# Vectura Limited

# Clinical Trial Protocol

**A Single-Dose, Open-Label, Randomized, Incomplete Block Design Trial to Characterize the Pharmacokinetics of VR647 Inhalation Suspension Delivered by the VR647 Inhalation System and Single Doses of Budesonide Delivered by a Conventional Jet Nebulizer in Pediatric Subjects Aged 4 to 8 Years with Wheezing, Reactive Airway Disease or Mild Asthma**

**PROTOCOL IDENTIFIER: VR647/1/002**

**Version 1.0 Date: 29 September 2017**

**IND Number: 126,135**

## TRIAL PERSONNEL

**Sponsor:**

Vectura Limited
1 Prospect West
Chippenham
Wiltshire SN14 6FH
United Kingdom
Tel: +44 1249 667700
[redacted]

**Responsible Medical Officer:**

Gary Burgess
VP-Medical
Vectura Limited
[redacted]

**Clinical Trial Manager:**

[redacted]
Study Manager
Vectura Limited
[redacted]

**Emergency Numbers**

**Emergency Contact:**

Gary Burgess
[redacted]

**Serious Adverse Event Reporting:**

Fax: +44 1483 431831 (Europe)
Fax: +1 617 507 9166 (United States)
Email: VecturaPV@primevigilance.com

**This trial will be conducted in compliance with:**

- **This protocol**
- **ICH E6(R2) GCP guidelines**
- **The applicable regulatory requirement(s)**
- **The general principles of the Declaration of Helsinki**

## PROTOCOL SYNOPSIS

<table>
<tr><td>Protocol identifier:</td><td>VR647/1/002</td></tr>
<tr><td>Trial title:</td><td>A Single-Dose, Open-Label, Randomized, Incomplete Block Design Trial to Characterize the Pharmacokinetics of VR647 Inhalation Suspension Delivered by the VR647 Inhalation System and Single Doses of Budesonide Delivered by a Conventional Jet Nebulizer in Pediatric Subjects Aged 4 to 8 Years with Wheezing, Reactive Airway Disease or Mild Asthma</td></tr>
<tr><td>Protocol version:</td><td>Version 1.0 Final</td></tr>
<tr><td>Sponsor:</td><td>Vectura Limited</td></tr>
<tr><td>Phase:</td><td>1</td></tr>
<tr><td>Objectives:</td><td>Primary objective:<ul><li>To characterize the pharmacokinetic (PK) profile of budesonide nebulizer suspension following administration of single oral inhalations of 5, 10 and 20 breaths of VR647 Inhalation Suspension delivered by the VR647 Inhalation System fitted with a mouthpiece and 1 mg/2 mL Pulmicort Respules® delivered by the conventional jet nebulizer.</li></ul>Secondary objectives:<ul><li>To evaluate parent(s')/legal guardian(s') satisfaction with the use of the conventional jet nebulizer and/or the VR647 Inhalation System fitted with a mouthpiece.</li><li>To evaluate the safety and tolerability of single doses of VR647 Inhalation Suspension delivered by the VR647 Inhalation System fitted with a mouthpiece in subjects with wheezing, reactive airway disease or mild asthma.</li></ul></td></tr>
<tr><td>Trial design:</td><td>This is an open-label, randomized, balanced, incomplete block design trial to characterize the PK of single doses of VR647 Inhalation Suspension delivered by the VR647 Inhalation System fitted with a mouthpiece and single doses of budesonide delivered by a conventional jet nebulizer in pediatric subjects aged 4 to 8 years with wheezing, reactive airway disease or mild asthma.<br>There will be a screening period of up to 30 days to confirm eligibility. Subjects who fulfill the enrollment criteria will be randomized to one of 12 treatment sequences (AB), (AC), (AD), (BA), (BC), (BD), (CA), (CB), (CD), (DA), (DB) or (DC), corresponding to the following treatment regimens:
<table>
<tr><th>Treatment regimen</th><th>Treatment description</th></tr>
<tr><td>A</td><td>5 breaths of VR647 Inhalation Suspension + VR647 Inhalation System</td></tr>
<tr><td>B</td><td>10 breaths of VR647 Inhalation Suspension + VR647 Inhalation System</td></tr>
<tr><td>C</td><td>20 breaths of VR647 Inhalation Suspension + VR647 Inhalation System</td></tr>
<tr><td>D</td><td>1 mg/2 mL Pulmicort Respules + conventional jet nebulizer</td></tr>
</table>
The Treatment Period will comprise two dosing visits, with a washout period of</td></tr>
</table>

| | |
|---|---|
| | 4 to 10 days between each dose. The PK of budesonide will be assessed at each dosing visit, with blood samples collected at the following time points: pre-dose, and at 20 minutes, 40 minutes, 1.5, 3, 4, 6 and 8 hours after the start of nebulization.<br>To aid with travel logistics due to early morning procedures on the day of dosing, sites may provide subjects and their parent(s)/legal guardian(s) the option of an overnight stay the day before dosing, until completion of procedures 8 hours after start of nebulization. Subjects will return to the clinic approximately 7 days after their last dose (second nebulization) for a followup assessment, which may instead be conducted by telephone interview with the parent(s)/legal guardian(s).<br>On each dosing day, the site staff will record on the inhalation checklist the overall quality of the inhalation maneuvers.<br>Parent(s')/legal guardian(s') satisfaction with the use of the conventional jet nebulizer and/or the VR647 Inhalation System and willingness to continue with the device(s) will be assessed by the modified Patient Satisfaction and Preference Questionnaire (PASAPQ).<br>Safety and tolerability will be assessed by measurement/recording of vital signs, physical examinations, adverse events (AEs), adverse device effects (ADEs), and concomitant medications. |
| **Sample size:** | The number of subjects for this trial is not based on any formal sample size calculation. Randomization of approximately 12 subjects to the trial is considered achievable. Subjects who discontinue from the trial early may be replaced with agreement from the sponsor in order to obtain data from 6 subjects for each PK profile.<br>The trial will aim to randomize at least one-third of subjects aged <7 years. |
| **Trial population:** | Male and female subjects 4 to 8 years of age, with physician-diagnosed wheezing, reactive airway disease or mild asthma. The diagnosis will be based on clinical criteria, subject and family history. Subjects should be otherwise healthy and should not suffer from any clinically significant medical conditions other than wheezing, reactive airway disease or asthma. Subjects should be using intermittent or regular non-steroidal medications commonly used for asthma, such as a short-acting $\beta_2$-agonist (SABA) or leukotriene receptor antagonist (LTRA), for a minimum of 28 days prior to entry into the trial.<br>Subjects must demonstrate they are able to use the VR647 Inhalation System and the conventional jet nebulizer effectively following training. |
| **Inclusion/Exclusion criteria:** | • **Inclusion criteria**<br>Subjects must fulfil all of the following criteria for entry into the trial.<br>1. Male or pre-menarchal female subjects.<br>2. Aged 4 to 8 years, inclusive.<br>3. Diagnosis of wheezing, reactive airway disease or mild asthma confirmed by a physician at least 3 months prior to screening.<br>4. Wheezing, reactive airway disease or mild asthma controlled by intermittent or regular non-steroidal medications commonly used for asthma, such as SABAs or LTRAs, for a minimum of 28 days prior to the Screening Visit.<br>5. Body weight ≥15 kg.<br>6. Parent(s')/legal guardian(s') ability to comprehend the nature of the trial and |

| | |
|---|---|
| | any hazards of their child participating in it. Parent(s')/legal guardian(s') ability to communicate satisfactorily with the investigator and support their child's participation in, and compliance with, the requirements of the entire trial.<br>7. Subject is able to demonstrate the ability to use the VR647 Inhalation System and the conventional jet nebulizer effectively during training.<br>8. Parent(s')/legal guardian(s') written consent for their child to participate after reading the consent form, and after having the opportunity to discuss the trial with the investigator or his/her delegate.<br>• **Exclusion criteria**<br>Subjects fulfilling any of the following exclusion criteria are not eligible for entry into the trial.<br>1. Clinically relevant abnormality (other than wheezing, reactive airway disease or mild asthma) identified at the screening assessment that, in the opinion of the investigator, could interfere with the objectives of the trial or the safety of the subject. The sponsor's medical officer should be consulted in case of any doubt.<br>2. Any medical condition (including respiratory tract infections) that, in the opinion of the investigator, could interfere with the objectives of the trial or the safety of the subject. The sponsor's medical officer should be consulted in case of any doubt.<br>3. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episodes.<br>4. Subjects currently using long-acting $\beta_2$-agonists.<br>5. History of surgery or medical intervention within 6 weeks before the Screening Visit, or planned surgery or medical intervention, that could interfere with the objectives of the trial or the safety of the subject.<br>6. Use of the following prescription medications within 28 days prior to the first treatment day: corticosteroids by any route, drugs that inhibit cytochrome P450 3A4 (CYP3A4; e.g. ritonavir and other drugs of this class for human immunodeficiency virus [HIV] prophylaxis, ketoconazole, itraconazole or similar azole anti-fungal drugs and macrolide antibiotics such as erythromycin). NOTE: Inhaled corticosteroid therapy should not be discontinued in order to satisfy this exclusion criterion if there is the possibility that this will result in a deterioration of the subject's asthma control.<br>7. Presence or history of severe adverse reaction or sensitivity to components of the trial medication.<br>8. Participation in another clinical trial of a new chemical entity, or new device within 30 days of dosing in this trial, or participation in this trial within 5 half-lives of receiving an experimental drug (whichever is longer).<br>9. Blood pressure or heart rate at screening considered abnormal by the investigator.<br>10. Family member of the subject or parent(s)/legal guardian(s) who is an |

<table>
<tr><td></td><td>employee of the investigational site or the sponsor, who is directly involved in the trial.</td></tr>
<tr><td>Test product, dose and mode of administration:</td><td>VR647 is the drug-device combination product consisting of VR647 Inhalation Suspension delivered by the VR647 Inhalation System, controlled by the VR647 Smart Card.<br>The VR647 Inhalation System comprises the VR647 Inhalation System 1 control unit that has an inspiration flow rate of 6 L/min, a nebulizer handset, a mouthpiece and a VR647 Smart Card designed specifically for this trial.<br>The VR647 Inhalation System is breath-actuated after a negative pressure is created at the mouthpiece on inhalation. Nebulization will continue until the target inhalation volume (i.e. the target number of breaths) is reached.<br>The investigational medicinal product is VR647 Inhalation Suspension (budesonide) 1 mg/2 mL. The dose of VR647 Inhalation Suspension administered to the subject will be controlled by individual study-specific VR647 Smart Cards configured to deliver 5, 10 or 20 breaths of VR647 Inhalation Suspension according to the following settings:
<table>
<tr><th>No. of breaths</th><th>Inspiration time (sec)</th><th>Predicted delivered dose (µg)[a]</th></tr>
<tr><td>5</td><td>4.0</td><td>16.2</td></tr>
<tr><td>10</td><td>4.0</td><td>29.4</td></tr>
<tr><td>20</td><td>4.0</td><td>53.6</td></tr>
</table>
a The predicted delivered dose represents the delivered (ex-mouthpiece) dose calculated according to the International Commission on Radiological Protection deposition model for orally inhaled particles.[1] The specific model used for the deposition calculation was published by Köbrich et al 1994.[2] The actual delivered dose (assessed in vitro) will be included in the clinical study report.<br>Commercial Pulmicort Respules (budesonide inhalation suspension 1 mg/2 mL) will be delivered by the conventional jet nebulizer (PARI Vios Aerosol Delivery System) operated to sputtering.<br>The VR647 Inhalation System and the conventional jet nebulizer will be set up by the trial site staff. Parental/legal guardian(s') assistance during administration will be permitted if required. Subjects and parent(s)/legal guardian(s) will receive training and demonstration for both the VR647 Inhalation System and the conventional jet nebulizer at the Screening Visit. Subjects must demonstrate that they are able to use the VR647 Inhalation System and the conventional jet nebulizer effectively following training. Additionally, prior to dosing, they will again be trained for the specific nebulizer to be used at each dosing visit, according to the randomization schedule.</td></tr>
<tr><td>Efficacy assessment:</td><td>Parent(s')/legal guardian(s') satisfaction with the use of the conventional jet nebulizer and/or the VR647 Inhalation System and willingness to continue with the device(s) will be evaluated using the modified PASAPQ.</td></tr>
</table>

| | |
|---|---|
| **Safety assessments:** | The safety and tolerability of VR647 will be assessed by measurement/recording of:<br>• Vital signs;<br>• Physical examination findings;<br>• AEs and ADEs;<br>• Concomitant medications. |
| **Pharmacokinetic variables:** | The following PK parameters will be derived for plasma budesonide for VR647 Inhalation Suspension and Pulmicort Respules:<br>• $AUC_{last}$: The area under the concentration-time curve, from time 0 to the last collection time point.<br>• $AUC_{inf}$: The area under the concentration-time curve, from time 0 to infinite time.<br>• $C_{max}$: Maximum observed concentration.<br>• $t_{max}$: Time to reach $C_{max}$.<br>• $t_{1/2}$: Time to reach terminal phase half-life. |
| **Endpoints:** | **Primary endpoints**<br>• The PK parameters $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, and $t_{1/2}$ of plasma budesonide (VR647 Inhalation Suspension or Pulmicort Respules).<br>**Secondary endpoints**<br>• Mean modified PASAPQ total score.<br>• Mean modified PASAPQ performance score.<br>• Mean modified PASAPQ satisfaction score.<br>• Mean modified PASAPQ score indicating willingness to continue with the device.<br>• Changes in vital signs.<br>• Changes in physical examination findings.<br>• AEs and serious adverse events (SAEs).<br>• ADEs and serious adverse device effects (SADEs).<br>• Use of concomitant medications. |
| **Statistical analysis:** | **Total Set**<br>The Total Set will consist of all subjects whose parent(s)/legal guardian(s) have signed an Informed Consent Form (ICF), including subjects withdrawn prior to randomization and randomized subjects who did not receive trial medication. Subject disposition will be summarized for the Total Set.<br>**Safety Set**<br>The Safety Set will be based on all randomized subjects (as treated) who receive at least one dose of trial medication. Subjects with documented failure to take at least one dose of trial medication after randomization will be excluded from the Safety Set. All available data for the Safety Set will be included in the safety analysis, which will be primarily descriptive.<br>All demographic and baseline characteristics will be summarized by descriptive |

| | |
|---|---|
| | statistics for the Safety Set.<br>**Full Analysis Set**<br>The Full Analysis Set (FAS) will include all subjects who provide evaluable data for the total score of the modified PASAPQ.<br>Analyses of the modified PASAPQ will be summarized by descriptive statistics for the FAS.<br>**Pharmacokinetic Set**<br>The PK Set will consist of all subjects who receive at least one dose of trial medication, have measurable plasma concentrations of budesonide and are without any major protocol deviation. The PK Set will be used for the PK analysis. The area under the curve (AUC) will be calculated using the log-linear trapezoidal method.<br>Descriptive statistics will be determined for PK parameters and exposure profiles of plasma budesonide levels delivered by the VR647 Inhalation System (via a mouthpiece) and the conventional jet nebulizer (via a mouthpiece) will be presented graphically. |
| **Duration of the trial:** | The total trial duration for each subject is approximately 47 days, which includes a 30-day screening period, two dosing visits with a washout period of 4 to 10 days between each dose, and a followup assessment approximately 7 days after last nebulization. |

## TABLE OF CONTENTS

## TABLE OF TABLES



## TABLE OF FIGURES

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation/Term | Definition |
|---|---|
| ADE | Adverse device effect |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AUC | Area under the curve |
| $AUC_{inf}$ | Area under the plasma concentration-time curve, from time 0 to infinite time |
| $AUC_{last}$ | Area under the plasma concentration-time curve, from time 0 to the last collection time point |
| CFR | Code of Federal Regulations |
| $C_{max}$ | Maximum observed concentration |
| CRF | Case Report Form |
| CV | Coefficient of variation |
| CYP3A4 | Cytochrome P450 3A4 |
| DMP | Data Management Plan |
| DPI | Dry powder inhaler |
| EDC | Electronic data capture |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GINA | Global Initiative for Asthma |
| GMP | Good Manufacturing Practice |
| HIV | Human immunodeficiency virus |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| $\lambda$ | Elimination rate constant |
| LTRA | Leukotriene receptor antagonist |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| PASAPQ | Patient Satisfaction and Preference Questionnaire |
| PI | Principal Investigator |
| PK | Pharmacokinetic(s) |
| pMDI | Pressurized metered-dose inhaler |
| PT | Preferred term |
| SABA | Short-acting $\beta_2$-agonist |
| SADE | Serious adverse device effect |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SDV | Source Data Verification |
| SEM | Standard error of the mean |
| SOC | System organ class |
| SOP | Standard Operating Procedure |
| $t_{1/2}$ | Time to reach terminal phase half-life |
| TEAE | Treatment-emergent adverse event |
| $t_{max}$ | Time to reach maximum observed concentration |
| UADE | Unanticipated adverse device effect |
| US | United States |
| VR647 | The drug-device combination product consisting of VR647 Inhalation Suspension delivered by the VR647 Inhalation System, controlled by the VR647 Smart Card |
| VR647 Inhalation Suspension | Budesonide 1 mg/2 mL |
| VR647 Inhalation System | The VR647 Inhalation System consists of the VR647 Inhalation System 1 control unit that has an inspiration flow rate of 6 L/min, a VR647 nebulizer handset, a mouthpiece and VR647 Smart Cards designed specifically for this trial |

# 1 BACKGROUND INFORMATION

## 1.1 Introduction

VR647 is a drug-device combination being developed in the United States (US) for the maintenance treatment of asthma and as a prophylactic therapy in children aged 12 months to 8 years. The drug-device combination product consists of VR647 Inhalation Suspension delivered by the VR647 Inhalation System, controlled by the VR647 Smart Card.

Asthma is a heterogeneous chronic inflammatory airway disease that is characterized by variable respiratory symptoms, recurrent episodes of reversible expiratory airflow limitation and episodic acute exacerbations of symptoms. Approximately 300 million people worldwide suffer from asthma. It is the most common chronic disease of childhood, and in up to half of people with asthma, symptoms begin during childhood. School absences, emergency department visits and hospitalizations make asthma the leading cause of childhood morbidity from chronic disease. The Global Initiative for Asthma (GINA) treatment guidance recommends a step-wise approach to asthma treatment, with the objective of maintaining asthma control whilst minimizing side effects associated with pharmacological treatment.[3]

Inhaled corticosteroids constitute an important component of asthma therapy, and are the preferred treatment for patients with asthma of any severity. Corticosteroids act locally at the site of administration to reduce inflammation and have been shown to inhibit multiple types of inflammatory cells and mediators involved in allergic and non-allergic-mediated inflammation. Hence a number of corticosteroids, including budesonide, have been developed as inhaled therapies for the treatment of asthma and are now considered as first-line therapy in all asthma treatment guidelines.

Budesonide is a potent glucocorticoid with a high selectivity for the glucocorticoid receptor and has been approved for use as an inhaled therapy for over 30 years. It has been marketed in a pressurized metered-dose inhaler (pMDI, Pulmicort®, AstraZeneca), as a dry powder inhaler (DPI, Pulmicort Turbuhaler®, AstraZeneca) and in the nebulized form (budesonide inhalation suspension, Pulmicort Respules®, AstraZeneca). Budesonide nebulizer suspension is one of the few controller therapies approved as a maintenance treatment of asthma and as prophylactic therapy in children less than 4 years of age. Hence it is an important treatment option for those children whose symptom pattern indicates asthma and who are uncontrolled, and/or have frequent wheezing episodes (3 or more episodes per season), and for older children who do not have the co-ordination and technique necessary to operate pMDI and

DPI devices.[3] However, compressed air-driven jet nebulizers, which are most commonly used to deliver nebulized therapy, have the disadvantage of long drug delivery times.

The VR647 Inhalation System is a novel, drug-specific breath-actuated nebulizer to deliver VR647 Inhalation Suspension (budesonide). The device actively controls the patient's inhalation flow rate and volume of aerosol delivered to the lungs during nebulization. The combination of a controlled rate and volume of aerosol delivery significantly increases drug deposition within the lungs, particularly to the peripheral airways and delivers drug only while the patient is inhaling. The system incorporates a Smart Card to precisely control drug delivery to the patient. These features make the VR647 Inhalation System more efficient than traditional jet nebulizers, reducing both the amount of drug that needs to be delivered and the time taken to administer treatment.

The goal of the VR647 clinical program is to demonstrate that the VR647 Inhalation System improves delivery of nebulized budesonide and reduces nebulization time when used as a maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age. In addition, by providing feedback on breathing technique during nebulization, and measuring treatment compliance for feedback to the patient, caregiver and healthcare professional, greater levels of asthma control may be observed than with currently available nebulized budesonide products, without compromising safety.

Based on preliminary data from Study VR647/1/001, the pharmacokinetics (PK) of budesonide after administration with the VR647 Inhalation System and a conventional jet nebulizer in both healthy and mild asthmatic adult subjects have been well characterized. With the addition of summary pediatric PK data presented for Pulmicort,[4] lung deposition modelling and allometry,[5] the PK for a range of doses in children using both devices have been predicted albeit with the use of underlying assumptions. The purpose of this trial is to characterize the PK of three doses (5, 10 and 20 breaths) of VR647 Inhalation Suspension administered by the VR647 Inhalation System to assess whether increased efficiency and faster delivery times with the VR647 Inhalation System observed in adults are maintained in pediatric subjects with wheezing, reactive airway disease or mild asthma. The PK and delivery time of budesonide nebulizer suspension delivered by conventional means will also be characterized. Notably, the VR647 Inhalation Suspension doses to be assessed in this trial are predicted to provide systemic exposures within the known safety limits for budesonide.

### 1.2 Name and Description of Investigational Medicinal Product(s)

The Investigational Medicinal Product is VR647 Inhalation Suspension (budesonide 1 mg/2 mL), which is delivered by the VR647 Inhalation System. The VR647 Inhalation System comprises the VR647 Inhalation System 1 control unit that has an inspiration flow rate of 6 L/min, a nebulizer handset, a mouthpiece, and VR647 Smart Cards designed specifically for this trial.

### 1.3 Nonclinical Data

A summary of nonclinical data relevant to budesonide inhalation suspension is described in Sections 10 and 13 of the Pulmicort Respules United States Prescribing Information.[6]

### 1.4 Clinical Data

Clinical studies conducted with VR647 Inhalation Suspension are described in the current VR647 Investigator's Brochure.[7]

In addition, Study VR647/1/001 was a randomized, open-label, crossover trial to compare the PK, safety and tolerability of single doses of VR647 Inhalation Suspension delivered by the VR647 Inhalation System with single doses of budesonide delivered by a conventional jet nebulizer in healthy adult volunteers and adult asthma subjects. Parts 1 and 2 included healthy volunteers and Part 3 included subjects with mild asthma. Dosing in this trial is complete; final data are pending.

### 1.5 Summary of Known and Potential Risks and Benefits

Delivery of budesonide by nebulization for the maintenance treatment and prophylactic therapy of asthma has been an approved and accepted treatment in children aged 12 months to 8 years of age since 2000 in the US[6] and in children 3 months to 12 years of age, children 12 years and older, and adults (including the elderly) in Europe[8] for over 30 years. Budesonide has a well-established and understood safety and efficacy profile. Thus the risks associated with the use of budesonide in this trial are well characterized.

The VR647 Inhalation System 1 is a variant of the 510(k) cleared AKITA JET® Inhalation System (K090730), with the following principal difference. The VR647 Inhalation System 1 provides an inhalation flow rate of 6 L/min, which is more suited to aerosol delivery in children, whereas the AKITA JET Inhalation System provides a flow rate of 12 L/min.

The safety monitoring practices employed by this protocol, i.e. vital signs, physical examination, concomitant medications, and adverse event (AE) and adverse device effect (ADE) questioning are adequate to protect the subjects' safety.

The total volume of blood planned for collection from each subject over the course of the trial (approximately 16 mL) presents no undue risk to the subjects.

### 1.6 Route of Administration, Dosage, Dosage Regimen and Treatment Period(s)

Single doses of VR647 Inhalation Suspension (5, 10 or 20 breaths) delivered by the VR647 Inhalation System, or Pulmicort Respules (budesonide inhalation suspension 1 mg/2 mL) delivered by the conventional jet nebulizer (PARI Vios® Aerosol Delivery System) will be administered.

The Treatment Period will include two dosing visits and subjects will be randomized to one of 12 treatment sequences, as follows:

**Table 1: Treatment sequences**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period 1** | A | A | A | B | B | B | C | C | C | D | D | D |
| **Period 2** | B | C | D | A | C | D | A | B | D | A | B | C |

A = 5 breaths of VR647 Inhalation Suspension + VR647 Inhalation System;
B = 10 breaths of VR647 Inhalation Suspension + VR647 Inhalation System;
C = 20 breaths of VR647 Inhalation Suspension + VR647 Inhalation System;
D = 1 mg/2 mL Pulmicort Respules + conventional jet nebulizer.

The dose of VR647 Inhalation Suspension administered to the subject will be controlled by individual trial-specific VR647 Smart Cards configured to deliver 5, 10 or 20 breaths of VR647 Inhalation Suspension according to the following settings:

**Table 2: Predicted doses delivered for VR647 inhalation suspension**

| Number of breaths | Inspiration time (sec) | Predicted delivered dose (µg)[a] |
|---|---|---|
| 5 | 4.0 | 16.2 |
| 10 | 4.0 | 29.4 |
| 20 | 4.0 | 53.6 |

[a] The predicted delivered dose represents the delivered (ex-mouthpiece) dose calculated according to the International Commission on Radiological Protection deposition model for orally inhaled particles.[1] The specific model used for the deposition calculation was published by Köbrich et al 1994.[2] The actual delivered dose (assessed in vitro) will be included in the clinical study report.

The VR647 Inhalation System is breath-actuated after a negative pressure is created at the mouthpiece on inhalation. Nebulization will continue until the target inhalation volume (i.e. the target number of breaths) is reached.

Pulmicort Respules will be administered until 1 minute after the nebulizer starts to sputter.

## 1.7 Population to be Studied

Male and female subjects aged 4 to 8 years, with physician-diagnosed wheezing, reactive airway disease or mild asthma will be enrolled in this trial. The diagnosis will be based on clinical criteria, subject and family history. Subjects should be otherwise healthy and should not suffer from any clinically significant medical conditions (other than wheezing, reactive airway disease or asthma) that, in the opinion of the investigator, could interfere with the objectives of the trial or the safety of the subject. Subjects should be using intermittent or regular non-steroidal medications commonly used for asthma, such as a short-acting $\beta_2$-agonist (SABA) or leukotriene receptor antagonist (LTRA), for a minimum of 28 days prior to screening for the trial.

Subjects must demonstrate they are able to use the VR647 Inhalation System and the conventional jet nebulizer effectively following training.

## 1.8 Compliance Statement

The trial will be conducted in compliance with the protocol, informed consent regulations, the Declaration of Helsinki and the International Council for Harmonization (ICH) guidelines related to Good Clinical Practice (GCP). In addition, the trial will adhere to all local regulatory requirements.

The electronic data capture (EDC) system and other applicable electronic systems used in the conduct of the trial will comply with the Food and Drug Administration (FDA), 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

All episodes of noncompliance will be documented and addressed.

# 2 OBJECTIVES

## 2.1 Primary Objective

To characterize the PK profile of budesonide nebulizer suspension following administration of single oral inhalations of 5, 10 and 20 breaths of VR647 Inhalation Suspension delivered by the VR647 Inhalation System fitted with a mouthpiece and 1 mg/2 mL Pulmicort Respules delivered by the conventional jet nebulizer.

## 2.2 Secondary Objectives

- To evaluate parent(s')/legal guardian(s') satisfaction with the use of the conventional jet nebulizer and/or the VR647 Inhalation System fitted with a mouthpiece.
- To evaluate the safety and tolerability of single doses of VR647 Inhalation Suspension delivered by the VR647 Inhalation System fitted with a mouthpiece in subjects with wheezing, reactive airway disease or mild asthma.

# 3 TRIAL DESIGN

## 3.1 Overall Trial Design and Plan

This is a Phase 1, open-label, randomized, balanced, incomplete block design trial to characterize the PK of single doses of VR647 Inhalation Suspension delivered by the VR647 Inhalation System fitted with a mouthpiece and single doses of budesonide delivered by the conventional jet nebulizer in pediatric subjects aged 4 to 8 years with wheezing, reactive airway disease or mild asthma.

The overall trial design is summarized in Figure 1.

**Figure 1: Overall trial design**

| **Screening Period** | | | **Treatment 1** | | **Treatment 2** | | **Followup** |
|---|---|---|---|---|---|---|---|
| **Visit 1** | | | **Visit 2** | | **Visit 3** | | **Visit 4/ Telephone interview** |
| Baseline measurements<br>Eligibility | | **Randomization** | Dose<br>PK<br>Safety<br>Efficacy | | Dose<br>PK<br>Safety<br>Efficacy | | Safety |
| Day -32 | Day 2 | | Day -1 | Day 1 | Day 7±3 | Day 8±3 | Day 15±2 |
| 2 to 30 days | | | 4 to 10 days | | 5 to 9 days | | |

There will be a screening period of up to 30 days to confirm eligibility. Subjects who fulfill the enrollment criteria will be randomized to one of 12 treatment sequences, as detailed in Section 1.6.

The VR647 Inhalation System and the conventional jet nebulizer will be set up by the trial site staff. Parental/legal guardian(s') assistance during administration will be permitted if required.

Subjects and parent(s)/legal guardian(s) will receive training and demonstration for both the VR647 Inhalation System and the conventional jet nebulizer at the Screening Visit. Subjects must demonstrate that they are able to use the VR647 Inhalation System and the conventional

jet nebulizer effectively following training. Additionally, prior to dosing, they will again be trained for the specific nebulizer to be used at each dosing visit, according to the randomization schedule.

The Treatment Period will comprise two dosing visits, with a washout period of 4 to 10 days between each dose. To aid with travel logistics due to early morning procedures on the day of dosing, sites may provide subjects and their parent(s)/legal guardian(s) the option of an overnight stay the day before dosing, until completion of procedures 8 hours after the start of nebulization.

Subjects will return to the clinic approximately 7 days after their last dose (second nebulization) for a followup assessment, which may instead be conducted by telephone interview with the parent(s)/legal guardian(s).

Blood samples for the assay of plasma budesonide levels will be collected at both dosing visits, at the times specified in Section 9.1.1.

On each dosing day, the site staff will record on the inhalation checklist the overall quality of the inhalation maneuvers.

Parent(s')/legal guardian(s') satisfaction with the use of the conventional jet nebulizer and/or VR647 Inhalation System and willingness to continue with the device(s) will be assessed by the modified Patient Satisfaction and Preference Questionnaire (PASAPQ).

Safety and tolerability will be assessed by measurement/recording of vital signs, physical examinations, AEs, ADEs, and concomitant medications.

## 3.2 Trial Endpoints

### 3.2.1 Primary Endpoints

The following PK parameters for plasma budesonide for VR647 Inhalation Suspension and Pulmicort Respules will be derived:

- $AUC_{last}$ The area under the concentration-time curve, from time 0 to the last collection time point.
- $AUC_{inf}$ The area under the concentration-time curve, from time 0 to infinite time.
- $C_{max}$ Maximum observed concentration.

- $t_{max}$ Time to reach $C_{max}$.
- $t_{1/2}$ Time to reach terminal phase half-life.

### 3.2.2 Secondary Endpoints

- Mean modified PASAPQ total score.
- Mean modified PASAPQ performance score.
- Mean modified PASAPQ satisfaction score.
- Mean modified PASAPQ score indicating willingness to continue with the device.
- Changes in vital signs.
- Changes in physical examination.
- AEs and serious adverse events (SAEs).
- ADEs and serious adverse device effects (SADEs).
- Use of concomitant medications.

## 3.3 Randomization

Each subject will be assigned a unique subject identification number upon screening. Subjects who complete all screening assessments and are confirmed as eligible by the Principal Investigator (PI or medically qualified designee) will be randomized to receive treatment according to one of 12 pre-defined treatment sequences, as detailed in Section 1.6.

## 3.4 Blinding

This is an open-label trial.

## 3.5 Trial Duration

The total trial duration for each subject is approximately 47 days, which includes a 30-day screening period, two dosing visits with a washout period of 4 to 10 days between each dose, and a followup assessment approximately 7 days after last nebulization.

### 3.6 Criteria for Stopping the Trial

The sponsor may terminate the trial at any time for any reason.

### 3.7 Definition of End of Trial

The end of the trial is defined as the last subject undergoing the last assessment of the trial.

# 4 TRIAL POPULATION

## 4.1 Number of Subjects

Approximately 12 subjects will be randomized in the trial. The trial will aim to randomize at least one-third of subjects aged <7 years.

## 4.2 Inclusion Criteria

Subjects must fulfil all of the following inclusion criteria for entry into the trial:

1. Male or pre-menarchal female subjects.
2. Aged 4 to 8 years, inclusive.
3. Diagnosis of wheezing, reactive airway disease or mild asthma confirmed by a physician at least 3 months prior to screening.
4. Wheezing, reactive airway disease or mild asthma controlled by intermittent or regular non-steroidal medications commonly used for asthma, such as SABAs or LTRAs, for a minimum of 28 days prior to the Screening Visit.
5. Body weight ≥15 kg.
6. Parent(s')/legal guardian(s') ability to comprehend the nature of the trial and any hazards of their child participating in it. Parent(s')/legal guardian(s') ability to communicate satisfactorily with the investigator and support their child's participation in, and compliance with, the requirements of the entire trial.
7. Subject is able to demonstrate the ability to use the VR647 Inhalation System and the conventional jet nebulizer effectively during training.
8. Parent(s')/legal guardian(s') written consent for their child to participate after reading the consent form, and after having the opportunity to discuss the trial with the investigator or his/her delegate.

### 4.3 Exclusion Criteria

Subjects fulfilling any of the following exclusion criteria are not eligible for entry into the trial:

1. Clinically relevant abnormality (other than wheezing, reactive airway disease or mild asthma) identified at the screening assessment that, in the opinion of the investigator, could interfere with the objectives of the trial or the safety of the subject. The sponsor's medical officer should be consulted in case of any doubt.
2. Any medical condition (including respiratory tract infections) that, in the opinion of the investigator, could interfere with the objectives of the trial or the safety of the subject. The sponsor's medical officer should be consulted in case of any doubt.
3. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episodes.
4. Subjects currently using long-acting $\beta_2$-agonists.
5. History of surgery or medical intervention within 6 weeks before the Screening Visit, or planned surgery or medical intervention, that could interfere with the objectives of the trial or the safety of the subject.
6. Use of the following prescription medications within 28 days prior to the first treatment day: corticosteroids by any route, drugs that inhibit cytochrome P450 3A4 (CYP3A4; e.g. ritonavir and other drugs of this class for human immunodeficiency virus [HIV] prophylaxis, ketoconazole, itraconazole or similar azole anti-fungal drugs and macrolide antibiotics such as erythromycin). NOTE: Inhaled corticosteroid therapy should not be discontinued in order to satisfy this exclusion criterion if there is the possibility that this will result in a deterioration of the subject's asthma control.
7. Presence or history of severe adverse reaction or sensitivity to components of the trial medication.
8. Participation in another clinical trial of a new chemical entity, or new device within 30 days of dosing in this trial, or participation in this trial within 5 half-lives of receiving an experimental drug (whichever is longer).
9. Blood pressure or heart rate at screening considered abnormal by the investigator.

10. Family member of the subject or parent(s)/legal guardian(s) who is an employee of the investigational site or the sponsor, who is directly involved in the trial.

### 4.4 Withdrawal of Subjects from the Trial

Each subject and their parent(s)/legal guardian(s) will be informed of their right to withdraw from the trial at any time and for any reason.

The investigator may withdraw a subject from the trial at any time if he/she considers that the subject's health is compromised by remaining in the trial or the subject or parent(s)/legal guardian(s) is (are) not sufficiently cooperative.

The investigator must complete a withdrawal form if a subject withdraws. The reasons for any subject withdrawal will be recorded on source documentation and also noted in the Case Report Form (CRF).

If a subject drops out or is withdrawn after one dose, every effort will be made to collect any AE/ADE and concomitant medication data, outstanding or occurring since that dose. Withdrawn subjects may not be rescreened for the trial.

In the event of any abnormalities considered to be clinically significant and related to the trial medication by the investigator, subjects will be followed up with appropriate medical management until there is a return to normal or baseline values.

Reasonable effort should be made by the investigator to contact all subjects by their parent(s)/legal guardian(s) for the followup assessment. All such efforts should be recorded in the source documentation.

### 4.5 Replacement of Subjects

Subjects who discontinue from the trial early may be replaced with agreement from the sponsor.

# 5 TREATMENT OF SUBJECTS

## 5.1 Description of Investigational Medicinal Product(s)

The Investigational Medicinal Product is VR647 Inhalation Suspension (budesonide) 1 mg/2 mL, which is delivered by the VR647 Inhalation System. The VR647 Inhalation System consists of the VR647 Inhalation System 1 control unit that has an inspiration flow rate of 6 L/min, a VR647 nebulizer handset, a mouthpiece and VR647 Smart Cards designed specifically for this trial.

VR647 Inhalation Suspension is a white to off-white sterile liquid suspension containing budesonide and the excipients sodium chloride, disodium edetate, Polysorbate 80, anhydrous citric acid and sodium citrate in water for injection.

VR647 Inhalation Suspension is presented in plastic strips of five single-dose ampules in sealed aluminum foil laminate pouches.

## 5.2 Supply, Packaging, Labelling and Storage

Manufacture, packaging and labelling of VR647 Inhalation Suspension will be performed according to Good Manufacturing Practice (GMP) standards by the sponsor or a vendor selected by the sponsor.

All supplies of VR647 Inhalation Suspension and the VR647 Inhalation System will be provided to the trial sites by the sponsor. Commercial Pulmicort Respules and the conventional jet nebulizer will be procured for trial use by the trial sites or a vendor appointed by the sponsor.

The PI or medically qualified designee will check the amount and condition of the drugs and nebulizers received and complete the acknowledgement of receipt form.

Products that require temperature control during shipment will be monitored during the shipping process and records retained by the sponsor and clinical site.

An initial shipment of supplies will be sent to the site/purchased by the site as required, and additional supplies may be sent/purchased upon request.

All trial products (trial drugs, VR647 Inhalation System, Smart Cards, etc.) must be stored in a secure environment with restricted access, under the appropriate storage conditions.

VR647 Inhalation Suspension should be stored upright below 77°F (25°C). It should not be refrigerated or frozen and should be stored in the original container in order to protect the

product from light. Pulmicort Respules should be stored upright at controlled room temperature (68 to 77°F [20 to 25°C]), and protected from light. If the storage conditions fall outside of this range, the site(s) will report the temperature excursion to the sponsor. The sponsor will provide disposition guidance regarding the ongoing use of the product. Used trial products should be stored in a location separate from unused trial products.

Records of the site storage conditions during the period of the trial must be maintained (e.g. records of the date and time and initials of person checking, and the daily (weekday) temperatures of the area used for storage of trial drug) and provided to the sponsor for retention in the Trial Master File.

Unit dose labelling of VR647 Inhalation Suspension and Pulmicort Respules for individual subject use will be performed by each site according to the randomization assignment.

### 5.3 Accountability Records

The PI (or medically qualified designee) is responsible for accountability of all used and unused trial drug supplies at the site.

A trial drug accountability form will be completed by the PI (or medically qualified designee) and filed in the Investigator Site File (ISF). The trial product accountability forms should be kept current.

At the end of the trial, a final trial drug reconciliation statement must be completed by the PI (or medically qualified designee) and provided to the sponsor.

All trial drug accountability forms must be made available for inspection by the monitor, sponsor or representative, and regulatory agency inspectors.

At the end of the trial, as directed in writing by the sponsor, and after final accountability has been verified by the trial monitor, all trial drug supplies including devices and unused, partially used, or empty ampules, will be destroyed by the site or an approved vendor, and a certificate of destruction issued to the sponsor. Smart Cards used for dosing subjects with the VR647 Inhalation System will be returned to the sponsor upon request.

The sponsor or representative must be granted access on reasonable request to check drug, device and Smart Card storage, dispensing procedures and accountability records.

## 5.4 Concomitant Medication and Dietary Supplements

Per the inclusion criteria (Section 4.2), eligible subjects will be taking non-steroidal medications commonly used for asthma, such as SABAs (e.g. albuterol) or LTRAs (e.g. montelukast), for a minimum of 28 days prior to the Screening Visit. The use of SABAs or LTRAs is allowed to continue during the trial. Albuterol should not be used for at least 6 hours before nebulization, as the resulting bronchodilation may artificially increase the plasma concentration of budesonide.

The following medications are prohibited within 28 days prior to the first treatment day and during the trial:

- Corticosteroids by any route including topical (apart from trial treatment).
- Oral or inhaled long-acting $\beta_2$-agonists.
- Inhibitors of CYP3A4, including
  - Ritonavir and drugs of this class for HIV prophylaxis.
  - Ketoconazole, itraconazole and similar azole antifungal drugs.
  - Macrolide antibiotics (e.g. erythromycin).

NOTE: Inhaled corticosteroid therapy should not be discontinued in order to satisfy the study exclusion criteria if there is the possibility that this will result in a deterioration of the subject's asthma control.

All prior and concomitant treatments, including dietary supplements, taken by subjects at the time of screening and during the trial will be recorded in the CRF, along with their daily dosage, duration and reasons for administration. Subjects who have received any prohibited concomitant treatment may be withdrawn from the trial at the discretion of the investigator.

## 5.5 Procedures for Monitoring Subject Compliance

Full training on the use and operation of the nebulizer systems will be provided by the sponsor to the trial site staff who will then train subjects and parent(s)/legal guardian(s). The training provided to the site staff will also include training on the maintenance of the nebulizer equipment. The VR647 Inhalation System and the conventional jet nebulizer will be set up by the trial site staff.

Subject compliance will be assessed by the site staff who will ensure that each randomized subject receives single doses of VR647 Inhalation Suspension using the VR647 Inhalation System or Pulmicort Respules using the conventional jet nebulizer, in accordance with the randomization scheme. Parental/legal guardian(s') assistance during administration will be permitted if required.

Start and stop times of nebulization will be captured in the CRFs by the site staff.

The site staff will record on the inhalation checklist the overall quality of the inhalation maneuvers.

Compliance with the VR647 Inhalation System will also be collected on the VR647 Smart Cards.

### 5.6 Life Style Restrictions

Not applicable.

# 6 TRIAL PROCEDURES

## 6.1 Schedule of Assessments

The schedule of procedures and assessments during the trial is summarized and presented in Table 4 (Section 17.1).

## 6.2 Trial Visits and Procedures

To aid with travel logistics due to early morning procedures on the day of dosing, sites may provide subjects and their parent(s)/legal guardian(s) the option of an overnight stay the day before dosing (Day -1 and Day 7 [±3 days] for Treatment Periods 1 and 2, respectively). Otherwise, subjects will be admitted on the day of dosing (Day 1 and Day 8 [±3 days] for Treatment Periods 1 and 2, respectively). All subjects will remain at the trial site on the dosing days until the completion of procedures 8 hours after the start of nebulization.

### 6.2.1 Visit 1 (Day -32 to Day -2): Screening

Screening evaluations will take place within 32 days prior to dosing. After obtaining written parental (or appropriate legal representative) informed consent, and written subject assent (as appropriate), the following assessments/procedures will be performed during the Screening Visit to evaluate subjects' eligibility to receive trial treatment:

- Collection of demographic data;
- Collection of medical and surgical history (including asthma history);
- Collection of prior and concomitant medications information;
- Vital signs;
- Physical examination;
- Measurement of height and weight;
- Training on use of both nebulizers for subjects and parent(s)/legal guardian(s);
- Confirmation of overall eligibility versus the inclusion and exclusion criteria;
- Recording of AEs.

### 6.2.2 Visit 2 (Day -1 to Day 1): Treatment Period 1

Subjects' continued eligibility will be confirmed according to the inclusion and exclusion criteria, and eligible subjects will be randomized to one of 12 treatment sequences, as detailed in Section 1.6.

#### *6.2.2.1 Pre-Dosing Procedures*

The following assessments/procedures will be performed on Day 1 prior to dosing:

- Nebulizer training for subjects and parent(s)/legal guardian(s);
- Collection of pre-dose PK blood sample;
- Vital signs;
- Collection of concomitant medications information;
- Recording of AEs.

#### *6.2.2.2 Post-Dosing Procedures*

The following assessments/procedures will be performed on Day 1 after dosing:

- Completion of the inhalation checklist;
- Collection of post-dosing PK blood samples at the times specified in Section 9.1.1;
- Vital signs;
- Completion of the modified PASAPQ;
- Collection of concomitant medications information;
- Recording of AEs and ADEs.

### 6.2.3 Visit 3 (Day 7±3 Days to Day 8±3 Days): Treatment Period 2

#### *6.2.3.1 Pre-Dosing Procedures*

The following assessments/procedures will be performed on Day 8 (±3 days) prior to dosing:

- Nebulizer training for subjects and parent(s)/legal guardian(s);

- Collection of pre-dose PK blood sample;
- Vital signs;
- Physical examination (if an AE was reported at any point during the trial and was ongoing prior to the second nebulization);
- Collection of concomitant medications information;
- Recording of AEs and ADEs.

#### *6.2.3.2 Post-Dosing Procedures*

The following assessments/procedures will be performed on Day 8 after dosing:

- Completion of the inhalation checklist;
- Collection of post-dosing PK blood samples at the times specified in Section 9.1.1;
- Vital signs;
- Physical examination;
- Completion of the modified PASAPQ;
- Collection of concomitant medications information;
- Recording of AEs and ADEs.

### 6.2.4 Visit 4 (Day 15±3 Days): Followup Assessment

Subjects will return to the clinic approximately 7 days after their last dose (second nebulization) for a followup assessment; which may instead be conducted by telephone interview with the parent(s)/legal guardian(s). During the followup assessment, concomitant medications information will be collected, and AEs and ADEs will be recorded.

### 6.2.5 Early Withdrawal Visit

For subjects withdrawn early from the trial (after first nebulization), the same assessments as at the Followup Assessment Visit will be conducted.

## 6.3 Total Blood Volume

The planned blood sample collections for PK assessments are as follows:

**Table 3: Approximate volume of blood collected for budesonide pharmacokinetics**

| Visit | Blood volume |
|---|---|
| Visit 2 (Period 1) | 8 x 1 mL |
| Visit 3 (Period 2) | 8 x 1 mL |
| Approximate total | 16 mL |

The total blood volume to be collected is approximately 16 mL; approximately 8 mL to be taken within any 24-hour period.

# 7 ASSESSMENT OF EFFICACY

## 7.1 Modified Patient Satisfaction and Preference Questionnaire

The PASAPQ[9] is a validated, multi-item measure of satisfaction and preference with inhaler devices that is designed to be easy to understand and administer to patients with asthma and chronic obstructive pulmonary disease. The modified PASAPQ is based on the original 15-item validated version of the PASAPQ and has been adapted to assess nebulizer use (and for this trial excludes assessment of set-up and handling, as this is performed by trial staff). The answers are measured using a 7-point scale for Questions 1 to 9 (1 means very dissatisfied and 7 means very satisfied) and a 100-point scale for Question 10. Four questions (Questions 1, 2, 6 and 7) generate the Performance domain, and the first 8 questions generate the Total Score domain. Question 9 asks for overall satisfaction with the device(s) used in the trial, and Question 10 asks for willingness to continue with the device(s) used in the trial. The modified PASAPQ is included in Section 17.3.

# 8 ASSESSMENT OF SAFETY AND TOLERABILITY

The PI or medically qualified designee will review results of safety assessments on a regular basis and the sponsor must be kept fully informed of any clinically significant findings either at screening or subsequently during trial conduct. All safety data will be recorded by the site staff in the CRF and in the source documents.

## 8.1 Medical and Surgical History

The PI or medically qualified designee will be responsible for review of the medical and surgical history of subjects obtained at screening to ensure that they meet the criteria for eligibility for the trial, including wheezing, reactive airway disease or mild asthma history.

The following documents may be needed for review:

- Parent(s)/legal guardian(s) or subject-volunteered information.
- Parent(s)/legal guardian(s) or subject responses to questioning by PI (or medically qualified designee).
- Confirmation of medical and surgical history (including asthma) and medication status will be requested from the primary care physician if deemed necessary.

## 8.2 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) will be assessed as presented in the Schedule of Assessments in Section 17.1.

Blood pressure and heart rate measurements will be recorded after 5 minutes' rest with subjects in a supine, semi-recumbent or seated position.

Any changes from baseline (pre-dose value on Day 1) in blood pressure and heart rate findings judged to be clinically significant by the PI (or medically qualified designee) will be recorded as AEs. In such cases, vital signs will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the PI (or medically qualified designee) or until the abnormality can be explained by an appropriate diagnosis.

## 8.3 Physical Examination

At the times presented in the Schedule of Assessments in Section 17.1, the PI or designated physician will perform complete physical examinations, which will consist of assessment of:

general appearance, ears, eyes, nose, throat, mouth, neck, thyroid, skin, cardiovascular, respiratory, abdomen, neurological, musculoskeletal, lymph nodes and extremities. Any changes from baseline judged to be clinically significant by the PI (or medically qualified designee) will be recorded as AEs.

## 8.4 Body Weight and Height

At the Screening Visit only, subjects' body weight will be measured in kilograms (kg) and height in meters (m), with subjects in light clothing and without shoes.

## 8.5 Adverse Events and Adverse Device Effects

### 8.5.1 Definition of an Adverse Event and Adverse Device Effect

The ICH E6(R2) GCP Guideline defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE can include an undesirable medical condition occurring at any time, even if no investigational medicinal product has been administered. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the CRF under specific efficacy assessments.

An ADE is any AE considered to be related to a medical device; this can include any AE resulting from insufficiencies and/or inadequacies in the instructions for use, deployment, installation, operation or any malfunction of the device); this includes any event that is a result of a use error or intentional misuse of the device.

These definitions include AEs/ADEs occurring from the time of the subject's parent(s)/legal guardian(s) giving informed consent until the End of Trial/early discontinuation.

Information on AEs/ADEs may be obtained by observation of subjects, information volunteered by the subject or the subject's parent(s)/legal guardian(s), or routine, non-leading questioning.

### 8.5.2 Categorization, Recording, and Followup of Adverse Events/Adverse Device Effects

Investigators must carefully monitor subjects for the occurrence of AEs/ADEs, including vital signs, and physical examination findings. Assessments must be made of the seriousness, severity and relationship to the administration of trial product (causality). These assessments must be made by the PI or delegated to a medically qualified designee. The PI is required to record the assessments in the CRF and subject medical notes.

During and following a subject's participation in this trial, the PI has to ensure that adequate medical care is provided to a subject for any AEs or ADEs related to the trial.

#### *8.5.2.1 Severity of Adverse Events/Adverse Device Effects*

Adverse events/ADEs will be classified by the PI according to the following criteria:

- **Mild:** transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Moderate:** mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- **Severe:** marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Changes in the severity of an AE/ADE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events/ADEs characterized as intermittent require documentation of onset and duration of each episode.

#### *8.5.2.2 Causality of Adverse Events/Adverse Device Effects*

The investigator will assess the possible relationship between the AE/ADE and the trial medication/device according to the following criteria:

- **Not related:** no temporal association, or the cause of the event has been identified, or the trial medication/device cannot be implicated.
- **Related:** at least possible temporal association, and other etiologies are not likely to be the cause.

#### *8.5.2.3 Followup of Adverse Events/Adverse Device Effects*

Any AEs/ADEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

For any AE/ADE which remains unresolved after completion of the Followup Visit, detailed evaluation and followup should be attempted until the AE/ADE has been resolved or a reasonable explanation for its persistence is reported.

All AEs/ADEs that occur during the Treatment Period up until the Followup Visit will be included in the clinical database. Serious AEs/ADEs must be followed to resolution, or the PI confirms in followup that the event is unlikely to resolve. After the Followup Visit, only AEs/ADEs brought to the PI's attention that are both serious and are thought to be related to the study medication/device should be reported to the sponsor.

### 8.5.3 Serious Adverse Event/Adverse Device Effect Assessment and Reporting to Sponsor

The PI must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as an SAE requiring immediate notification to the sponsor (or medically qualified designee).

An SAE is any AE that:

- Results in death;
- Is life-threatening (i.e. in the opinion of the investigator, the subject is at immediate risk of death from the AE);
- Results in inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
- Results in congenital anomaly/birth defect in the offspring of a subject who received the investigational medicinal product;
- Constitutes an important medical event that may not result in death, be life-threatening, or require hospitalization when, based upon appropriate medical judgement, may jeopardize

the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

An SADE is an ADE that results in any of the consequences characteristic of an SAE.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The PI must report all SAEs, regardless of treatment sequence or suspected relationship to the test product, and all ADEs to the sponsor's pharmacovigilance vendor **within 24 hours** of knowledge of the event, using the SAE report form.

**SAE Reporting:** **Fax: +44 1483 431831 (Europe)**
**Fax: +1 617 507 9166 (USA)**
**Email: VecturaPV@primevigilance.com**

The following information is the minimum that must be provided:

- Investigator/reporter's name and contact details;
- Subject identification number;
- Suspect drug/medical device;
- Description of the SAE or ADE, including criteria for seriousness, if applicable.

The additional information included in the SAE/ADE form must be provided to the sponsor's pharmacovigilance vendor as soon as it is available. The investigator should always provide an assessment of causality for each event reported. Upon receipt of the initial report, the investigator's causality assessment will be requested if it was not provided.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE/ADE considered as the

foremost untoward medical occurrence from secondary AEs/ADEs which occurred as complications.

The investigators should follow up the event until resolution or stabilization of the condition. Followup information received should be reported to the sponsor's pharmacovigilance vendor according to the same routes and timelines as an initial report.

### 8.5.4 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical concern specific to the sponsor's product or program. Such an event might warrant further investigation in order to characterize and understand it.

The following have been identified as AESIs for VR647 Inhalation Suspension, based upon the known safety profile of conventionally nebulized budesonide inhalation suspension:

- Infections: upper and lower respiratory tract infections; oropharyngeal candidiasis.
- Upper respiratory tract: hoarseness, cough, throat irritation.
- Eye disorders: media opacities including cataract, glaucoma, increased intraocular pressure.
- Endocrine disorders: hypothalamic–pituitary–adrenal axis suppression.

All AESIs are to be recorded on the AE pages of the CRF and assessed in the same manner as an AE, including seriousness. Serious AESIs should be reported to the sponsor's pharmacovigilance vendor according to the procedure described in Section 8.5.3.

### 8.5.5 Deaths

All AEs/ADEs resulting in death during the trial or followup period must be reported as SAEs/SADEs, as applicable.

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction),
- Outcome: fatal.

The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be "death" or "sudden death".

### 8.5.6 Reporting to Competent Authorities, Institutional Review Boards and Other Investigators

The sponsor will ensure that processes are in place for submission of reports of Serious Unexpected Suspected Adverse Reactions occurring during the trial to the Competent Authorities, IRBs and other investigators concerned by the investigational medicinal product. Reporting will be in accordance with the applicable regulatory requirements.

The sponsor must report the results of an evaluation of an UADE to the FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.

Details of procedures and responsibilities will be documented in a safety management plan for the trial.

## 8.6 Emergency Procedures

Following discharge from the trial site after the Screening Visit, the investigator will ensure all subjects and their parent(s)/legal guardian(s) are provided with a 24-hour emergency phone number, which allows the subject's parent(s)/legal guardian(s) to contact trial personnel directly.

Investigators will be provided with an "out of hours" contact number for the sponsor in the event of a medical emergency.

## 8.7 Guidance for Overdose

The potential for acute toxic effects following overdose of trial treatment is low. If inhaled corticosteroids are used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism or growth suppression may occur, as detailed in Section 10 of the Pulmicort Respules United States Prescribing Information.[6]

## 8.8 Product Complaints

Product complaints should be reported directly to the respective manufacturers, according to standard spontaneous reporting mechanisms.

# 9 PHARMACOKINETIC ASSESSMENTS

## 9.1 Pharmacokinetic Procedures

### 9.1.1 Pharmacokinetic Sampling Schedule

Plasma concentrations of budesonide will be assessed in blood samples taken at each dosing visit using a validated method. Blood samples will be collected at the following time points: pre-dose, and at 20 minutes, 40 minutes, 1.5, 3, 4, 6 and 8 hours after start of nebulization. A window of ±5 minutes and ±10 minutes will be permitted for sampling time points 0 to 4 hours and 6 to 8 hours, respectively.

### 9.1.2 Pharmacokinetic Sample Preparation, Shipment and Analyses

Blood samples will be shipped to a sponsor-designated bioanalytical laboratory that will perform the analyses, using a validated method. Assay methodology and procedures will be described in an analytical plan.

Full details relating to the sample processing, labelling, storage, shipment and destruction procedures will be documented in the trial-specific laboratory manual.

# 10 STATISTICAL CONSIDERATIONS

This section describes the statistical analysis foreseen at the time of planning the trial. Any deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in a Statistical Analysis Plan (SAP), which will be written and finalized before database lock. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations. Any further deviations and/or alterations to the statistical analysis will be justified in the clinical study report.

## 10.1 Sample Size Determination

The number of subjects for this trial is not based on any formal sample size calculation. Randomization of approximately 12 subjects to the trial is considered achievable. Subjects who discontinue from the trial early may be replaced with agreement from the sponsor in order to obtain data from 6 subjects for each PK profile.

The trial will aim to randomize at least one-third of subjects aged <7 years.

## 10.2 Analysis Sets

### 10.2.1 Total Set

The Total Set will consist of all subjects whose parent(s)/legal guardian(s) have signed an Informed Consent Form (ICF), including subjects withdrawn prior to randomization and randomized subjects who did not receive trial medication.

### 10.2.2 Safety Set

The Safety Set will be based on all randomized subjects (as treated) who receive at least one dose of trial medication. Subjects with documented failure to take at least one dose of trial medication after randomization will be excluded from the Safety Set.

### 10.2.3 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who provide evaluable data for the total score of the modified PASAPQ.

### 10.2.4 Pharmacokinetic Set

The PK Set will consist of all subjects who receive at least one dose of trial medication, have measurable plasma concentrations of budesonide and are without any major protocol deviation.

## 10.3 Statistical Analyses

All individual data as well as results of statistical analyses will be presented in individual subject data listings and statistical summary tables. In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation (SD), minimum, median and maximum. Categorical data will be summarized as number and percentage of subjects. The geometric mean, standard error of the mean (SEM) and coefficient of variation (CV) will be reported for PK variables where appropriate.

### 10.3.1 Disposition Data

Subject disposition will be listed by subject and will be summarized for the Total Set.

A table or listing of subjects that discontinued will be provided with the reason for discontinuation.

### 10.3.2 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be summarized by descriptive statistics for the Safety Set.

Demographic data and baseline characteristics will be listed by subject.

### 10.3.3 Modified PASAPQ

Analyses of the modified PASAPQ will be summarized by descriptive statistics for the FAS.

### 10.3.4 Safety Analysis

All available data for the Safety Set will be included in the safety analysis, which will be primarily descriptive.

The baseline for the safety analysis will be the last observed data prior to first nebulization.

#### 10.3.4.1 Vital Signs

At each time point, absolute values and change from baseline of blood pressure, heart rate and temperature will be summarized by descriptive statistics.

Vital signs data will be listed by subject.

#### 10.3.4.2 Physical Examination

Physical examination data will be listed by subject only.

#### 10.3.4.3 Adverse Events and Adverse Device Effects

All AEs in the clinical trial database will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; version to be specified in the Data Management Plan [DMP]), which will be used to summarize AEs by primary system organ class (SOC) and preferred term (PT). All AEs will be displayed in listings by treatment allocation.

A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the specific treatment. If a subject experiences an event both prior to and after starting administration of treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (i.e. it is reported with a new start date) after starting administration of the specific treatment, and prior to the start of another treatment, if any. All TEAEs collected during the investigational period will be summarized.

All TEAEs will be presented per dose of VR647 or Pulmicort at the time of the onset of the TEAE, and will be tabulated by primary SOC and PT for each treatment, and by severity and relationship to trial product. Tables of TEAEs leading to discontinuation from the trial, AESIs and SAEs will be presented.

An ADE is defined as an AE related to the device. All ADEs will be presented according to the medical device used at the time of onset, and will be tabulated by primary SOC, PT and severity.

#### 10.3.4.4 Concomitant Medications

Concomitant medications will be distinguished between ‘concomitant medications at randomization’ and ‘medications starting after randomization’. Concomitant medications at randomization are medications that started before the date of randomization and stopped after the date of randomization or remained ongoing at the end of the trial, and medications starting after randomization are medications that started on or after the date of randomization.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (version to be specified in the DMP) and will be listed by VR647 dose or Pulmicort and by overall with the number and percentage of subjects receiving concomitant medication by Drug Class and Preferred name.

### 10.3.5 Pharmacokinetic Analysis

The PK Set will be used for the PK analysis. The following PK parameters for plasma budesonide (VR647 Inhalation Suspension or Pulmicort Respules) will be listed by subject and their descriptive statistics will be presented by treatment:

- $AUC_{last}$ – as calculated by the linear-log trapezoidal method.
- $AUC_{inf}$ – calculated as the sum of $AUC_{last}$ plus the ratio of the last measurable plasma concentration ($C_{last}$) to the elimination rate constant ($\lambda$); $AUC_{inf} = AUC_{last} + (C_{last}/\lambda z)$.
- $C_{max}$.
- $t_{max}$ – if the maximum value occurs at more than one time point, $t_{max}$ is defined as the first time point with this value.
- $t_{1/2}$.

Exposure profiles of budesonide levels delivered by the VR647 Inhalation System and the conventional jet nebulizer will be presented graphically.

### 10.3.6 Handling of Withdrawals and Missing Data

Details will be provided in the SAP.

### 10.3.7 Protocol Deviations

Any protocol deviations that occur during the conduct of the trial must be fully documented by the PI and the sponsor must be notified. The impact of major protocol deviations will be assessed by the sponsor.

# 11 QUALITY CONTROL AND QUALITY ASSURANCE

## 11.1 Monitoring

The sponsor will assign an appropriately qualified monitor who will be responsible for visiting the sites at regular intervals throughout the trial in order to verify adherence to the protocol, trial product accountability, completeness and accuracy of the data entered in the CRFs and to perform Source Data Verification (SDV) of data recorded in the CRFs, in accordance with applicable regulations and standard operating procedures (SOPs).

The PI is responsible for the validity of all data collected at the site.

The CRF is expected to be completed an ongoing basis to allow regular review by the trial monitor.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the PI and should ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented. Additionally, the monitor will provide a written report, including copies of correspondence with the investigator, to the sponsor, following each visit.

The frequency and nature of monitoring will be agreed with the sponsor and documented prior to commencement of the trial. The monitor must have direct access to subject medical records and other trial-related source documents. The PI and trial staff will be expected to cooperate with the monitor, to be available during the monitoring visit to answer questions and to ensure that any problems detected are resolved in a timely manner.

## 11.2 Audits and Inspections

In accordance with ICH GCP, the sponsor may select this trial for audit. During the site audit, the sponsor/sponsor representative will carry out an inspection of site facilities (e.g. pharmacy, drug storage areas, laboratory) and review trial-related records in order to evaluate the trial compliance with the sponsor/vendor SOPs, protocol, ICH GCP, the general principles of the Declaration of Helsinki and applicable local regulations. The PI must also agree to inspection of all trial documents by the regulatory authorities and the IRB.

The PI and site personnel should be available to provide information and answer questions as necessary. Should the PI be notified of a regulatory inspection involving this trial, they must notify the sponsor immediately.

### 11.3 Data Quality Assurance

The PI and trial staff are responsible for maintaining a comprehensive filing system (ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial at the site and the quality of the data produced.

Quality assurance and quality control systems will be implemented and maintained using written SOPs to ensure that the trial is conducted, and that the data are generated, recorded and reported in compliance with the protocol, GCP, the general principles of the Declaration of Helsinki and the applicable regulatory requirements.

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Source documents (including all demographic and medical information, CRFs, and a copy of the signed ICF indicating the study number and title) for each subject in the study will be maintained by the investigator (generally in the subject's files), and all information in the CRFs must be traceable to the source documents.

All data should be recorded directly into the subject's medical record as source data. The documents, which will be considered as source data, will be confirmed at the Trial Initiation Visit and documented and reviewed by the monitor at each Monitoring Visit.

# 12 REGULATORY AND ETHICAL CONSIDERATIONS

This trial will be conducted in compliance with the Declaration of Helsinki and the ICH GCP Consolidated Guideline E6(R2) (Note for Guidance CPMP/135/95), applicable US CFR, and domestic legal stipulations.

The investigator(s) will provide the sponsor with their current scientific Curriculum Vitae (signed and dated) prior to start of the trial.

## 12.1 Institutional Review Board Approval

The trial protocol, ICF, informed assent form (if applicable), Investigator's Brochure, available safety information, subject recruitment procedures (e.g. advertisements), information about payments and compensation available to the subjects and documentation evidencing the PI's qualifications should be submitted to the Institutional Review Board (IRB) for ethical review and approval prior to the trial start. A copy of the dated approval letter from the IRB stating the study title, and/or study number must be provided to the sponsor before the start of screening and release of supplies. The written approval should identify all documents reviewed by name and version. A list of the names and functions of the IRB members will be obtained for the sponsor's and PI's records.

The PI/sponsor will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB trial review. The PI/sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor whether an amendment is considered substantial or non-substantial, i.e. whether it requires submission to an IRB for approval or notification only.

## 12.2 Regulatory Approval

As required by local regulations, the sponsor will ensure approval of the appropriate regulatory authorities is obtained prior to trial initiation.

Safety updates for VR647 will be prepared by the sponsor as required, for submission to the relevant regulatory authority.

## 12.3 Informed Consent

No trial-related procedures will be performed before written parental/legal guardian(s') informed consent, and written subject assent (as appropriate) are obtained.

The PI or 'designee' (the designee must be on the 'site delegation of responsibilities log' to obtain informed consent and assent) will explain the aims, methods, anticipated benefits and potential risks of participating in the trial and should inform the subject and the subject's parent(s)/legal guardian(s) that participation is voluntary and that the subject can withdraw from the trial at any time. Each subject's parent(s)/legal guardian(s) will be given an ICF to read and be given adequate time to ask questions. In accordance with ICH GCP and 21 CFR 50, informed consent shall be documented by the use of an ICF approved by the IRB. The ICF will be signed and personally dated by the subject's parent(s)/legal guardian(s). If appropriate, written subject assent will be obtained.

The IRB-approved ICF and informed assent form (if applicable) will be signed (and witnessed if necessary) in accordance with the procedures agreed by the IRB granting trial approval.

Informed consent will be documented in the subject's medical records, as required by 21 CFR Part 312.62. The subject's parent(s)/legal guardian(s) should be given a copy of their signed and dated ICF, and the original ICF should be filed in the ISF.

### 12.4 Subject Confidentiality

A subject identification number assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs/ADEs and/or other trial-related data. Personal information will be treated as confidential, but may need to be reviewed by authorized representatives of the sponsor (e.g. monitor or auditor) or the regulatory authorities. Consent to direct access to the subject's original medical records for data verification purposes must be obtained from the subject's parent(s)/legal guardian(s) prior to a subject's participation in the trial.

For all subjects enrolled into the trial, the investigator must maintain a list of names and identifying information (e.g. date of birth, subject identification number, date of trial enrollment). The subject identification list will be kept by the investigator in the trial master file.

Whenever a subject name is revealed on a document required by the sponsor, the name must be blacked out permanently by the site personnel, leaving the year of birth visible, and annotated with the subject identification number.

### 12.5 Protocol Amendments

Any change in trial design may be made in consultation with the investigators and must be agreed upon by the sponsor. Protocol amendments may need to be notified to and may require approval by the pertinent regulatory authorities and the IRBs. Subject ICFs, informed assent forms, and CRFs must be reviewed and modified where appropriate. Subjects and their parent(s)/legal guardian(s) must be notified of any changes and parent(s)/legal guardian(s) must give additional written consent (and subjects must give assent, if appropriate) on the amended consent form (and assent form, if applicable). The investigator is responsible for ensuring that the IRB approves an amended protocol, ICF, assent form and any other amended documents and that the amended ICFs are signed by all parent(s)/legal guardian(s) of subjects subsequently entering the trial and those currently in the trial if affected by the amendment, and, if applicable, that subjects subsequently entering the trial and those currently in the trial sign amended assent forms if affected by the amendment.

### 12.6 Investigator Responsibilities

Investigator responsibilities are set out in ICH E6(R2) GCP and in the local regulations. Sponsor staff or an authorized representative will evaluate and approve all investigators who in turn will select their staff.

The investigator must ensure that all persons assisting with the trial are adequately informed about the protocol, amendments, trial treatments, as well as trial-related duties and functions. The investigator is responsible for supervising all persons to whom tasks have been delegated.

The investigator will maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

# 13 DATA HANDLING AND RECORD KEEPING

## 13.1 Data Capture

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

An EDC system will be utilized for this trial, with data captured on electronic CRFs.

## 13.2 Data Management

Data will be handled and processed according to the data management provider's SOPs, which are written based on the principles of GCP. At all times, appropriate backup copies of the database and related software files will be maintained and the information will be appropriately protected from unauthorized access.

The CRF will be based on the trial protocol. All CRF data, including laboratory data, will be included in an integrated database. At the end of the trial, the integrated database will be locked when the database is deemed clean (i.e. all data entry, validation, database edits, medical coding and SAE/SADE reconciliation complete). The data will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations.

## 13.3 Record Archiving and Retention

The PI and trial staff are responsible for maintaining a comprehensive ISF of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced at the site. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8.

In addition, all original source documents supporting entries in the CRF must be included in the subject's medical file and maintained for at least 5 years and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The ISF must be retained in accordance with ICH GCP, 21 CFR 312.62(c) or longer if required by applicable regulatory requirements or by the sponsor. The investigator or his/her institution should retain essential documents until written instructions for their destruction are obtained from the sponsor. If the PI wishes to assign the trial records to another party or to

another location, prior approval in writing must be obtained from the sponsor. Any transfer of records must be fully documented.

## 14 FINANCING AND INSURANCE

The costs necessary to perform the trial will be agreed with the investigator and will be documented in a separate financial agreement that will be signed by the investigator and the sponsor, prior to the trial commencing.

The sponsor has adequate insurance coverage for trial-related, medicine-induced injury, and other liabilities incurred during clinical trials that will provide compensation for any trial-related injury.

## 15 PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the sponsor's publication strategy and will also be used in submissions to regulatory authorities.

The sponsor will ensure that applicable requirements are met to register the trial or publish the results thereof.

## 16 REFERENCES


1 The International Commission on Radiological Protection, 1994. Human respiratory tract model for radiological protection, ICRP publication 66, Software.

2 Köbrich R, Rudolf G, Stahlhofen W. A mathematical model of mass deposition in man. British Occupational Hygiene Society, Vol. 38.

3 Global Initiative for Asthma (GINA) 2017. Global strategy for asthma management and prevention. http://www.ginasthma.org.

4 Agertoft L, Andersen A, Weibull E, Pedersen S. Systemic availability and pharmacokinetics of nebulised budesonide in preschool children. Arch Dis Child. 1999;80(3):241-7.

5 Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941-52.

6 PULMICORT RESPULES - budesonide inhalation suspension. Prescribing Information. AstraZeneca. 2016.

7 Vectura Ltd. Investigator's Brochure Version 2.0, 09 December 2016.

8 PULMICORT RESPULES - budesonide suspension. Summary of Product Characteristics. AstraZeneca. Last revised 2016.

9 Kozma CM, Slaton TL, Monz BU, Hodder R, Reese PR. Development and validation of a patient satisfaction and preference questionnaire for inhalation devices. Treat Respir Med. 2005;4(1):41-52.

# 17 APPENDICES

## 17.1 Appendix 1 – Schedule of Assessments

This page is intentionally blank.

## Table 4: Schedule of assessments

| Visit procedures and assessments | Screening Visit 1 | Period 1 Visit 2 | | Period 2 Visit 3 | | Followup[1] Visit 4/Early Withdrawal |
|---|---|---|---|---|---|---|
| **Trial day** | **Day -32** | **Day -1** | **Day 1** | **Day 7** | **Day 8** | **Day 15** |
| **Visit window** | **+30 days** | | | **±3 days** | **±3 days** | **±2 days** |
| Eligibility | | | | | | |
| Informed consent (and assent, if applicable) | X | | | | | |
| Demographics | X | | | | | |
| Asthma history | X | | | | | |
| Medical and surgical history | X | | | | | |
| Height and weight | X | | | | | |
| Inclusion/exclusion criteria | X | X | X[2] | | | |

1 Followup visit may be completed by telephone.
2 To be completed prior to dosing on Day 1 if not already completed on Day -1.

## Table 4: Schedule of assessments

| Visit procedures and assessments | Screening Visit 1 | Period 1 Visit 2 | | Period 2 Visit 3 | | Followup[1] Visit 4/Early Withdrawal |
|---|---|---|---|---|---|---|
| **Trial day** | **Day -32** | **Day -1** | **Day 1** | **Day 7** | **Day 8** | **Day 15** |
| **Visit window** | **+30 days** | | | **±3 days** | **±3 days** | **±2 days** |
| Safety assessments | | | | | | |
| Vital signs[3,4] | X | | X[5] | | X[5] | |
| Physical examination | X | | | | X | |
| Concomitant medication | X | X | X | X | X | X |
| AEs and ADEs | X | X | X | X | X | X |
| Dosing procedures | | | | | | |
| Nebulizer training | X[6] | | X[7] | | X[7] | |
| Randomization | | | X | | | |
| Drug administration | | | X | | X | |

3 Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.
4 When more than one procedure is scheduled at a specific time point, PK blood sampling should be performed on time. Vital signs should be performed as close as possible to the scheduled time point.
5 Vital signs at pre-dose, and at 30 minutes after start of nebulization.
6 To be eligible, subjects must demonstrate the ability to use the VR647 Inhalation System and the conventional jet nebulizer effectively, assessed by completion of a screening inhalation checklist.
7 Before dosing.

## Table 4: Schedule of assessments

| Visit procedures and assessments | Screening Visit 1 | Period 1 Visit 2 | | Period 2 Visit 3 | | Followup[1] Visit 4/Early Withdrawal |
|---|---|---|---|---|---|---|
| **Trial day** | **Day -32** | **Day -1** | **Day 1** | **Day 7** | **Day 8** | **Day 15** |
| **Visit window** | **+30 days** | | | **±3 days** | **±3 days** | **±2 days** |
| Inhalation checklist | | | X | | X | |
| Efficacy assessments | | | | | | |
| Modified PASAPQ | | | X | | X | |
| Blood sampling | | | | | | |
| Blood sampling for PK[4,8] | | | X | | X | |
| Admission for overnight stay[9] | | X | | X | | |
| Discharge from site[10] | | | X | | X | |

Abbreviations: ADE = adverse device effect; AE = adverse event; PASAPQ = Patient Satisfaction and Preference Questionnaire; PK = pharmacokinetics.

8 Blood samples for assay of plasma budesonide levels will be taken pre-dose, and at 20 minutes, 40 minutes, 1.5, 3, 4, 6 and 8 hours after start of nebulization. A window of ± 5 minutes and ± 10 minutes will be permitted for sampling time points 0 to 4 hours and 6 to 8 hours, respectively.

9 Optional: To aid with travel logistics due to early morning procedures on the day of dosing, sites may provide subjects and their parent(s)/legal guardian(s) the option of an overnight stay the day before dosing, until completion of procedures 8 hours after start of nebulization.

10 After blood samples collected for assay of plasma budesonide 8 hours post start of nebulization.

## 17.2 Appendix 2 – Protocol Amendments

This is the first version of the protocol.

## 17.3 Appendix 3 – Modified Patient Satisfaction and Preference Questionnaire

This page is intentionally blank.

## Modified Patient Satisfaction and Preference Questionnaire (mPASAPQ)

Relationship to subject ☐ **mother/female guardian** or ☐ **father/male guardian**

The questionnaire consists of answers to the question "As a parent/guardian observing your child in the trial, how satisfied are you:"

1). that the nebulizer works reliably?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

2). with the ease of inhaling a dose from the nebulizer?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

3). with the training provided?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

4). with the size of the nebulizer control unit and handset?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

5). that the nebulizer looks durable (hard wearing)?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

6). with using the nebulizer?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

7). with the overall treatment time?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

8). with the ease of holding the nebulizer during use?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

9). Overall, how satisfied are you with the nebulizer?

| Very dissatisfied | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Very satisfied |
|---|---|---|---|---|---|---|---|---|

10). Please indicate how willing you would be for your child to use the nebulizer used during the study by providing a value between 0 (indicating that you would not be willing for this nebulizer to be used) and 100 (indicating that you would definitely be willing for it to be used).

| Not Willing | | Definitely Willing |
|---|---|---|
| | 0 ——— 100 | |

*The answers are measured using a 7-point scale for questions 1 to 9 (1 means very dissatisfied and 7 means very satisfied) and a 100-point scale for question 10. The first 8 questions generate the Performance domain (4 questions: Q1, 2, 6 & 7) and the Total Score domain (all 8 questions). Question 9 asks for overall satisfaction with the device used in the study, and Question 10 asks for willingness to continue with the device used in the study.*

*Modified version based on the original 15-Item validated version of the PASAPQ.*

*Validation: Kozma CM1, Slaton TL, Monz BU, Hodder R, Reese PR. Development and validation of a patient satisfaction and preference questionnaire for inhalation devices. Treat Respir Med. 2005;4(1):41-52.*

## 17.4 Appendix 4 – Principal Investigator's Agreement

**Title:** A Single-Dose, Open-Label, Randomized, Incomplete Block Design Trial to Characterize the Pharmacokinetics of VR647 Inhalation Suspension Delivered by the VR647 Inhalation System and Single Doses of Budesonide Delivered by a Conventional Jet Nebulizer in Pediatric Subjects Aged 4 to 8 Years with Wheezing, Reactive Airway Disease or Mild Asthma

**Protocol No.:** VR647/1/002

**Version/Date: Version 1.0/ 29 September 2017**

I agree with the content of this protocol and the confidential nature of the documentation made as part of this trial. I also acknowledge that the sponsor of the trial has the right to discontinue the trial at any time. I have read the protocol and understand it and will work to it and to all applicable clinical research guidelines including the ICH GCP consolidated Guideline E6(R2), designated standard operating procedures, national laws and regulations and the principles of the Declaration of Helsinki (amended by 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013).

Signature Date dd mmm yyyy

Name:

Title: Principal Investigator