assuming 5% loss from Enrolled population to mITT population, 1550 subjects will be enrolled in this study. Subjects will be enrolled in 2:2:1 proportion (Test: RLD: Placebo respectively) as 620:620:310.

5.2. 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).

5.3. 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.

5.4. Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject will be withdrawn from the study and the Sponsor or AXIS must be contacted. An exception may be granted in rare circumstances where there is a compelling safety reason to allow the subject to continue. In these rare cases, the PI must obtain documented approval from the Sponsor or designee to allow the subject to continue in the study. Subjects who withdraw themselves or withdrawn by PI for lack of efficacy or Adverse events will be provided free available treatment as per the clinical practice of the PI. PI/ study team need to educate the subjects for completion of study and must make all possible efforts to contact the subject if they do not visit the site as per the schedule within window period.

In addition, study drug will be stopped and subject can be withdrawn from the study in the following circumstances:

- The investigator decides that the subject must be withdrawn
- Subjects who experience asthma exacerbations that requires treatment with systemic corticosteroids, LABA and high dose ICS's
- If subject develops a medical condition that requires consistent use of prohibited medication
- Use of rescue medication more than 600 micrograms per day
- If FEV1 value is < 45 % on Day 21+ 1
- The subject is unwilling to continue in the study
- Violation of criteria listed in the Protocol
- Noncompliance with Protocol
- Any treated subject who has an adverse reaction to study medication that threatens his/her well-being if continued in the study
- If the Investigator decides to stop the treatment
- The Investigator or the Sponsor, for any reason, decides to stop the study

Subjects who withdraw from the study early will have early withdrawal procedures performed. Subjects who withdraw from the study will not be replaced.

6.0 STUDY ENDPOINTS

6.1. Efficacy Endpoints

Primary Endpoint:

- Mean change in Forced Expiratory volume in 1 second (FEV 1) from baseline (visit 3) to end of study visit (visit 5).

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.

Secondary Endpoints:

- Mean change in FeNO value from base line (visit 1 & 3) to end of study visit (visit 5)
- Percentage of subjects with reduction of FeNO from Baseline (Visit 1 & 3) to End of Study (Visit 5)

6.2. Safety Endpoints

Safety will be assessed based on reported adverse events, serious adverse events and laboratory assessments**.**

7.0 ASSESSMENT OF STUDY ENDPOINTS

7.1. Assessment of Efficacy Endpoints

The primary efficacy endpoint will be evaluated on mean change in Forced Expiratory Volume in 1 second (FEV1) from baseline (Visit 3) to end of study (Visit 5).

The secondary efficacy endpoints will be evaluated on mean change in FeNO value from baseline (visit 1 & 3) to end of study visit (visit 5) and percentage of subjects with reduction of FeNO from baseline (visit 1 & 3) to end of study visit (visit 5).

7.2. Assessment of Safety Endpoints

Safety will be assessed based on following for

- Clinical Laboratory investigation
- Vital signs evaluation
- General and systemic examination
- Reported Adverse Events and Serious adverse events

7.2.1. Clinical Laboratory Evaluations

All laboratory investigations shall be performed at designated laboratory (NABL Accredited).

Approximately 15 mL of venous blood for routine tests will be withdrawn at screening and end of study. Additional blood may be withdrawn if deemed necessary.

1. Hematology Panel: Hemoglobin (Hb%), Hematocrit, White blood cell count (WBC), Total differential count, Red blood cell count (RBC), Platelet count
2. Renal function tests: BUN, Creatinine
3. Liver function tests: Albumin, Alkaline phosphatase, Total bilirubin, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)
4. Random blood sugar
5. Serum electrolytes: Sodium, Potassium and Chloride
6. Serum pregnancy test (at screening only for females of child bearing potential)

Additional laboratory evaluations may be performed, if deemed necessary (for safety reasons), but should be informed to the Medical Manager / CRA and shall be notified to the EC. Any unscheduled lab test required by the Investigator for safety reasons, site specific local laboratory can be approached.

7.2.2. Vital Signs

Vital signs (Blood Pressure, Pulse Rate, Body temperature and Respiratory rate) will be recorded at all the visits and at any time at the discretion of the Investigator. Systolic BP will be measured after the subject has rested for at least 5 minutes in supine position.

7.2.3. General and Systemic Evaluation

A general and systemic examination will be conducted by a physician at each study visit and includes (at a minimum) a thorough examination of Head, Neck, Eye, Ear, Nose, Throat, Skin & Appendages, Renal, Cardiovascular, Pulmonary, Reproductive, Endocrine, Gastrointestinal, Nervous System, Musculoskeletal, Peripheral Vascular system and Psychiatric.

7.2.4. Adverse events

All reported adverse events and serious adverse events will be recorded and reported as per section Adverse Events.

8.0 ADVERSE EVENTS

8.1. Definitions

The following International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) AE definitions apply to this study:

Adverse Event: An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
Serious Adverse Event: An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death.
- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in patient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient is enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital abnormality/birth defect.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

An adverse drug reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. ‘‘Unexpected,’’ as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in

the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Each and every unexpected adverse event observed during study will be medically managed Investigator team at site and followed up till resolution or stabilization. All the details of UAE will be captured in AE pages of CRF/ eCRF. If UAE qualifies for any of the SAE criteria the timelines for recording and reporting the UAE will be as per SAE timelines.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

8.2. Severity

The severity of unsolicited AEs will be characterized as "mild", "moderate", or "severe" according to the following definitions:

Table VIII: Severity of adverse reactions

Mild	Moderate	Severe
Events are usually transient and do not interfere with the subject's daily activities.	Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.	Events interrupt the subject's usual daily activity.

8.3. Relationship

The causal relationship between the study drug and the AE has to be characterized as related, unrelated, unlikely, possible, probable, or unknown (unable to judge).

Table IX: Causality Assessment

Related	Events can be classified as "related" when there is a direct possibility that the study drug cause AE.
Unrelated	Events can be classified as "unrelated" if there is not a reasonable possibility that the study drug caused the AE.
Unlikely	An "unlikely" relationship suggests that only a remote connection exists between the study drug and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.
Possible	A "possible" relationship suggests that the association of the AE with

	the study drug is unknown; however, the AE is not reasonably supported by other conditions.
Probable	A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.
Unknown	All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

8.4. Reporting of Adverse Events

Adverse Events

All AEs that occur in a subject from the time subject signs the ICF for the study, regardless of severity, causality, and whether or not they occurred during the course of the trial are to be recorded in the appropriate AE pages (either 'serious' or 'non-serious') in the CRFs/ eCRFs. Investigator shall complete all the details requested including dates of onset, severity, action taken, treatment measures, outcome, and relationship to study drug, and any other treatment measures undertaken. Each event should be recorded separately.

At the End of study visit, subjects will be queried regarding any AEs that have occurred since the Treatment visit. Subjects will be asked to volunteer information with a non-leading question such as, "How have you felt since your last visit?" Study center personnel will then record all pertinent information in the subject's CRF/ eCRF.

Serious Adverse Events

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, Investigator must report the event as per Appendix XI to sponsor/AXIS, Licensing authority and ethics committee. Sponsor/AXIS with Investigator shall send SAE report after due analysis to Licensing authority, ethics committee and head of the institute where trial is being conducted within 14 days. Investigator shall ensure that ethics committee shall send SAE report and its opinion on financial compensation within 30 days to the licensing authority. Sponsor shall pay compensation as per the orders by licensing authority within 30 days of receipt of orders from licensing authority. A follow up report shall be sent to sponsor/AXIS, Licensing authority, and

head of the institute where trial is conducted within 14 days of the occurrence of SAE which shall include outcome and treatment provided. If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE form to the SAE fax number +91-40-4040 8060 or email to safety@axisclinicals.com. SAE form (as per appendix XI compliance) shall be sent to licensing authority and Ethics committee which accorded approval at the site. Even if an initial report is made aware by the site personnel telephonically to the sponsor or AXIS representative, an SAE form completed with all available details must still be faxed within 24 hours of knowledge of the event at the study center.

Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, treatments administered for the events, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the subject's CRF/eCRF and SAE form. All SAEs are to be followed up by the study staff until resolution or until the SAE is deemed stable. The Sponsor or AXIS may contact the study center to solicit additional information or follow up on the event.

The original CRF/ eCRF pages should be returned immediately to the CRF/eCRF binder. The information must include at least the following:

- Name, address, and telephone number of the reporting Investigator.
- Study drug and Protocol Number.
- Subject identification number, initials, sex, and date of birth.
- Description of the SAE, measures taken, and outcome.
- Preliminary classification of causal relationship by the Investigator.

Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor /AXIS and the original placed in the SAE section of the CRF/ eCRF binder.

In the case of fatal or life-threatening events please also immediately telephone the Safety Surveillance and Reporting Unit:

Country	Name/Phone number:
India	Dr. Subhra Lahiri Associate Vice President – Clinical Research AXIS Clinicals Limited. 1-121/1, Miyapur, Hyderabad-500049 Direct : +91-40-40408064 Fax : +91-40-40408060 Mobile : +91-8886221089 e-mail : subhra.l@axisclinicals.com safety@axisclinicals.com
India	Dr. Mohd. Sajid Medical Manager AXIS Clinicals Limited 1-121/1, Miyapur, Hyderabad 500049, India. Tel: +91 40 4040 8267 Fax: +91 4040 8003/8060 Mob: +91 9739812605 Email: Sajid.m@axisclinicals.com

In case of an accidental overdose, the study center personnel will take necessary measures to bring the subject to a stable state and will report overdose to AXIS Clinicals.

8.5. Follow-up of Adverse Events

Any AEs observed after signing the ICF till study completion will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the PI does not expect any further deterioration of the condition.

8.6. Asthma exacerbations

Asthma exacerbations

Asthma exacerbations are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function, i.e. they represent a change from the subject's usual status that is sufficient to require a change in treatment.

* Exacerbations are identified as events characterized by a change from the subject's previous status.

Severe asthma exacerbations

Severe asthma exacerbations are defined as events that require urgent action on the part of the subject and physician to prevent a serious outcome, such as hospitalization or death from asthma.

Management of asthma exacerbations

All asthma exacerbations would be managed by stepwise approach as suggested by the Global initiative for asthma 2018 strategy for asthma management & prevention. Please see the Appendix -6 for more details.

9.0 STUDY TREATMENTS

9.1. Description of Investigational Product

Group-I: Test
Name: 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
Name: QVAR® 40 mcg (Beclomethasone dipropionate hydrofluoroalkane), Inhalation Aerosol;
Manufactured 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 (0.04 mg/ INH) of Study medication (Test/ Reference/ Placebo) twice daily.

9.2. Investigational product Administration

As per randomization schedule, subjects will be randomized to either the Test or Reference or Placebo in 2:2:1 ratio.

Instructions for Use
There are 2 main parts of your inhaler including the:

- Metal canister that holds the medicine (See Figure A)
- Plastic actuator that sprays the medicine from the canister (See Figure A)

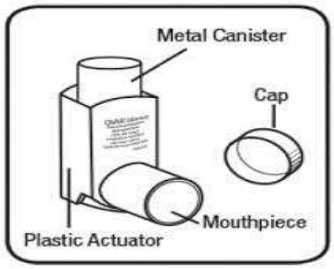


Figure A

- The inhaler has a protective dust cap that covers the mouthpiece of the actuator (See Figure A). The protective dust cap should be removed before use.
- The inhaler comes with a dose counter located on the back of the actuator (See Figure B). The dose counter window will show you the number of actuations (puffs) of medicine remaining in units of 2. The inhaler contains "120" actuations (puffs).

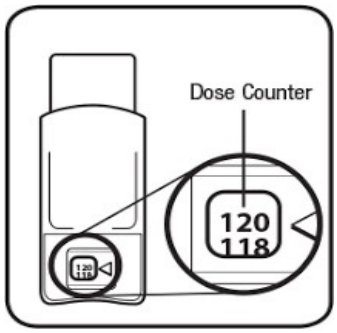


Figure B

- The first time you use inhaler, the dose counter will show "120" actuations remaining (See Figure B). Each time you press the metal canister, a puff of medicine is released and the dose counter will count down.
- When the dose counter reaches 0, it will continue to show 0 and you should replace your inhaler.
- The dose counter cannot be reset and is permanently attached to the actuator. Never change the numbers for the dose counter or touch the pin inside the actuator

Do not remove the metal canister from the plastic actuator.

Before using your inhaler:

Remove the cap from the mouthpiece of the actuator (See Figure C). Check the mouthpiece for objects before use. Make sure the metal canister is fully inserted into the actuator.

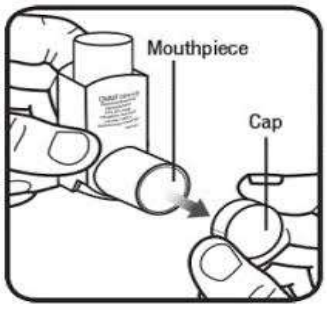


Figure C

Priming your inhaler:

Before you use your inhaler for the first time or if you have not used your Inhaler for more than 10 days, you will need to prime your Inhaler.

- Before priming, the inhaler will show a black dot in the dose counter window (See Figure D).

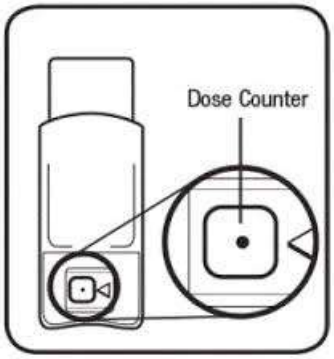


Figure D

- Hold the Inhaler in the upright position and with the mouthpiece pointing away from you.
- Press down on the metal canister 2 times and release 2 actuations (puffs) into the air and away from your face.
- After priming 2 times, the dose counter should read "120."

Your Inhaler is now ready to use.

Using your inhaler:

Step 1: Remove the cap from the mouthpiece of the actuator (See Figure C). Check the mouthpiece for objects before use. Make sure the metal canister is fully inserted into the actuator.

Step 2: Breathe out as fully as you comfortably can. Hold the inhaler in the upright position (See Figure E). Close your lips around the mouthpiece, keeping your tongue below it.

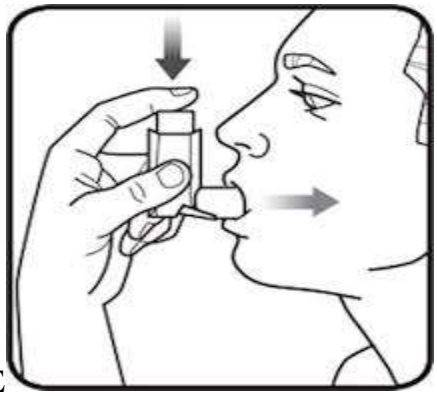


Figure E

Step 3: While breathing in deeply and slowly, press down on the metal canister with your finger (See Figure E). When you have finished breathing in, hold your breath as long as you comfortably can (5 to 10 seconds).

Step 4: Take your finger off the metal canister and remove the inhaler from your mouth. Breathe out gently.

After using your inhaler:

- Replace the cap over the mouthpiece right away after use.
- You should rinse your mouth with water after you finish using inhaler.
- Clean the mouthpiece of your inhaler weekly with a clean, dry tissue or cloth.
- Do not wash or put any part of your inhaler in water[10].

9.3. Packaging and Labeling of Study drug

Packaging and labeling of study medication will be conducted as per applicable regulations by the third party. Study medication will be supplied by Aurobindo Pharma Ltd to the third party service provider engaged for randomization and drug supply management.

9.4. Randomization

This will be randomized and double blind study. 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.

A computerized randomization code will be generated by third party or designate, appropriate to the study design.

A third party or designate will provide password protected study randomization code via a secure file transfer procedure prior to the start of the study to the IWRS vendor. Only those individuals performing investigational medicinal product dispensing/ reconciliation activities are to have access to the randomization code. No further distribution of the randomization code to individuals not involved in dispensing the investigational medicinal products is permitted without proper documentation and rationale. If the randomization is maintained in paper format (i.e. hard copy), it will be retained with limited access under lock and key. Study participants will be aware that they will receive different formulations of a same drug without being informed which product (Test or Reference or Placebo) is being administered. Furthermore, the randomization code will not be available to the physician and nursing staff involved in the collection, monitoring, revision, or evaluation of adverse events or to clinical staff who could have an impact on the outcome of the study.

The randomization code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Qualified Investigator to complete a serious adverse event report or the clinical report. In such situations, the randomization information will be accessed through IWRS by the designated individual(s) pharmacist, and the date and reason for breaking the blind must be recorded.

Biostatistics group or designate will release the randomization code to designated study team members following the release of the study data. The randomization code will be used for subject assignment to treatment and for statistical and reporting purposes.

Screening number assigned to a study subject will remain the same throughout the study. The subjects may participate in the study only once and discontinued subjects must not be re-enrolled. If subject withdraws consent after randomization allotted or does not receive study treatment for any reason, the randomization number will not be re-used.

No member of study site or the study team will have access to randomization code until completion of the study statistical analysis.

Subject Identification Code Numbering System

Once a subject's eligibility criteria is satisfied, the subject will be assigned with screening number, starting with three digit site number followed by three digit subject number (e.g., 201001) in chronological order of enrollment in each site. The Investigator will issue the Study Drug to the subject as per IWRS method. If subject discontinues the study, the subject number will not be reused, and the subject will not be allowed to reenter the study.

9.5. Masking and Unmasking

This is a Randomized, Multiple-dose, Double-blind, Placebo Controlled, Parallel group and Multicentric study. It will be ensured that neither subject nor investigator/research team can differentiate between test, reference and placebo. The treatment each subject will receive will not be disclosed to the investigators, study center personnel, subject, sponsor, or AXIS staff involved in the study conduct, monitoring, data review or analysis. The treatment codes will be held by the independent third party.

Neither any member of study site nor the study team will have access to randomization code until completion of the study and database lock.

9.6. Treatment Compliance

Compliance will be assessed by subject diary and inhalation records of study medication. This will be recorded in the CRF/ 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 and completed the evaluation within the designated visit.

Example: If subject received 18 doses of study medication and discontinued from study on day 11. Study medication needs to be taken twice daily for 28 days, hence the expected number of doses would be 56. Treatment Compliance = 18/56 X 100= 32.1%.

9.7. Prohibited Medications

During the study no other asthma medication will be allowed except investigational product and Salbutamol rescue inhalation. Due to the nature of the study and the Test product, certain medications which may interfere with the interpretation of the study results are prohibited 04 weeks before study enrollment as well as during the course of the study. These are outlined below:

1. ß2 Blockers
2. Anti-arrhythmitics, anti-depressants, MOA inhibitors
3. Inhaled or other forms of Corticosteriods, LABA
4. Anticholinergics, Anti-histamines, Nedocromil, Sodium Cromoglycate, Leukotriene antagonists, Xanthine derivatives, Ephedrine.

9.8. Study Drug Accountability

Study medication will be provided by the Sponsor to the investigators through a third party packaging vendor. Study medication shall be kept under controlled access i.e., locked area with restricted access at investigator site and will be supplied only to suitable subjects under the responsibility of investigator/ study personnel. Study medication shall be stored under specified storage conditions as mentioned in the IP label. Investigator/ Study personnel will receive study medication and will document the same in applicable documents.

A record of study medication dispensed to trial subjects and returned shall be appropriately documented in IP logs provided by Axis/ third party.
At the end of study or in between if required investigator will return the used/ unused/ expired/ defective/ empty/ partially used study medication to third party and will document the same. Study medication can be destructed at site as per applicable regulations in presence of authorized study personnel and certificate for destruction shall be obtained and filed in Trial Master File and copy in Site Master File.

Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drugs using the IP Accountability Forms. These forms must be available for inspection at any time.

10.0 STATISTICS AND DATA COLLECTION

A general description of the statistical methods to be used to analyze the data is outlined below. Specific detailed description of analyses including list of displays will be provided in the Statistical Analysis Plan which will be finalized before clinical study data base lock. Data management plan will be prepared and finalized before data base designing.

General Analysis Considerations

Continuous data will be described using non-missing observations (n), Mean, Standard Deviation, Median, Minimum and Maximum values. Categorical data will be described using counts and percentages. Analyses will be performed using SAS version 9.2 or above.

Unless specified otherwise, all statistical testing will be two-sided and will be performed using significance (α) level of 0.05.

10.1. Sample Size Calculation

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.

Assuming 5% loss from Enrolled population to mITT population, 1550 subjects will be enrolled in this study. Subjects will be enrolled in 2:2:1 proportion (Test: RLD: Placebo respectively).

Randomization

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. Randomization schedule will be generated using appropriate software package.

10.2. Subject Disposition

Number of subjects screened, entered run-in period, randomized, completed and discontinued will be presented along with reasons for screen failure and study discontinuation. Number of subjects assigned to various analysis populations will be presented. Reasons for exclusions from mITT and PP population will be listed by subject.

10.2.1. Safety Population

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

10.2.2. mITT Population

The mITT population will include all randomized subjects who meet all inclusion/exclusion criteria, receive study treatment, and have at least one post baseline efficacy assessment. 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. 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.

10.2.3. Per Protocol Population

The PP population will include all randomized subjects who meet all inclusion/exclusion criteria, are found to be compliant with the assigned study treatment, who return to the study site for the primary endpoint visit at 4 weeks (+/- 2 days) OR discontinue from the study as a treatment failure, 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 to 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 unblinding of data. Summary of subjects with Major vs. Minor Protocol deviations will be provided along with listing.

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.

10.3. Subject Characteristics

Summary for Demographic and Baseline disease characteristics will be presented. These will include age, sex, race, ethnicity, body weight, height, body mass index, duration of asthma, prior use of anti-asthmatic treatments and baseline FEV1 values as well as FEV1 as percent of predicted.

Summary statistics of compliance to study treatment and duration of exposure will be presented.

10.4. Analysis of Efficacy Data

10.4.1. Primary Efficacy Variable

Mean change in Forced Expiratory volume in 1 second (FEV 1) from baseline (visit 3) to Week 4 i.e. end of study visit (visit 5), will be analysed as primary end point.

FEV1 will be recorded at Visit 5 in the morning, prior to the dosing of inhaled medications.

"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.

10.4.2. 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: $\mu_T / \mu_R \leq \theta 1$ or $\mu_T / \mu_R \geq \theta 2$ versus H_A: $\theta_1 < \mu_T / \mu_R < \theta_2$

Where μ_T = mean of test treatment, and μ_R = 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 by Fieller's Theorem 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 and reference products to be considered equivalent to each other.

Superiority

Analysis of Covariance will be used to compare each active 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 ($p<0.05$), 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.

10.4.3. Secondary Efficacy Variables

- Mean change in FeNO value from base line (visit 3) to end of study visit (visit 5)
- Percentage of subjects with reduction of FeNO from Baseline (Visit 3) to End of Study (Visit 5)

10.4.4. Secondary Analysis

Descriptive Summary statistics will be presented for all secondary endpoints for active treatment groups.

Number and percentage of subjects meeting the criteria for reduction (atleast 20 % for FeNO ≥ 50 ppb values and atleast 10 % for FeNO < 50 ppb) in FeNO will be presented.

10.4.5. Imputation for Missing Data

For subjects included in the mITT population, and for those PP subjects who discontinue due to lack of treatment efficacy, Last Observation Carried Forward (LOCF) imputation will be used to impute missing EOS values for FEV1. If a subject discontinued due to lack of efficacy does

not have a post baseline value, then the baseline value will be carried forward. No imputation will be performed for missing safety data.

10.5. Safety Analysis

Summary of adverse events, Treatment Emergent Adverse Events, Serious adverse event, events leading to discontinuation and treatment related adverse events will be presented for each arm.

Summary of Vital signs and Laboratory parameter values at relevant time-points as well as change from baseline will be presented. Summary of use of various concomitant medications will be presented. By Subject data listings will be presented for all safety data captured on CRF/ eCRF.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP), AXIS/sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Site Initiation visit
- Early site visits post-enrollment
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, sponsor and/or AXIS Clinical Quality Assurance (CQA) Department may conduct periodic audits of the study processes, including, but not limited to study site, site visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

11.1. Direct Access to Source Documents and Study Monitoring

Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject entered into the study.

Investigator will allow the sponsor, AXIS, and authorized regulatory authorities to have direct access to all documents pertaining to the study.

The Sponsor has engaged the services of a Contract Research Organization (CRO), AXIS Clinicals, to perform all monitoring functions within this clinical study. AXIS' monitors will work in accordance with sponsor or AXIS' SOPs and have the same rights and responsibilities as monitors from the sponsor organization. Monitors will establish and maintain regular contact between the PI and the sponsor.

Monitors will evaluate the competence of the study site, informing the sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors

will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in CRF/eCRF with corresponding source data and to inform the PI of any errors or additions. Monitors will also direct adherence to the protocol at the investigator site. They will liaise with the sponsor for supply of study drugs and ensure appropriate storage conditions are maintained at investigator site.

Monitoring visits will be conducted according to the, ICH E6 Guideline for GCP, Monitoring plan and applicable local regulations. The monitor will visit the site while subjects are enrolled in the study at regular intervals according to the monitoring plan. The monitor will make written reports to the Sponsor on each occasion when contact with the PI is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the CRFs/ eCRFs will be compared with the original source documents (source data verification).

During the monitoring visit, the following items must be accessible for review but not limited to:

- Source documents, including ICFs, for all screened subjects (Monitor will conduct 100% source document verification)
- CRFs/ eCRFs for all subjects
- Investigational Product Accountability
- Site Master File
- Drug supply and clinical supply cabinets
- Storage of lab samples and study medication

All study staff will also need to make themselves available for review of monitoring issues.

11.2. Data Management/ Coding

Data generated within this clinical study will be handled according to relevant SOPs of the Clinical Data Management department of AXIS. In addition, inconsistency in data identified during the data cleaning process is resolved by issuing queries to site. The AE terms reported in the study will be coded using MedDRA.

11.3. Quality Assurance Audit

Investigator sites, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or AXIS. In addition, inspections may be conducted by regulatory bodies at their discretion.

The PI must notify Sponsor or AXIS promptly of any inspections scheduled by regulatory authorities.

11.4. Data Collection

Entries in CRF/eCRFs legible entries will be made. Any correction to the entered data will be made as per the CRF/ eCRF filling instructions. All corrections shall be authenticated with proper audit trail. Accuracy of the data will be attested by signatures off investigator. For laboratory values, Laboratory reports will be considered as source document.

For laboratory values, laboratory reports will be considered as source document.

12.0 ETHICS

12.1. Ethics Committee

Ethics committee (EC) approval will be obtained from an EC registered with CDSCO. PI will provide the Sponsor or AXIS with documentation of Institutional Ethics Committee (IEC) approval of the protocol, ICF and all documents required as per applicable regulations before the study may begin at the study sites. EC shall maintain all the study records for not less than 5 years from the date of study completion or termination of the trial. PI will supply documentation to the Sponsor or AXIS of required EC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The PI will report promptly to the EC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the PI will submit written summaries of the study status to the EC annually, or more frequently if requested by the EC. Upon completion of the study, the PI will provide the EC with a brief report of the outcome of the study, if required.

12.2. Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for GCP and/ or the applicable local drug and data protection laws and regulations.

12.3. Regulatory Approval

Study will be initiated only after obtaining approval from DCGI.

12.4. Subject Information and Informed Consent

A freely given informed consent will be obtained from all the subjects prior to any study specific procedures being carried out. In obtaining ICF investigator will comply with all applicable regulatory requirements, GCP and Ethical principles that have their origin in declaration of Helsinki. Investigator /designee shall fully inform the subject about all pertinent aspects of study including written informed consent. Subject will be given ample time to read informed consent and investigator shall address all the queries raised by the subject. Investigator/ designee shall also sign the ICF. A copy of completed signed ICF shall be given to subject. Subject shall be made aware of all the risks and benefits involved in the study. Subjects will also be made aware that in case of trial related injury/death, free medical management and financial compensation will be provided to subject/ nominee.

Subject will also be informed that they are free to withdraw at any point of time during the study. Written consent must be given by the subject and/or legal representative, only after the receipt of detailed information on the study.

Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

13.0 STUDY ADMINISTRATION

13.1. Administrative Structure

The following table provides a list of key individuals and their roles from the Sponsor and AXIS who will contribute to this study.

Table X: Study Administration Structure

Sponsor	**CRO**
Aurobindo Pharma Research Center-II Survey No -71&72, Indrakaran Village, Kandi Mandal, Sangareddy Dist -500 090, Telangana, India, Tel. no: +91-40-23040262,	**AXIS Clinicals Limited** 1-121/1, Miyapur Hyderabad-500049, INDIA Direct: +91-40-40408064 Fax: +91-40-40408060 E-mail: subhra.l@axisclinicals.com
IP Supplies	**Medical Monitoring and Support**
Aurolife, a subsidiary of Aurobindo Pharma, USA, Inc. 2929 Weck Dr., Durham, NC 27709	Dr. Mohammed Sajid Medical Manager-Clinical Research AXIS Clinicals Limited, 1-121/1, Miyapur, Hyderabad 500049, INDIA. Tel: +91 40 4040 8270 Email: Sajid.m@Axisclinicals.com
Statistical Analysis	**Drug Safety Reporting**
Mandar Oak, 1002, Siddhivinayaka, Plot No-03, Sector 14, New Panvel (W), Navi Mumbai, Maharashtra-410206, India AND/ OR Nadamuni Naidu.K Head of Biostatistics Inductive Quotient, Cavery's City Plaza, 2nd Floor, Sundar Nagar, Andhra Bank Building, Hyderabad-500038. Telephone: +91 40 23722238 Email id: naidu.adusumalli@inductivequotient.com	AXIS Clinicals Ltd, 1-121/1, Miyapur Hyderabad 500049, INDIA

Clinical Monitoring	Quality Assurance
AXIS Clinicals Ltd 1-121/1, Miyapur Hyderabad 500049, INDIA	AXIS Clinicals Ltd 1-121/1, Miyapur Hyderabad 500049, INDIA
Data Management and CDISC Facility	**Medical Writing**
AXIS Clinicals Ltd 1-121/1, Miyapur Hyderabad 500049, INDIA	AXIS Clinicals Ltd 1-121/1, Miyapur Hyderabad 500049, INDIA
Laboratory Services	
Any Designated Laboratory	

13.2. Data Handling and Record Keeping

The PI must maintain essential study documents (protocol and protocol amendments, completed CRF/eCRF, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 20 years after completion of all regulatory activity. These documents should be retained for a longer period if required by the applicable regulatory requirements and/ or the hospital/ institution in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to sponsor. The PI must contact sponsor prior to disposing of any study records.

13.3. Investigator Information

13.3.1. Investigator Obligations

This study will be conducted in accordance with the ICH-GCP, Nov 2016; and the applicable regulatory requirements inclusive of the GCP, Schedule Y- Drugs and Cosmetics (2nd Amendment) Rules, 2005 of Central Drugs Standard Control Organization (CDSCO) and ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2017); and the ethical principles that have their origin in the Declaration of Helsinki.

13.3.2. Protocol Deviations and Protocol Waivers

Investigator will conduct this study in accordance with protocol approved by IEC and DCGI. Under no circumstances, investigator shall deviate from protocol without prior permission from sponsor and EC.

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

In case of Pre planned protocol deviation i.e., protocol waivers, approval from Axis Clinicals shall be obtained.

13.3.3. Publication Policy

The rights of publication lie solely with sponsor.

13.3.4. Data Ownership

The data collected in this study are the sole property of Aurobindo Pharma, but not the hospital subject's record.

13.4. Financing and Insurance

Aurobindo Pharma is funding this study. In the event of study-related injury or death, insurance for the subjects and indemnity of the investigators and those of their employees, servants or agents, whose participation in this study has been documented, will be provided by Aurobindo Pharma, USA Inc. Insurance and liability will be in accordance with applicable law and GCP (ICH, November 2016). In case of SAEs occurring to clinical trial subject, Aurobindo Pharma will provide free medical management as long as required along with financial compensation in case of trial related injury and death.

14.0 REFERENCES

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8. Draft Guidance on Beclomethasone https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM481768.pdf
9. HIGHLIGHTS OF PRESCRIBING INFORMATION: QVAR® (beclomethasone dipropionate HFA), inhalation aerosol, for oral inhalation use https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020911s029s030lbl.pdf
10. Instructions for Use QVAR (Kyü-vär) (beclomethasone dipropionate HFA) Inhalation Aerosol https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020911s025lbl.pdf
11. GINA guidelines 2018
12. An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications

APPENDIX 1: SPONSOR PROTOCOL AGREEMENT

PROTOCOL 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) (0.04 mg/ INH) in male and/ or female subjects with Asthma [GroupI (Test): Beclomethasone Dipropionate 0.04 mg/ INH; Group II (Reference): QVAR® 40 mcg (Beclomethasone dipropionate HFA); and Group III: Placebo].

PROTOCOL NO: CR176-17

I, on behalf of Aurobindo Pharma have read reviewed and understood this protocol and thus approve it. I agree to comply with the applicable regulatory requirements of ICH – Good Clinical Practice, Schedule Y, Declaration of Helsinki, 21 CFR 312.120 and 21 CFR 320 regarding the obligations and role as a Sponsor of this study.

Signature Sponsor: _____ Date: _____

Printed Name: Dr. M. Joseph

Sponsor Title: Associate Vice President-Clinical Affairs
Specialty Products

Address of Sponsor: APL Research Centre-II,
Aurobindo Pharma Limited,
Survey No. 71 & 72, Indrakaran Village,
Kandi Mandal, Sangareddy dist – 502329, India.
Telephone: +91-8455223700, Ext: 1516
Mobile no: +91-9765800454.

APPENDIX 2: INVESTIGATOR PROTOCOL AGREEMENT

PROTOCOL 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) (0.04 mg/ INH) in male and/ or female subjects with Asthma [GroupI (Test): Beclomethasone Dipropionate 0.04 mg/ INH; Group II (Reference): QVAR® 40 mcg (Beclomethasone dipropionate HFA); and Group III: Placebo].

PROTOCOL NO: CR176-17

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staffs receive the appropriate information throughout the study.

Name:	
Address:	
Phone Number:	
Signature	Date

APPENDIX 3: Investigator's Global Evaluation (Assessed by Investigators)

An investigator-rated test measured on a 7-point scale, with scores ranging from 1 (very much improved) to 7 (very much worse); used to rate change in subject's condition over the course of the study.

Rate total improvement whether or not in your judgement it is due entirely to drug treatment.

Compared to his/her condition at Visit 3, how much has he/she changed?

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse.

APPENDIX 4: ASTHMA CONTROL QUESTIONNAIRE TEST

Patient's Name:_____ Today's Date:_____

Asthma Control Test™ (ACT) is:

- A quick test that provides a numerical score to assess asthma control.
- Recognized by the National Institutes of Health (NIH) in its 2007 asthma guidelines.[1]
- Clinically validated against spirometry and specialist assessment.[2]

PATIENTS:
1. Answer each question and write the answer number in the box to the right of each question.
2. Add your answers and write your total score in the TOTAL box shown below.
3. Discuss your results with your doctor.

									SCORE
1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?	All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	
2. During the past **4 weeks**, how often have you had shortness of breath?	More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	
3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	
4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	
5. How would you rate your **asthma** control during the **past 4 weeks**?	Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	
											TOTAL

If your score is 19 or less, your asthma may not be under control.

APPENDIX 5: NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM-ASTHMA DIAGNOSIS CRITERIA

i) Wheezing (high-pitched whistling sounds when breathing out) ☐ Yes ☐ No

(A lack of wheezing and a normal chest examination do not exclude asthma)

ii) History of any of the following:

- Cough (worse particularly at night) ☐ Yes ☐ No
- Recurrent wheeze ☐ Yes ☐ No
- Recurrent difficulty in breathing ☐ Yes ☐ No
- Recurrent chest tightness ☐ Yes ☐ No

iii) Symptoms occur or worsen in the presence of (any one of the following or more):

- Exercise ☐ Yes ☐ No
- Viral infection ☐ Yes ☐ No
- Inhalant allergens (e.g., animals with fur or hair, house-dust mites, mold, pollen) ☐ Yes ☐ No
- Irritants (tobacco or wood smoke, airborne chemicals) ☐ Yes ☐ No
- Changes in weather ☐ Yes ☐ No
- Strong emotional expression (laughing or crying hard) ☐ Yes ☐ No
- Stress ☐ Yes ☐ No
- Menstrual cycles ☐ Yes ☐ No

iv) Symptoms occur or worsen at night, awakening the patient ☐ Yes ☐ No

v) Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present ☐ Yes ☐ No

vi) Airflow obstruction is at least partially reversible, measured by spirometry ☐ Yes ☐ No

(Reversibility is determined by an increase in FEV1 of >200 mL and ≥12 percent from baseline measure after inhalation of short-acting beta2-agonist)

APPENDIX 6: ESCAPE CRITERIA FOR ASTHMA

Escape Criteria for Asthma

Assessing exacerbation severity

A brief focused history and relevant physical examination should be conducted concurrently with the prompt initiation of therapy, and findings documented in the notes. If the subject shows signs of severe life-threatening exacerbation, treatment with SABA, controlled oxygen and systemic corticosteroids should be initiated while arranging for the subject's urgent transfer to an acute care facility where monitoring and expertise are more readily available. Milder exacerbation can usually be treat in a primary care setting, depending on resources and expertise.

History

The history should include

- Timing of onset and cause of the present exacerbation
- Severity of asthma symptoms including any limiting exercise or disturbing sleep
- Any symptoms of anaphylaxis
- Risk factors for asthma related death

Physical examination

Physical examination should assess

- Signs of exacerbations severity including vital signs
- Complicating factors (eg. Pneumonia, pneumothorax etc)
- Signs of alternative conditions that could explain acute breathlessness (eg. Cardiac failure, pulmonary embolism etc)

Objective assessment

- Pulse oximetry, saturation level if <90% aggressive therapy would be needed
- Pulmonary function test (PEF/FEV1)

Treating Exacerbations

The main initial therapies include repetitive administration of SABA, early introduction of systemic corticosteroids and controlled flow oxygen supplementation. The aim is to rapidly relieve airflow obstruction and hypoxemia.

Inhaled short acting Beta$_2$ agonists

For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4-10 puffs every 20 minutes for the first hour) is usually the most effective and efficient way to achieve rapid reversal airflow limitation. After the first hour, the dose of SABA required varies from 4-10 puffs every 3-4 hours up to 6-10 puffs every 1-2 hours or more often. No additional SABA is needed if there is a good response to initial treatment.

Delivery of SABA by spacer device would be more beneficial.

Controlled oxygen Therapy (If available)

Oxygen therapy should be titrated against pulse oximetry (if available) to maintain oxygen saturation at 93-95%.

Systemic corticosteroids

Oral corticosteroids (OCS) should be given promptly, especially if the condition of subject deteriorating or had already increased his/her reliever and controller medication before presenting. The recommended dose of prednisolone is 1mg/kg body weight or maximum of 50mg/day. OCS should usually be continued for 5-7 days.

Controlled medication

The dose of controller medications should be increased for period of 2-4 weeks.

Antibiotics

Use of antibiotics generally not recommended unless there is strong evidence of lung infections.

Reviewing of responses

During treatment, subjects should be closely monitored and treatment titrated according to their response. Subjects who presents with signs of severe life-threatening exacerbations should be transferred immediately to an acute care facility.

Follow up

Discharge medications should include as needed reliever medications, short course of OCS and for more subject's regular controller treatment. Inhaler technique and adherence should be reviewed before discharge.

Management of asthma exacerbations & severe asthma exacerbations