

Tiotropium Bromide Inhalation Solution GSP304-201 A Dose Ranging, Parallel Group, Active (Spiriva® Respimat®) And Placebo Controlled Study To Assess Relative Bioavailability, Pharmacodynamics And Safety Of Three Doses Of Tiotropium Bromide Inhalation Solution In Subjects With Mild To Moderate Chronic Obstructive Pulmonary Disease.

Identifiers                      NCT03118765

Date of Document              13 April 2017

**TIOTROPIUM BROMIDE INHALATION SOLUTION**  
**GSP304-201**  
**A DOSE RANGING, PARALLEL GROUP, ACTIVE**  
**(SPIRIVA® RESPIMAT®) AND PLACEBO-**  
**CONTROLLED STUDY TO ASSESS RELATIVE**  
**BIOAVAILABILITY, PHARMACODYNAMICS AND**  
**SAFETY OF THREE DOSES OF TIOTROPIUM**  
**BROMIDE INHALATION SOLUTION IN SUBJECTS**  
**WITH MILD TO MODERATE CHRONIC**  
**OBSTRUCTIVE PULMONARY DISEASE**

<b>Phase of Development</b>	Phase 2
<b>Sponsor</b>	Glenmark Specialty SA Avenue Léopold-Robert 37 2300 La Chaux-de-Fonds Switzerland
<b>Protocol Number</b>	GSP304-201
<b>IND Number</b>	131794
<b>Approved by</b>	Fred Grossman, DO, FAPA
<b>Protocol Version</b>	Version 3.0 Final
<b>Date</b>	11-Apr-2017
<b>Supersedes</b>	Version 2.0
<b>PROTOCOL HISTORY</b>	
<b>Original protocol</b>	Version 1.0, 11-Oct-2016
<b>Amendment 1</b>	Version 2.0, 05-Jan-2017
<b>Amendment 2</b>	Version 3.0, 11-Apr-2017

This study must be conducted in accordance with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

## **INVESTIGATOR'S AGREEMENT**

I have received and read the Investigator's Brochure for GSP304 (tiotropium bromide) Inhalation Solution. I have read the GSP304-201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator:

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Signature of Investigator

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Date

**SPONSOR'S SIGNATURE**

This protocol reflects the Sponsor's current knowledge of GSP304 as applicable to this study. It has been designed to achieve the stated objectives while minimizing exposure to, and risk from, both the products being used and the assessments. The assessments are all considered to be appropriate, capable of validating the stated objectives of the study, and of providing the necessary information to ensure subject safety. The protocol has been designed according to the principles of the ICH guidelines for GCP, and the Declaration of Helsinki. It has undergone both medical and scientific review by the Sponsor. The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the case report forms (CRFs).

- We hereby agree to conduct the study in accordance with this protocol and the above-mentioned guidance/ regulation.
- We agree to comply with all relevant standard operating procedures (SOP) required for the conduct of this study.
- We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

Signed on behalf of the Sponsor:

Clinical Lead:



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13 April 2017  
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**2. SYNOPSIS**

<b>Name of Sponsor/Company:</b> Glenmark Specialty, SA
<b>Name of Investigational Product:</b> GSP304 (tiotropium bromide) Inhalation Solution
<b>Name of Active Ingredient:</b> Tiotropium Bromide
<b>Title of Study:</b> A Dose Ranging, Parallel Group, Active (Spiriva® Respimat®) and Placebo-controlled Study to Assess Relative Bioavailability, Pharmacodynamics and Safety of Three Doses of Tiotropium Bromide Inhalation Solution in Subjects With Mild to Moderate Chronic Obstructive Pulmonary Disease
<b>Phase of development: 2</b>
<b>Objectives:</b> <b>Primary:</b> To assess the relative bioavailability of GSP304 (tiotropium bromide) Inhalation Solution at dose levels of [REDACTED] compared with Spiriva® Respimat® inhalation spray (5 µg QD) in subjects with COPD. To characterize the dose response of GSP304 at dose levels of [REDACTED] with respect to pharmacodynamics (PD). <b>Secondary:</b> To assess the safety and tolerability of GSP304 at dose levels of [REDACTED]
<b>Methodology:</b> This is a phase 2, randomized, parallel group, active- and placebo-controlled, 5-arm study to compare the PK profile of 3 blinded doses of GSP304 with open label Spiriva® Respimat®. The study will also evaluate the dose response PD profile of 3 blinded doses of GSP304 compared with blinded GSP304 placebo, using spirometry in subjects with mild to moderate COPD. A total of 155 male and female subjects will be randomized in a 1:1:1:1:1 ratio to one of 5 treatment arms. A subject will receive 1 of the 3 double-blind doses of GSP304, or double-blind GSP304 placebo, or open-label Spiriva® Respimat®. The study will include a screening period of up to 2 weeks, followed by a 2 week run-in period, 3 weeks of treatment, and a 2 week post treatment follow up period. The total duration of study participation will be approximately 9 weeks. In this study, PK of tiotropium in plasma and urine will be assessed on Day 1 and on Day 21 (at steady state).
<b>Number of subjects (planned):</b> A total of 155 subjects will be randomized in this study.
<b>Study Endpoints</b> <b>Primary Endpoints</b> <ul style="list-style-type: none"> <li>The PK endpoints for tiotropium in plasma to assess the relative bioavailability are:             <ul style="list-style-type: none"> <li>Peak concentrations during the dosing interval at steady-state (<math>C_{maxSS}</math>)</li> <li>Area under the plasma concentration-time curve over the dosing interval at steady state (<math>AUC_{0-tauSS}</math>)</li> </ul> </li> </ul>

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<ul style="list-style-type: none"> <li>Change from baseline in trough forced expiratory volume in one second (FEV<sub>1</sub>) at 24 hours after the last dose of treatment on Day 21 in comparison with placebo</li> </ul> <b>Secondary Endpoints</b> <ul style="list-style-type: none"> <li>Amount (A<sub>etau</sub>) and fraction of dose (F<sub>e</sub>) of tiotropium excreted in urine over the dosing interval on Day 1 and Day 21</li> <li>Peak concentrations during the dosing interval (C<sub>max</sub>) on Day 1</li> <li>Area under the plasma concentration-time curve over the dosing interval (AUC<sub>0-tau</sub>) on Day 1</li> <li>Time of peak drug concentration over the dosing interval (t<sub>max</sub>) on Day 1 and Day 21</li> <li>Average concentration during a dosing interval at steady state (C<sub>avss</sub>) on Day 21</li> <li>Accumulation ratio (R<sub>ac</sub>)</li> <li>Change from baseline in peak FEV<sub>1</sub> within 12 hours post-dose on Day 1 and Day 21</li> <li>Change from baseline in forced vital capacity (FVC) on Day 1 and Day 21</li> <li>Change from baseline in time-normalized area under the curve for FEV<sub>1</sub> measured over 12 hours on Day 1 and Day 21</li> </ul> <b>Safety Endpoints</b> <ul style="list-style-type: none"> <li>Vital signs, laboratory parameters, 12-lead electrocardiogram (ECG)</li> <li>Incidence of all adverse events (AEs)</li> </ul>
<b>Diagnosis and main criteria for inclusion:</b> Males and females of non-childbearing potential ≥40 and ≤85 years of age with a primary clinical diagnosis of mild to moderate COPD, a FEV <sub>1</sub> /FVC ratio of <70% and a baseline FEV <sub>1</sub> of ≥50% of predicted normal value as per the NHANES III predicted normal values at screening.
<b>Investigational product, dosage and mode of administration:</b> Name of Investigational Products: Test Treatment T1: GSP304 (tiotropium bromide) Inhalation Solution, [REDACTED] Test Treatment T2: GSP304 (tiotropium bromide) Inhalation Solution, [REDACTED] Test Treatment T3: GSP304 (tiotropium bromide) Inhalation Solution, [REDACTED] Dosage Form: Inhalation Solution Dosage: Oral inhalation of either T1, T2, or T3 Dosage Frequency: [REDACTED] Mode of Administration: By oral inhalation using a nebulizer
<b>Comparator, dosage and mode of administration:</b> Placebo to match GSP304 Dosage Form: Inhalation Solution Dosage: Oral inhalation Dosage Frequency: [REDACTED] Mode of Administration: By oral inhalation using a nebulizer
<b>Reference therapy, dosage and mode of administration:</b> Name of Comparator: Spiriva® Respimat® inhalation spray 2.5 µg per actuation

<b>Name of Sponsor/Company:</b> <b>Glenmark Specialty, SA</b>
Dosage Form: Inhalation Spray Dosage: 5 µg (2 actuations of 2.5 µg each) Dosage Frequency: Once daily (QD) Mode of Administration: By oral inhalation using Respimat® Soft Mist Inhaler
<b>Duration of treatment:</b> 3 weeks (21 days)
<b>Criteria for evaluation:</b> <b>Efficacy:</b> Spirometry FEV <sub>1</sub> and FVC Refer to 'Pharmacodynamic Assessments' sub-section below. <b>Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic Assessments:</b> <b>Pharmacokinetic Assessments</b> Blood samples (approximately 6 mL) will be collected in dipotassium ethylenediaminetetraacetic acid (EDTA) coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and 2, 4, 6, 10, 15, 30, 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. The pre-dose sample on Day 1 should be collected within 30 minutes prior to dosing while on Days 7, 14, and 21 the pre-dose sample should be collected within 10 minutes prior to the morning dose. On Day 1 and Day 21, samples will be collected within the following collection windows: For the 2 minute sample, within a window of ±30 seconds For the 4, 6, 10, 15, and 30 minute samples, within a window of ± 1 minute For the 45, 60, 75, 90 minute, and 2.0 hour samples, within a window of ± 2 minutes For the 4, 6, 8, 12, 16, 20 and 24 hour samples, within a window of ± 5 minutes. In addition, urine will be collected into pre-weighed containers at pre-dose (within 1 hour prior to dosing), and at the following intervals post-dose from 0-6, 6-12, and 12-24 hours on Day 1 and Day 21. Collection time intervals and the accurate weights of containers before and after urine collection at each interval will be noted. In each urine container, approximately 5 mL of 1M citric acid must be added prior to start of collection. Plasma and urine concentrations of tiotropium will be quantified by a validated liquid chromatography-mass spectrometry (LC/MS/MS) method. <b>Pharmacokinetic Parameters</b> <b>Plasma:</b> <ul style="list-style-type: none"> <li>• AUC<sub>0-tauSS</sub></li> <li>• C<sub>maxSS</sub>, C<sub>minSS</sub>, C<sub>avSS</sub></li> <li>• C<sub>max</sub> on Day 1</li> <li>• t<sub>max</sub> on Day 1 and Day 14</li> <li>• AUC<sub>0-tau</sub> on Day 1</li> <li>• R<sub>ac</sub></li> </ul> <b>Urine:</b> <ul style="list-style-type: none"> <li>• A<sub>etau</sub> and F<sub>e</sub></li> </ul>

**Name of Sponsor/Company:****Glenmark Specialty, SA*****Additional Pharmacokinetics***

Additional parameters may be evaluated depending on the data obtained during the study.

**Pharmacodynamic, Biomarker, and Pharmacogenomic Assessments**

In addition to screening, pre-dose FEV<sub>1</sub> and FVC will be assessed at -45 minutes and -15 minutes prior to dosing on Day 1, Day 7, Day 14, and Day 21. Trough FEV<sub>1</sub> will be assessed on Day 22 (ie, 24 hours after the Day 21 dose).

On Day 1 and Day 21, FEV<sub>1</sub> will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes ( $\pm 3$  minutes), 15 minutes ( $\pm 2$  minutes), 30 minutes ( $\pm 5$  minutes), 60 minutes, 90 minutes, and 2 hours (120 minutes); and post-dose at 4, 6, 8, 10, 12, 23 hours 15 minutes and 23 hours 45 minutes post dose. The window for 1-hour spirometry and thereafter is  $\pm 5$  minutes.

***FEV<sub>1</sub>***

FEV<sub>1</sub> is the volume of air forcibly exhaled in one second as measured by a spirometer.

***Pre- dose trough FEV<sub>1</sub>***

It is defined as the mean of FEV<sub>1</sub> values obtained -45 minutes and -15 minutes pre-morning dose at Day 1.

***Peak FEV<sub>1</sub>***

It is defined as the maximum FEV<sub>1</sub> over the period of 12 hours post-morning dose.

***Trough FEV<sub>1</sub>***

It is defined as the mean FEV<sub>1</sub> obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.

***Baseline FEV<sub>1</sub>***

It is defined as the average of the pre-dose FEV<sub>1</sub> measured at -45 minutes and -15 minutes at Day 1

***FVC***

FVC is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.

***Baseline FVC***

It is defined as the average of the pre-dose FVC measured at -45 minutes and -15 minutes at Day 1.

**Safety:**

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs), clinical laboratory measurements, vital signs, 12-lead ECG, and physical examinations.

**Statistical methods:**

Detailed statistical methods will be provided in the Statistical Analysis Plan (SAP).

**Analysis Sets****Full Analysis Set (FAS)**

This will include all subjects who are randomized, have received at least 1 dose of study medication and have at least 1 post-baseline PD assessment. This analysis set will be the primary analysis set for the PD endpoints.

**Safety Analysis Set (SAF)**

This will include all subjects who are randomized and received at least 1 dose of study medication. All safety endpoints will use the SAF unless otherwise specified.



**Per Protocol Analysis Set (PP)**

This will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have exclusionary major protocol deviations. Major and exclusionary protocol deviations will be defined in the SAP and by clinical review prior to unblinding.

**PK Analysis Set (PKAS)**

This will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have exclusionary major protocol deviations. The PKAS will be used to analyze the PK endpoints unless otherwise specified in the SAP. Major and exclusionary protocol deviations will be defined in the SAP and by clinical review prior to unblinding.

**Determination of Sample Size**

A sample size of 28 subjects per treatment arm will have 90% power to detect a difference in mean change from baseline in trough FEV<sub>1</sub> of 150 mL between GSP304 and GSP304 placebo assuming a 2-sided alpha of 5% and a standard deviation (SD) of 170 mL. These assumptions are based on available literature from similar studies conducted for Spiriva® Respimat®.

Given the overall 1:1:1:1:1 study treatment allocation ratio, 140 subjects are required for the analysis of the primary endpoint. Assuming a dropout rate of approximately 10%, a total of 155 subjects (31 subjects per treatment arm) will be randomized.

This sample size is also considered to be sufficient for the relative bioavailability endpoint.

**Pharmacodynamic Analyses**

The PD comparisons will be made between each dose of GSP304 and GSP304 placebo.

**Analysis of Primary Pharmacodynamic Endpoint.**

Change from baseline in trough FEV<sub>1</sub> at 24-hours after the last dose of treatment on Day 21 in comparison to GSP304 placebo.

The primary endpoint measures the change from baseline in trough FEV<sub>1</sub> at 24 hours after the last dose of treatment on Day 21. This will be analyzed using a Mixed-effect Model Repeated Measure (MMRM) model to produce treatment differences for each dose of GSP304 vs GSP304 placebo. The MMRM model will include pre-dose data from all visits (Days 7, 14, and 21) and fixed terms for treatment, visit, baseline, center, treatment by visit and baseline by visit interactions. The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 95% confidence intervals (CIs). Multiple imputation-based methods will be considered as a sensitivity analysis for missing data, with further detail provided in the SAP.

The primary endpoint will be analyzed using the FAS and primary inference will be based at Day 21. A sensitivity analysis will be based on the PP Analysis Set.

**Analysis of Secondary Pharmacodynamic Endpoints**

Analysis of secondary PD endpoints will be performed on the FAS.

Change from baseline in peak FEV<sub>1</sub> within 12 hours post dose on Day 1 and Day 21: This endpoint measures the peak FEV<sub>1</sub> from the serial readings taken through 12 hours post-dose and then calculates the change from baseline. The change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 versus GSP304 placebo.

Change from baseline in FVC on Day 1 and Day 21: The change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 versus GSP304 placebo.

Change from baseline in time-normalized area under the curve for FEV<sub>1</sub> measured over 12 hours on Day 1 and Day 21: The endpoint measures a series of FEV<sub>1</sub> readings taken within 12 hours of dosing. The trapezoidal rule will be used to calculate AUC<sub>0-12h</sub> and then normalized to the length of time. The

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change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 versus GSP304 placebo.

All PD data will also be displayed in summaries and listings.

**Pharmacokinetic, Pharmacogenomic, and Other Biomarker Analyses****Pharmacokinetic Analyses**

Pharmacokinetic analysis will be performed using the PKAS.

**Plasma:** Individual subject plasma PK parameters will be determined from plasma concentrations using non-compartmental methods for each subject using appropriate software. Actual collection times will be used for the analyses.

**Urine:** Amount and fraction of dose of tiotropium excreted in urine during the collected time interval in individual subjects will be estimated. Actual collection times and urine volumes will be used for the estimation.

Additional parameters may be evaluated depending on the data obtained during the study.

The derived PK parameters will be listed by subject and summarized by treatment. Wherever appropriate, data will be visualized by means of graphical representations. For the summaries, descriptive statistics for all relevant PK parameters will include: n, mean, SD, coefficient of variation (%CV), minimum, median, maximum, geometric mean and geometric mean %CV.

The plasma concentrations and amount in urine of tiotropium will also be listed by subject, summarized by treatment, and presented graphically as mean plots, and individual plots.

**Statistical Analysis of Pharmacokinetic Parameters**

An analysis of variance (ANOVA) will be performed on the ln-transformed PK parameters  $AUC_{0-\tau_{SS}}$ , and  $C_{maxSS}$ . The ANOVA model will include treatment as fixed effect. The results from the model will be back-transformed and the adjusted geometric means for each treatment and the estimated treatment ratios for the treatment comparisons will be presented together with 90% CIs.

The ratios and corresponding 90% CIs will be expressed as a percentage.

The following comparisons will be made:

Test Treatment T1 versus Reference Treatment

Test Treatment T2 versus Reference Treatment

Test Treatment T3 versus Reference Treatment

For GSP304, dose-proportionality of tiotropium  $C_{maxSS}$  and  $AUC_{0-\tau_{SS}}$  parameters will be assessed using a power model (linear regression relating log-transformed  $C_{maxSS}$  and  $AUC_{0-\tau_{SS}}$  to the log-transformed dose). Estimates of the mean slopes of log-transformed dose will be reported along with corresponding 90% CIs. Dose proportionality will also be assessed based on amount of tiotropium excreted in urine. More detail will be provided in the SAP.

**Pharmacogenomic, and Other Biomarker Analyses**

Not applicable.

**Safety Analyses**

All safety analyses will be performed on the SAF and will be presented by the study treatment. Safety data will be summarized descriptively. Data describing quantitative measures will be summarized as mean, SD, median and range (minimum and maximum). Qualitative variables will be presented as counts and percentages.

All safety data will also be displayed in listings.

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<b>Other Analyses</b> Not applicable.

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**4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

The following abbreviations and specialist terms are used in this study protocol.

**Table 1: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
AE	adverse event
$A_{\text{etau}}$	cumulative amount of unchanged drug excreted into the urine over the dosing interval
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
$AUC_{0-\text{tau}}$	area under the concentration-time profile over the dosing interval
$AUC_{0-\text{tauSS}}$	area under the concentration-time profile over the dosing interval at steady state
BMI	body mass index
BP	blood pressure
$C_{\text{avSS}}$	average concentration during a dosing interval at steady state
$C_{\text{max}}$	peak concentrations during the dosing interval
$C_{\text{maxSS}}$	peak concentrations during the dosing interval at steady-state
$C_{\text{minSS}}$	minimum of trough concentrations during the dosing interval at steady-state
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CT	computed tomography
DPI	dry powder inhaler
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
$F_e$	fraction of drug excreted into the urine
$FEV_1$	forced expiratory volume over 1 second
FVC	forced vital capacity
GI	gastrointestinal
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B antibody

Abbreviation or Specialist Term	Explanation
HCV	hepatitis C virus
ICF	informed consent form
IEC	independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LABA	long-acting beta <sub>2</sub> -agonist
LAMA	long-acting muscarinic antagonist
LC/MS/MS	liquid chromatography-mass spectrometry
MDI	metered dose inhaler
MMRM	Mixed-effect Model Repeated Measure
MRHDID	maximum recommended human daily inhaled dose
PD	pharmacodynamics
%CV	coefficient of variation
PK	pharmacokinetics
PP	per protocol analysis set
QD	once daily
R <sub>ac</sub>	accumulation ratio
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAF	safety analysis set
SD	standard deviation
t <sub>max</sub>	time of peak drug concentration
US	United States
USPI	United States Prescribing Information



## 5. INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.<sup>1</sup>

Inhaled cigarette smoke and other noxious particles such as smoke from biomass fuels cause lung inflammation, a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation, and in turn, results in breathlessness and other characteristic symptoms of COPD.<sup>1</sup>

COPD is the fourth leading cause of death in the world<sup>1</sup> and represents an important public health challenge. It is a major cause of poor health and contributes significantly to healthcare costs and comorbidity.<sup>2,3</sup> According to World Health Organization estimates, globally, 65 million people have moderate to severe COPD. More than 3 million people died of COPD in 2012, which corresponded to 6% of all deaths globally that year.<sup>4</sup> Total deaths from COPD are projected to increase by more than 30% in the next 10 years and estimates show that COPD could become the third leading cause of death worldwide by 2030.<sup>5</sup> It is a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years, and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and the changing age structure of the world's population (with more people living longer and therefore expressing the long-term effects of exposure to COPD risk factors).<sup>1</sup>

In the United States (US), COPD affects an estimated 27 million Americans. Approximately 12 million adults in the US are diagnosed with COPD, and 120,000 die from it each year. An additional 12 million adults in the US are thought to have undiagnosed COPD.<sup>6</sup> It results in 1.5 million visits to the emergency room and more than 15 million physician visits every year, and 739,000 hospitalizations.<sup>7</sup> Specifically in the US, it is estimated that economic cost of COPD in 2010 was close to \$50 billion. This includes \$29.5 billion in direct health care expenditures and \$20.4 billion in indirect costs.<sup>8</sup>

Although there is no cure for COPD, there are many therapeutic options that can help control and relieve associated symptoms. Inhaled pharmacologic therapies for COPD consist of short-acting bronchodilators, long-acting beta<sub>2</sub>-agonists (LABA), long-acting muscarinic antagonists (LAMA), combination of LABA plus LAMA, and inhaled corticosteroids in combination with LABA.<sup>9</sup> The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document recommends the use of one or more long-acting bronchodilators for the maintenance treatment of COPD. The use of bronchodilators should be prescribed according to the patient's airflow limitation, history of exacerbations, and symptoms.<sup>9</sup>

There is a pressing need to develop drugs for COPD because the global prevalence of COPD is rising, the disease is associated with significant morbidity and mortality, and current treatment options are limited. The Sponsor has developed a tiotropium bromide inhalation solution to be used with a nebulizer and plans to conduct this dose ranging study with an objective to evaluate pharmacokinetics (PK) and pharmacodynamics (PD) effects of 3 doses of tiotropium bromide

inhalation solution in subjects with mild to moderate COPD by comparing with Spiriva® Respimat®.

### 5.1. Investigational Product: Mechanism of Action

Tiotropium is a LAMA and has similar affinity to the subtypes of muscarinic receptors, M<sub>1</sub> to M<sub>5</sub>. In the airways, it exhibits pharmacological effects through inhibition of M<sub>3</sub>-receptors in the smooth muscle leading to bronchodilation. Tiotropium is approved in the US, European Union, and other countries for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD.<sup>9</sup> Safety and efficacy of tiotropium (ie Spiriva®) has been well-established from many large randomized controlled studies including long-term outcome studies. Extensive use of this class of drugs in a wide range of doses in clinical settings has shown them to be well-tolerated without significant safety concerns.<sup>9</sup> Tiotropium is currently available as an inhalation spray (Spiriva® Respimat®) administered as a dose of 5 µg once daily (QD) or dry powder inhalation (Spiriva® HandiHaler®) as 18 µg QD.<sup>10,11</sup> However, tiotropium is not available as an inhalation solution to be used with a nebulizer. While metered dose inhalers (MDIs) and dry powder inhalers (DPIs) are widely used for different medications by patients with COPD, delivery by nebulization provides an effective alternative in patients who do not receive an optimal dose from inhalers. This may be due to poor coordination, an inability to inhale rapidly and forcefully, an inability to hold breath for the allotted time (up to 10 seconds) after the dose and exhalation into the device before or after the dose delivery.<sup>12,13</sup>

### 5.2. Nonclinical Experience

No toxicity, non-clinical PK, or drug metabolism studies have been conducted with GSP304 to date. The preclinical pharmacological and toxicological profiles of tiotropium bromide have been well-established in various pre-clinical studies supporting inhalation powder (Spiriva® HandiHaler®) and inhalation spray (Spiriva® Respimat®). The clinical steady state PK parameters of Respimat® (5 µg tiotropium) and HandiHaler® (18 µg tiotropium) were approximately similar (area under the concentration time curve over 6 hours of dosing [AUC<sub>0-6</sub>]: 24.4 and 32.1 ng.h/mL and peak concentration during the dosing interval (C<sub>max</sub>) 12.4 and 15.4 ng/L, respectively) despite of a 3.6 fold difference in their maximum recommended human daily inhalation dose (MRHDID). Based on the observation that the MRHDID of Respimat® and HandiHaler® produce similar systemic exposure to tiotropium, the exposure multiples between animals and humans documented in the US Prescribing Information (USPI) for the HandiHaler tiotropium dose have been maintained, and are relevant for Spiriva® Respimat®.<sup>14</sup> Nonclinical and clinical data for tiotropium bromide have been extracted from the USPI of Spiriva® Respimat®, and US Food and Drug Administration review data for tiotropium bromide, available under the Freedom of Information Act of the US, and published literature. A concise summary of the nonclinical data of tiotropium is presented below.

Tiotropium bromide had no effect on human Ether-à-go-go-Related Gene-mediated potassium channel current in human embryonic kidney cells nor did it affect action potential configuration in isolated guinea pig papillary muscles in vitro. Tiotropium at therapeutic plasma concentrations may increase heart rate and inhibit salivation and gastrointestinal (GI) motility. The inhibition of salivation occurs at concentrations 5 times lower than the bronchodilation in guinea pigs, suggesting that the salivation is probably the earliest indicator of tiotropium side



effects. These effects appear to be secondary pharmacological activity typical of muscarinic antagonists.<sup>15</sup>

Acute toxicity of tiotropium was studied in mice, rats, and dogs by intravenous, oral and inhalation administration. Signs of toxicity included reduced motility, tremor, dyspnea, tachycardia, hunched posture, coprostatics, convulsion, and eventually, deaths. The approximate inhalation lethal dose 50% values in mice, rats and dogs were more than 6.5, 21 and 30 mg/kg, respectively (approximately 1756, 11351 and 54054 times the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis, respectively). The majority of repeat dose inhalation studies were conducted using aqueous aerosols as the formulation, while some studies used lactose powder. The duration of treatment was up to 3 months in mice and 1 year in rats and dogs. Tiotropium possesses a toxicity profile typical of a muscarinic anticholinergic agent. The target organs of tiotropium toxicity include the eye, GI tract, respiratory tract, urinary bladder, salivary glands and heart. The no observed adverse effect level decreased as the treatment duration increased: The no observed adverse effect levels in 4-, 13- and 52-week inhalation toxicity studies were 2300, 70 and 13  $\mu\text{g}/\text{kg}/\text{day}$  (estimated pulmonary doses were 161, 4.9 and 0.9  $\mu\text{g}/\text{kg}/\text{day}$ , respectively) in rats and 287, 12 and 5.2  $\mu\text{g}/\text{kg}/\text{day}$  in dogs (estimated pulmonary doses were 28.7, 1.0 and 0.5  $\mu\text{g}/\text{kg}/\text{day}$ , respectively). In rats, these doses are approximately 1243, 38 and 7 times, respectively the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis and in dogs these doses are approximately 517, 22 and 9 times, respectively the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis.<sup>16</sup>

Tiotropium was not mutagenic in various genotoxicity assays and no evidence of tumorigenicity was observed in mouse [83- and 101-week inhalation studies in females and males, respectively] and rat (104-week inhalation study) carcinogenicity studies at doses corresponding to approximately 30, 40, and 0.5 times the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis, respectively.<sup>11</sup>

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation doses of 78  $\mu\text{g}/\text{kg}/\text{day}$  or greater (approximately 40 times the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis). No such effects were observed at 9  $\mu\text{g}/\text{kg}/\text{day}$  (approximately 5 times the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis). However, the fertility index was not affected at inhalation doses up to 1689  $\mu\text{g}/\text{kg}/\text{day}$  (approximately 910 times the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis).<sup>11</sup>

Tiotropium was not teratogenic in rats and rabbits at maternal inhalation doses of 1471 and 7  $\mu\text{g}/\text{kg}/\text{day}$ , respectively (approximately 790 and 8 times the MRHDID, respectively on a  $\mu\text{g}/\text{m}^2$  basis). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at a maternal inhalation dose of 78  $\mu\text{g}/\text{kg}/\text{day}$  (approximately 40 times the MRHDID, on a  $\mu\text{g}/\text{m}^2$  basis). In rabbits, tiotropium caused an increase in post-implantation loss at a maternal inhalation dose of 400  $\mu\text{g}/\text{kg}/\text{day}$  (approximately 430 times the MRHDID on a  $\mu\text{g}/\text{m}^2$  basis). Such effects were not observed at maternal inhalation doses of 9 and 88  $\mu\text{g}/\text{kg}/\text{day}$  in rats and rabbits, respectively (approximately 5 and 95 times the MRHDID, respectively on a  $\mu\text{g}/\text{m}^2$  basis).<sup>11</sup>

### 5.3. Clinical Experience

The safety, efficacy, and PK profile for tiotropium bromide is well-established when inhaled as an inhalation powder<sup>11</sup> or inhalation spray.<sup>10</sup> Spiriva® has been approved in the US for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for

reducing COPD exacerbations. Spiriva® HandiHaler® was approved on January 30, 2004 (NDA 21-395) and Respimat® was approved on September 24, 2014 (NDA 21-936).

However, there is no approved tiotropium bromide product such as GSP304 for use as a nebulized solution.

## **6. STUDY OBJECTIVES AND PURPOSE**

### **6.1. Primary Objectives**

The primary objectives are:

- To assess the relative bioavailability of GSP304 (tiotropium bromide) Inhalation Solution at dose levels of [REDACTED] compared with Spiriva® Respimat® inhalation spray (5 µg QD) in subjects with COPD.
- To characterize the dose response of GSP304 at dose levels of [REDACTED] with respect to PD.

### **6.2. Secondary Objective**

The secondary objective is to assess the safety and tolerability of GSP304 at dose levels of [REDACTED]

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is a phase 2, randomized, parallel group, active- and placebo-controlled, 5-arm study to compare the PK profile of 3 blinded doses of GSP304 with open label Spiriva® Respimat®. The study will also evaluate the dose response PD profile of 3 blinded doses of GSP304 compared with blinded GSP304 placebo, using spirometry in subjects with mild to moderate COPD. A total of 155 male and female subjects will be randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment arms. A subject will receive 1 of the 3 double-blind doses of GSP304, or double-blind GSP304 placebo, or open-label Spiriva® Respimat®. The study will include a screening period of up to 2 weeks, followed by a 2-week run-in period, 3 weeks of treatment, and a 2-week post treatment follow-up period. The total duration of study participation will be approximately 9 weeks. In this study, PK of tiotropium in plasma and urine will be assessed on Day 1 and on Day 21 (at steady state).

The study consists of the following periods, as depicted in [Figure 1](#) and described below:

**Screening** (Day -28 to Day -15): Up to 2 weeks (14 days), during which the Screening visit (Visit 1) will occur.

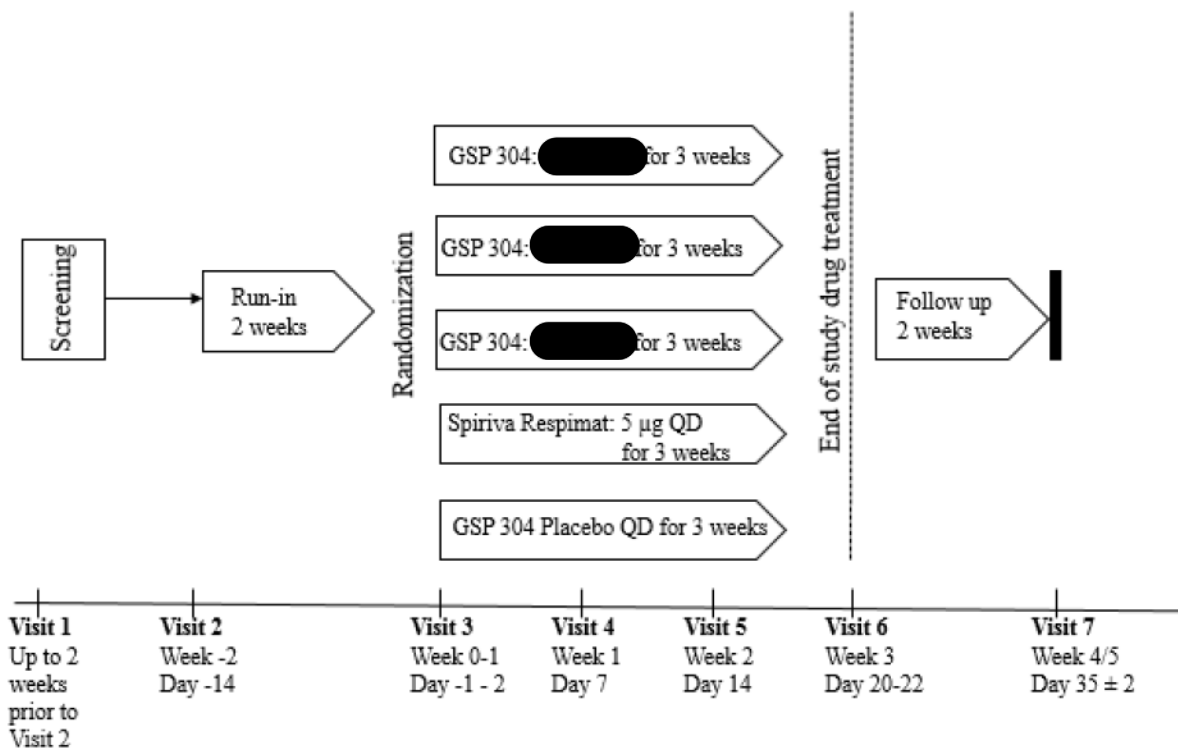
**Run-in Period** (Day -14 to Day -2): 2 weeks (14 days), during which Visit 2 will occur.

**Treatment Period** (Day -1 to Day 22): 3 weeks during which Visits 3, 4, 5, and 6 will occur. Treatment (GSP304/GSP304 placebo/Spiriva® Respimat®) will be administered on Days 1 through 21.

**Post treatment Follow-up** (Day 35 ± 2 days): 14 days after the last dose, the Follow-up visit, Visit 7, will occur on Day 35 ± 2. In the event of early withdrawal, Visit 7 procedures will be performed as soon as possible after a subject withdraws from the study (See Section 8.3 for details).

The total duration of study participation will be approximately 9 weeks for each subject. Subjects will be required to attend the clinic for all scheduled study visits (Visit 1-7).

The end of the study will be the date of the last study visit for the last randomized subject in the study.

**Figure 1: Study Design**

QD = once daily

**Table 2: Schedule of Assessments**

Activity/Observation	Screening	Run-In	Study Treatment								End of Study (Follow Up)
Day	D-28 to D-15	D-14 to D -2	D-1 (clinic check-in)	D1	D2 (clinic check-out)	D7 (ambulatory visit)	D14 (ambulatory visit)	D20 (clinic check-in)	D21	D22 (clinic check-out)	D35 (±2)
Visit ID	1	2	3	3	3	4	5	6	6	6	7
Informed consent	×										
Demographic data	×										
Medical and treatment history	×										
Vital signs <sup>1</sup>	×		×	×	×	×	×	×	×	×	×
Physical examination <sup>2</sup>	×		×			×	×	×			
Inclusion/Exclusion criteria	×		×								
Chest x-ray (if applicable)	×										
Device training	×	×									
12 lead ECG	×			×					×		
Laboratory investigations (hematology, biochemistry, and urine analysis) <sup>3</sup>	×					×	×		×		×



Activity/Observation	Screening	Run-In	Study Treatment								End of Study (Follow Up)
Day	D-28 to D-15	D-14 to D -2	D-1 (clinic check-in)	D1	D2 (clinic check-out)	D7 (ambulatory visit)	D14 (ambulatory visit)	D20 (clinic check-in)	D21	D22 (clinic check-out)	D35 (±2)
Visit ID	1	2	3	3	3	4	5	6	6	6	7
Urine analysis for drugs of abuse and urine cotinine	×		×					×			
Blood alcohol test	×		×					×			
FSH screening (if applicable)	×										
Pregnancy testing <sup>7</sup>	×		×								×
In-clinic stay			×	×	×			×	×	×	
Randomization and IP assignment				×							
Administration of study medication <sup>8</sup>				×	×	×	×	×	×		
PK sampling (blood and urine)				×	×	×	×		×	×	
Spirometry <sup>10</sup>	×			×	×	×	×		×	×	
Adverse events monitoring	×	×	×	×	×	×	×	×	×	×	×
Concomitant medication	×	×	×	×	×	×	×	×	×	×	×

<sup>1</sup> Heart rate, blood pressure (systolic and diastolic), respiratory rate and body temperature. Blood pressure can be taken in the same manner (ie, seated or supine position) at every study visit. On Day 1 and 14: Vital signs will be measured within 1 hour before study drug administration in the morning (prior to pre-dose spirometry and PK procedures) and 1 hour after the morning dose.

- <sup>2</sup> Comprehensive physical examination will be performed at screening; a targeted examination will be done if an adverse event occurs at the discretion of the Investigator.
- <sup>3</sup> Additional training may be provided on Day-1 if required, at the Investigator's discretion.
- <sup>4</sup> Triplicate ECG will be performed at the screening visit.
- <sup>5</sup> Refer to [Appendix 2](#).
- <sup>6</sup> FSH (follicle stimulating hormone) screening will be performed at Screening for all females to confirm non-childbearing potential (FSH>40 IU/L).
- <sup>7</sup> Females only; serum pregnancy testing at Screening, urine pregnancy testing at Day -1 (clinic check in) and End of Study (Follow-up).
- <sup>8</sup> On days on which subject visits are scheduled, subjects will take the study drug at the Investigator site (ie, after any required pre-dose blood samples and pre-dose PD measures have been collected), EXCEPT on Day 20 when subjects will be requested to take the study medication at home as instructed by the study staff. On all other days, subjects will be requested to take the study medication at home as instructed by the study staff.
- <sup>9</sup> Blood samples (approximately 6 mL) will be collected in dipotassium EDTA coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and post morning-dose at 2 minutes, 4, 6, 10, 15, 30, and 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. Blood samples for PK should not be drawn or processed in the same room that the subject was dosed with study medication. The pre-dose sample on Day 1 should be collected within 30 minutes prior to dosing while on Days 7, 14, and 21 the pre-dose sample should be collected within 10 minutes prior to the morning dose. On Day 1 and Day 21, samples will be collected at 2 minute with a window period of  $\pm 30$  seconds, a window period of  $\pm 1$  minute for other samples up to 30 minutes;  $\pm 2$  minutes up to 2 hours and  $\pm 5$  minutes up to 12 hours. In addition, urine will be collected at pre-dose (within 1 hour prior to dosing), 0-6, 6-12, 12-24 hours on Day 1 and Day 21 in pre-weighed containers with approximately 5 mL of 1M citric acid added prior to start of collection in each container. All post-dose timings are relative to the end of dosing (ie, end of nebulization of GSP304/GSP304 placebo or after the second actuation of Spiriva® Respimat®).
- <sup>10</sup> Pre-dose forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) will be assessed on at -45 minutes and 15 minutes prior to dosing on Day 1, Day 7, Day 14, and Day 21. Trough FEV<sub>1</sub> will be assessed on Day 22 (ie, 24 hours after Day 21 dose). On Day 1 and Day 21, FEV<sub>1</sub> will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes ( $\pm 3$  minutes), 15 minutes ( $\pm 2$  minutes), 30 minutes ( $\pm 5$  minutes), 60 minutes, 90 minutes, and 2 hours (120 minutes); and post-dose at 4, 6, 8, 10, 12, 23 hours 15 minutes and 23 hours 45 minutes post-dose. All post-dose timings are relative to the end of dosing (ie, end of nebulization of GSP304/GSP304 placebo or after the second actuation of Spiriva® Respimat®). The window for 1-hour spirometry and thereafter is  $\pm 5$  minutes.

### 7.1.1. Screening and Run-in

Screening will occur between Day -28 and Day -15. The purpose of screening is to obtain informed consent and to establish protocol eligibility. Written informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in [Section 16.3](#).

After informed consent is obtained, subjects will be evaluated for eligibility based on the inclusion and exclusion criteria (see [Section 8](#)), which will require review of medical history (including smoking history) and concomitant medications, vital signs, physical examination, assessment of subject's current COPD severity by spirometry, 12-lead electrocardiogram (ECG), chest X-ray (if no chest x-ray or computed tomography (CT) scan was taken within 6 months prior to study start, or if recent results are unavailable for review), clinical laboratory evaluations (hematology, blood chemistry, urinalysis), serum alcohol test, urinalysis for drugs of abuse and cotinine, serology testing for hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibody, serum pregnancy testing for all female subjects, and follicle stimulating hormone (FSH) screening for all females to confirm non-childbearing potential. Adverse event (AE) monitoring will begin after informed consent is obtained.

If the subject is taking any prohibited medication/s at the time of screening, then washout should be performed for appropriate duration (Refer to [Appendix 1](#)) before the screening spirometry.

Appropriate Screening electronic case report form (eCRF) must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

After the Screening visit, subjects meeting the eligibility criteria and the safety laboratory test results, HbsAg and HCV antibody test results, will undergo a Run-in period of 14 days. Subjects will be instructed not to use the prohibited medications during this run-in period and only rescue medication ([Section 9.2.1](#)) will be allowed as required. Device training (for GSP304 and Spiriva® Respimat®) will be provided to all subjects once during screening, and once during the run-in period at Visit 2. Additional device training may be provided to the subjects at Investigator's discretion at other visits eg, at Visit 3 before dosing. Subjects will be provided with a diary to record the symptoms of exacerbation, AEs if experienced, and rescue medications including other new medication if used during the Screening or Run-in periods.

Repeat of screening evaluations are allowed in cases where abnormal result(s) are noted during the Screening Period that are believed to be related to an error or a transient and/or reversible condition. Results of the repeated assessment must be available during the screening period.

Subjects who fail to satisfy inclusion/exclusion criteria may rescreen once for the study.

### 7.1.2. Treatment Period

Following the run-in period, subjects will attend the study clinic in the evening on Day -1 (Visit 3) for clinic check-in. The subjects' eligibility will be confirmed by the Investigator. Following confirmation of eligibility, subjects will be randomized (1:1:1:1) in the morning on Day 1 to receive treatments with either one of 3 dose levels of blinded GSP304 [REDACTED]



■■■■■, blinded GSP304 placebo QD, or open-label Spiriva® Respimat® (2.5 µg, 2 actuations, QD). On days on which subject visits are scheduled, subjects will take the study drug at the Investigator site (ie, after any required pre-dose blood samples and pre-dose PD measures have been collected). On all other days, subjects will be requested to take the study medication at home as instructed by the study staff, at approximately the same time the study medication was dosed on Day 1. Subjects will receive the first dose of the allocated study medication in the morning on Day 1 (during Visit 3) at the clinic. During the Treatment period there are 4 scheduled visits; Visit 3 (Day -1 to Day 2), Visit 4 (Day 7), Visit 5 (Day 14), and Visit 6 (Day 20 to Day 22). Subjects will stay in the clinic as in-patients for about 36 to 48 hours at Visit 3 and Visit 6. Visit 4 and Visit 5 will be out-patient ambulatory visits. At each scheduled visit, the Investigator and site staff will perform various assessments as described in Table 2. Subjects will record in the diary any symptoms of exacerbation, use of study drug, rescue and other new concomitant medication and any AEs if experienced during the treatment period. Subjects will bring their study medication (and nebulizer, if required for treatment administration, per randomization group) and the diary to the clinic at each scheduled visit for supervised self-administration of the morning dose at the clinic, and for the Investigator and site staff to assess each subject's compliance with the dosing regimen.

Blood (approximately 6 mL, or a little more than a teaspoon of blood) and urine samples will be collected for PK at the time points noted in Table 2. The accurate volume of urine will be noted.

#### **7.1.3. Follow-up**

At the Follow-up visit on Day 35 ± 2 days (Visit 7), subjects will undergo safety assessments as described in Table 2.

#### **7.1.4. Extension Phase**

An extension phase is not planned for this study.

### **7.2. Discussion of Study Design, Including Choice of Control Groups**

#### **7.2.1. Study Rationale**

Tiotropium bromide is a long-acting anticholinergic with specificity for muscarinic receptors. It is currently approved as Spiriva® HandiHaler® (tiotropium bromide inhalation powder) and Spiriva® Respimat® (tiotropium bromide inhalation spray) for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.

The choice of inhaler device depends on several factors, including availability, cost, the prescribing physician, and the patient's skills and ability.<sup>9</sup> The effectiveness of the product will depend on the delivery device used and the patient's ability to use the device correctly. If a patient cannot or does not use the delivery device as intended, the intended dose may not be delivered to the lung, resulting in the potential for reduced efficacy. Patient errors are common with all devices<sup>17</sup>, and the Sponsor has not identified additional risks described in published literature associated with the use of a nebulizer.

A set of clinical practice guidelines for aerosol delivery device selection have been established by the Grading of Recommendations Assessment, Development, and Evaluation criteria.<sup>18</sup> These criteria recommend the use of a nebulizer for adults who cannot coordinate the use of other devices, such as an MDI or a DPI. In particular, patients with COPD may have problems with coordination and may experience difficulties when using an MDI when actuation needs to be synchronized with the start of inhalation. Nebulizer use might also be more practical for patients with COPD, who may have severely overinflated lungs, when a slow flow and breath hold are required for MDI use and cannot be maintained, or for patients who cannot generate enough inspiratory flow required for DPI use.<sup>9,17</sup> In addition, nebulizer therapy (or MDI) is recommended for drug delivery during noninvasive ventilation.

The Sponsor has developed a tiotropium bromide inhalation solution (GSP304) for administration by nebulization. This dose-ranging study aims to provide insight on the appropriate dose of tiotropium bromide inhalation solution to be delivered to the lungs via a nebulizer. The proposed indication of this product will be for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD.

### 7.2.2. Study Design

This is a phase 2, randomized, parallel group, active- and placebo-controlled, 5-arm study to compare the PK profile of 3 blinded doses of GSP304 with open-label Spiriva® Respimat®. A parallel-group design has been selected over a cross-over design to prevent any potential “carry-over effect,” and significantly extended study duration due to multiple cross-over treatment with long washout periods (at least 1-2 weeks for each washout).

The planned treatment duration of the study is 3 weeks because the plateau of effect of FEV<sub>1</sub> for tiotropium delivered by inhalation aerosol is reached within 2 weeks.<sup>19, 20</sup> Furthermore, it is estimated that tiotropium will reach steady state for systemic exposure within 1 week. Therefore, the treatment duration of 3 weeks in this study is expected to be sufficient to reach PK and PD steady state and confirm the dose-response of tiotropium bromide inhalation solution.

Spiriva® Respimat® is selected as the active comparator for the present study (versus Spiriva® HandiHaler®) because both GSP304 and Spiriva® Respimat® are formulated as a tiotropium bromide inhalation solution, whereas Spiriva® HandiHaler® is a tiotropium bromide inhalation powder for inhalation.

This design would enable determination of a dose of GSP304 that would have a comparable PK profile with Spiriva® Respimat® in patients with COPD.

### 7.2.3. Dose selection

This is the first-in-human study with GSP304 (tiotropium bromide) Inhalation Solution. In the absence of reported PK or clinical data comparing tiotropium delivered via a nebulizer or Spiriva® HandiHaler® or Spiriva® Respimat®, a range of dose strengths [REDACTED] (with respect to tiotropium) will be tested to identify an appropriate dose of GSP304 to be delivered to the lungs via a nebulizer in subjects with COPD. During the preliminary development of inhaled tiotropium bromide (Spiriva® HandiHaler®) tiotropium delivered via a nebulizer was tested at doses [REDACTED] in healthy subjects.<sup>21</sup> Based on preliminary in vitro study data, a dose of approximately [REDACTED] delivered via an [REDACTED]

████████████████████ results in a similar Fine Particle Dose ██████████ as 5 µg Spiriva® Respimat.

The following dose strengths of GSP304 (tiotropium bromide) Inhalation Solution will be used in this study ██████████. The dose strengths to be used in this study for delivery via a nebulizer are higher than the approved Spiriva® Respimat® dose strength, because the Respimat® Soft Mist Inhaler uses mechanical energy to increase efficiency of the device, therefore reducing the nominal dose of tiotropium required to produce equivalent clinical efficacy of either a nebulizer or DPI. The Sponsor has not identified any study in published literature that directly compares a nebulizer and the Respimat® Soft Mist Inhaler.<sup>22,23</sup> The PK of GSP304 at these doses will be compared with the approved dose of Spiriva® Respimat® (5 µg QD), which is supplied for this study as an open-label marketed product.

#### **7.2.4. Population**

To be considered for inclusion in this study, a subject must have a primary diagnosis of mild or moderate COPD (defined as post bronchodilator FEV<sub>1</sub>/FVC ratio of <70% and FEV<sub>1</sub> of ≥50% of predicted normal value as per the NHANES III predicted normal values at screening).

The PD dose response of GSP304 and the marketed comparator will be compared by measurement of FEV<sub>1</sub>. For this reason, the Sponsor proposes that subjects with mild (GOLD 1) to moderate (GOLD 2) COPD will participate in this phase 2 study. The frequency of treatment of GSP304 used in this phase 2 study is the same as the approved Spiriva® Respimat® that is indicated for use in patients with mild, moderate and severe symptoms of COPD.<sup>10</sup>

#### **7.3. Number of Subjects**

A total of 155 male and female subjects of non-childbearing potential, ≥40 but ≤85 years of age will be randomized in this study.

#### **7.4. Treatment Assignment**

Each subject will be randomized to 1 of 5 treatment arms in a 1:1:1:1:1 ratio, to receive 1 of 3 doses of double-blinded GSP304, or double-blinded GSP304 placebo, or open-label Spiriva® Respimat®.

#### **7.5. Dose Adjustment Criteria**

Not applicable.

#### **7.6. Criteria for Study Termination**

If the Investigator, or the Sponsor's Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;



- Failure to enroll subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug product.

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The Institutional Review Board (IRB)/independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## **7.7. Benefit-Risk Assessment**

### **7.7.1. Evaluation of Benefit**

A total of 6614 subjects with COPD (2801 receiving Spiriva® Respimat® 5 µg and 2798 receiving placebo) were studied in 5 confirmatory studies of Spiriva® Respimat®.<sup>10</sup> These studies enrolled subjects who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV<sub>1</sub> less than or equal to 60% of predicted and a ratio of FEV<sub>1</sub>/FVC of less than or equal to 0.7. All treatments were administered [REDACTED]. Change from baseline in trough FEV<sub>1</sub> was a primary endpoint in all studies. Three studies included COPD exacerbations as primary endpoints. Spiriva® Respimat® 5 µg demonstrated significant improvement in trough FEV<sub>1</sub> compared with placebo in all 5 confirmatory studies.

Pooled analysis of 2 studies showed a significant reduction [REDACTED] exacerbations/patient year), compared with placebo [REDACTED] exacerbations/patient year [REDACTED] 95% confidence interval [CI [REDACTED], of COPD exacerbations (defined as a complex of respiratory events/symptoms with a duration of ≥3 days with 2 or more of the following AEs [increase of symptoms or new onset]: shortness of breath/dyspnea/shallow, rapid breathing; sputum production [volume]; occurrence of purulent sputum; cough; wheezing; chest tightness). In a third study, exacerbation was lower in subjects taking Spiriva® Respimat® 5 µg compared with subjects on placebo and the risk of COPD exacerbation-related hospitalization was reduced compared with placebo [REDACTED].

### **7.7.2. Assessment of Risk**

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching, may occur after administration of tiotropium bromide. Subjects with a history of allergic reaction to the

anti-cholinergic or any components of the study medications will be excluded from study participation.

Inhaled medicines, including tiotropium bromide, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta<sub>2</sub>-agonist such as albuterol. Albuterol/salbutamol MDI will be permitted throughout the study as rescue medication ([Section 9.2.1](#)).

Tiotropium bromide should be used with caution in patients with narrow-angle glaucoma or urinary retention. Investigators and subjects should be alert for signs and symptoms of acute narrow-angle glaucoma (eg, eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema) or urinary retention (eg, difficulty passing urine, painful urination). Subjects with clinically significant unstable medical abnormalities will be excluded from study participation.

As a predominantly renally-excreted drug, subjects with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with tiotropium bromide should be monitored closely for anticholinergic side effects. Subjects with clinically relevant laboratory results will be excluded from study participation.

There are no adequate and well-controlled studies in pregnant women. Tiotropium bromide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because the risk to a fetus is unknown, only women of non-childbearing potential (as defined in [Section 8](#)) will eligible for study participation.

The most common adverse reactions of tiotropium bromide inhalation powder (>5% incidence in Spiriva® HandiHaler® 1-year placebo controlled studies) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis.<sup>11</sup> The most commonly reported adverse reactions of tiotropium bromide inhalation spray (>3% and higher than placebo) were pharyngitis, cough, dry mouth, and sinusitis.<sup>10</sup>

Pooled analysis of safety data from 29 clinical studies conducted with Spiriva® suggested that there is an increased risk of stroke (2 cases per 1000) with tiotropium bromide treatment,<sup>24</sup> that raised safety concerns and prompted further long-term safety studies to evaluate risk. A long-term safety study (UPLIFT) followed approximately 6000 subjects over 4 years and concluded that the long-term use of tiotropium bromide does not increase the risk of stroke, heart attack, or death due to a cardiovascular cause. These findings support the cardiac safety of tiotropium bromide in patients with COPD.<sup>25</sup> In the UPLIFT study, rate ratios for overall AEs, SAEs, and fatal AEs favored Spiriva® HandiHaler® versus placebo treatment. However, data from additional studies has been interpreted to indicate that an increased risk of mortality associated with the use of Spiriva® Respimat® is possible.<sup>26</sup>

A long-term, randomized, double-blind study (TIOSPIR) was conducted to prospectively evaluate safety and exacerbation efficacy of Spiriva® Respimat® versus Spiriva® Handihaler®.<sup>27</sup> The results of the TIOSPIR study demonstrated that the safety profile and exacerbation efficiency of Spiriva® Respimat® 5 µg or 2.5 µg was similar to that of Spiriva® HandiHaler® 18 µg for subjects with COPD. The mortality risk for Spiriva® Respimat® 5 µg or 2.5 µg was similar to that of Spiriva® HandiHaler® 18 µg, with hazard ratios of 0.96 and 1.00 for Spiriva®



Respimat® 5 µg and 2.5 µg versus Spiriva® HandiHaler® 18 µg, respectively. The risks of exacerbations and major adverse cardiovascular events were similar in all 3 treatment groups.<sup>28</sup>

### 7.7.3. Benefit-Risk Conclusion

The safety, efficacy, and PK profile for tiotropium bromide is well-established when inhaled as an inhalation powder (Spiriva® HandiHaler®)<sup>11</sup> or inhalation spray (Spiriva® Respimat®).<sup>10</sup> Tiotropium bromide has been approved in the US for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations. GSP304 (tiotropium bromide) Inhalation Solution is being developed with the expectation that the selected dose will result in systemic exposure to tiotropium that is comparable to the approved dose of Spiriva®. Since the safety of tiotropium bromide at its therapeutic dose is well-established in large long-term clinical studies, the Sponsor considers it reasonable to expect that the safety profile of GSP304 will be similar to the approved products (Spiriva® HandiHaler® and Spiriva® Respimat®). In addition, a nebulizer has been selected for the delivery of GSP304 because this type of device may offer benefit for patients with COPD who have difficulty with coordination or have low inspiratory rates.

## **8. SELECTION AND WITHDRAWAL OF SUBJECTS**

### **8.1. Subject Inclusion Criteria**

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Provide written informed consent.
2. Willing and able to comply with all aspects of the protocol and able to appropriately use the inhalation device.
3. Male and female subjects  $\geq 40$  years and  $\leq 85$  years of age at the time of consent.
4. Subject must have a primary diagnosis of mild or moderate COPD defined as post-bronchodilator FEV<sub>1</sub>/FVC ratio of  $< 70\%$  and FEV<sub>1</sub> of  $\geq 50\%$  of predicted normal value as per the NHANES III predicted normal values at screening.
5. Willing to stop all other COPD medications or other medications which will interfere with the study results for the entire duration of the study, except albuterol/salbutamol as needed.
6. Female subjects must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day-1, and must be of non-childbearing potential, defined as:
  - a. Postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high FSH level ( $> 40$  IU/L) in the postmenopausal range may be used to confirm a postmenopausal woman not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - b. Permanently sterile, including surgical sterilization by hysterectomy, bilateral tubal ligation/salpingectomy, and bilateral oophorectomy.
7. Men with partners of childbearing potential must be willing to use condoms in combination with a second effective method of contraception during the study. Each man will be considered as potent unless surgically sterilized (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate).
8. Current or ex-smoker with  $\geq 10$  pack-year smoking history.
9. Subjects must have a body mass index (BMI) of at least  $16 \text{ kg/m}^2$  but no more than  $30 \text{ kg/m}^2$ .
10. Subjects must be willing to remain in the residential facility for 2 separate periods of 36 to 48 hours (Day -1 through Day 2 and Day 20 through Day 22) and to visit the facility for 3 separate ambulatory sample visits.
11. Subjects must agree to refrain from strenuous activities, throughout the study, from the screening visit until after the end of study/early termination visit.

### **8.2. Subject Exclusion Criteria**

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Any history of or concomitant medical condition that in the opinion of the Investigator would compromise the subject's ability to safely complete the study.
2. Currently enrolled in another clinical study or have used any investigational product, study drug, or device within 30 days or 5 half-lives, whichever is longer, preceding informed consent or scheduled to participate in another clinical study involving an investigational product or investigational drug during the course of this study.
3. Subject has had a febrile illness within 3 days before screening.
4. Subject has any clinically significant unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular, respiratory, GI, hepatic, or renal systems, which, in the opinion of the Investigator, may affect the safety of the subject.
5. Subject has a history of malignancy or currently has malignancy other than non melanomatous skin cancer. (Subjects who have been cancer-free for 5 years or more [prior to randomization] may be enrolled.)
6. Subjects with a chest x-ray/CT scan that suggests a diagnosis other than COPD (eg, pneumonia, other infection, atelectasis, or pneumothorax or other active/ongoing pulmonary conditions) and taken within 6 months prior to study start. If there is no chest x-ray or CT scan taken within 6 months prior to study start, or if recent results are unavailable for review, a chest x-ray must be performed.
7. An abnormal and, in the judgment of the Investigator, clinically significant 12-lead ECG. For the purposes of this study, an abnormal ECG will be defined as a 12-lead tracing which is interpreted with (but not limited to) any of the following:
  - Clinically significant conduction abnormalities (eg, left bundle branch block, Wolff-Parkinson-White syndrome)
  - Myocardial ischemia
  - Clinically significant arrhythmias (eg, atrial fibrillation, ventricular tachycardia)
  - A mean QTcB value at screening  $\geq 450$  msec (for males) /  $\geq 470$  msec (for females) and, the QTcB of all 3 screening ECGs are not within 10% of the mean, or an ECG that is not suitable for QT measurements (eg poorly defined termination of the T wave)
8. Has a clinically relevant laboratory abnormality or a clinically significant condition, in the judgment of the Investigator, such as (but not limited to):
  - Unstable ischemic heart disease, left ventricular failure (New York Heart Association Class III and IV), history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation). Subjects with such events not considered clinically significant by the Investigator will be considered for inclusion in the study.
  - Uncontrolled hypo- or hyperthyroidism, hypokalaemia or hyperadrenergic state or any condition, which might compromise subject's safety or compliance, interfere with evaluation, or preclude completion of the study.

- Tiotropium bromide should be used with caution in patients with narrow-angle glaucoma or urinary retention.
9. Subjects with a screening serum creatinine value >1.5 mg/dL.
  10. Use of oral/parenteral corticosteroids or antibiotics for COPD within 6 weeks or depot corticosteroids within 3 months prior to screening or subject has had a change in dose or type of any medications for COPD within 14 days before screening.
  11. Hospitalization for COPD exacerbation or pneumonia within 3 months prior to screening.
  12. Subjects with a history of asthma, with the exception of outgrown childhood asthma, defined as transient wheezers outgrown by 5 years of age.<sup>29</sup>
  13. Subject has a known history of alpha 1 antitrypsin deficiency-related emphysema.
  14. Subject has a history of lung resection of more than one full lobe or being a recipient of a lung or major organ transplant.
  15. Subject requires nocturnal oxygen or continuous supplemental oxygen therapy.
  16. Subject with history of a positive result for HBsAg or HCV antibody.
  17. Subject is known to be seropositive for human immunodeficiency virus.
  18. Female subject is pregnant or lactating.
  19. Female subject who (a) is of childbearing potential, or (b) is post-menopausal and is taking any form of hormone replacement therapy.
  20. Subject has a disorder or history of a condition that may interfere with drug absorption, distribution, metabolism, or excretion (eg, malabsorption, GI surgery).
  21. Subject is a staff member or relative of a staff member.
  22. Subject has a positive serum alcohol test during screening. Subjects with a known history of alcohol use may be enrolled in the study if the alcohol use is not indicative of abuse, as considered by the Investigator.
  23. Subject has a history or suspected history of abuse of a barbiturate, amphetamine, or narcotic and/or has a positive screening result for any of these substances at study start. Note: Positive drug screening results are not exclusionary for prescription narcotics, amphetamines, or barbiturates, if taken only as prescribed under the supervision of a physician for a well-documented medical indication, without any evidence or suspicion of abuse. However, methadone and cannabinoids are exclusionary for this study even when taken by prescription.
  24. Subject has a history of allergic reaction to the anti-cholinergic or any components of the study medications.
  25. Subject is unable to stop the medications at the defined times prior to screening spirometry as defined in [Appendix 1](#).
  26. Subject has received oral anticoagulant therapy within 90 days before screening except use of low dose aspirin (up to 325 mg daily) to prevent heart attack or a stroke. Certain



types of anticoagulant therapy (eg, clopidogrel, prasugrel) may be permitted, but all must be reviewed on a case-by-case basis with the Medical Monitor.

27. Subject has had significant blood loss (>500 mL) or donated blood within 60 days preceding screening or plans to donate blood during or within 60 days after completing the study.
28. Subject has had an acute illness within 10 days of Day 1.
29. Intake of grapefruit, Seville oranges, or pomelo containing food or beverages within 7 days prior to receiving the first dose of study treatment until collection of the final PK blood sample.
30. Subject is not willing to comply with dietary restrictions specified in the protocol.

### **8.3. Subject Withdrawal Criteria**

A subject may voluntarily discontinue study participation at any time after giving informed consent and before the completion of the study. The Investigator may also discontinue the subject's study participation at any time at his/her discretion and for any reason.

The reasons for subject withdrawal will be recorded and may include, but are not limited to:

1. Withdrawal of consent by the subject to continue in the study.
2. Development of a serious or intolerable AE that necessitates discontinuation at the discretion of the Investigator (AE section of case report form [CRF] must be completed; includes serious adverse event [SAE], any death).
3. In the opinion of the Investigator, continued participation is not in the best interest of the subject.
4. In the opinion of the Investigator, the subject does not adhere to the study procedures.
5. Protocol deviation that, in the opinion of the Sponsor and Investigator, warrants discontinuation from the study.
6. The Investigator may withdraw the subject from the study for any of the following:
  - a. The subject suffers from significant inter-current illness or undergoes surgery during the course of the study.
  - b. The subject requires concomitant medication, which may interfere with the PK properties of the study medication.
7. Subject is unable to comply with spirometry washout criteria.
8. Experienced a COPD exacerbation defined as worsening of the following 2 or more major symptoms for at least 2 consecutive days:
  - a. Dyspnea
  - b. Sputum volume
  - c. Sputum purulence

OR



A worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days:

- a. Sore throat
- b. Colds (nasal discharge and/or nasal congestion)
- c. Fever without other cause
- d. Cough

Note: A COPD exacerbation is considered of moderate severity if treatment with systemic glucocorticosteroids or antibiotics or both is required. A COPD exacerbation is considered to be severe if hospitalization will be required. An emergency room visit of longer than 24 hours will be considered a hospitalization. A COPD exacerbation shall be reported as an AE and may be considered serious if it meets the serious criteria for SAE reporting (see [Section 12.2.5](#)).

9. Demonstrated clinically significant changes in laboratory parameters or ECG recordings.

Any subject withdrawal during the study, along with the reason for withdrawal, must be documented in the source documents and eCRFs.




All follow-up assessments should be conducted at the Early Withdrawal visit (Visit 7 procedures). The follow-up visit should be performed as soon as possible after a subject withdraws from the study. If a subject is lost to follow up (fails to return for study visits), reasonable efforts should be made to determine why the subject failed to return. This information should be documented in source documents and in eCRFs.

Subjects discontinued from the study at any stage after the first dose of study drug will be included in the safety analysis. Discontinued subjects will not be replaced.

**9. TREATMENT OF SUBJECTS****9.1. Description of Study Drug**

Table 3 and Table 4 provide a description of the double-blind GSP304, double-blind GSP304 placebo, and the open label Spiriva® Respimat® comparator to be used in the study.

**Table 3: GSP304**

<b>Product Name:</b>	GSP304	GSP304	GSP304
<b>Dosage Form:</b>	inhalation solution	inhalation solution	inhalation solution
<b>Unit Dose</b>			
<b>Route of Administration</b>	oral inhalation	oral inhalation	oral inhalation
<b>Method of Administration</b>	nebulization	nebulization	nebulization
<b>Physical Description</b>	a clear solution in a semi-transparent, soft plastic ampule	a clear solution in a semi-transparent, soft plastic ampule	a clear solution in a semi-transparent, soft plastic ampule

**Table 4: Other Study Drugs**

	<b>Comparator Product</b>	<b>GSP304 Placebo</b>
<b>Product Name:</b>	Spiriva® Respimat®	Matching placebo for GSP304
<b>Dosage Form:</b>	inhalation spray for oral inhalation	inhalation solution
<b>Unit Dose</b>	2.5 µg	0 µg
<b>Route of Administration</b>	oral inhalation	oral inhalation
<b>Method of Administration</b>	metered spray for inhalation	nebulization
<b>Physical Description</b>	a clear solution in a green/grey plastic Respimat® inhaler	a clear solution in a semi-transparent, soft plastic ampule
<b>Manufacturer</b>	Boehringer Ingelheim Pharma GmbH & Co	Glenmark or designee

## 9.2. Concomitant Medications

The details of the prohibited prior medications and their washout period are provided in [Appendix 1](#). Any medication (including over-the-counter medications) or therapy administered to the subject during the study (other than study drug/treatment, starting at the date of informed consent, will be recorded on the Prior & Concomitant Medication eCRF or Concomitant Non-Drug Treatment eCRF. The Investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the Investigator will record the medical condition on the Medical & Surgical History eCRF.

### 9.2.1. Rescue Medication(s)

Albuterol/salbutamol MDI will be permitted throughout the study as rescue medication. Subjects will be trained to abstain from using albuterol/salbutamol MDI, 6 hours prior to start of each visit. If this is not possible, the visit will need to be rescheduled. Albuterol/salbutamol will be sourced from local commercial stock. Any rescue medication(s) taken will be recorded in the subject diary and appropriate eCRFs.

## 9.3. Lifestyle and/or Dietary Restrictions

Subjects will not be allowed to consume the following foods or drinks:

Intake of grapefruit, Seville oranges, or pomelo-containing foods or beverages within 7 days prior to the first dose of study treatment until after collection of the final PK blood sample.

Foods containing poppy seeds for 48 hours prior to first dosing until the final PK blood sample.

Alcohol for 48 hours prior to dosing until study completion.

For additional restrictions on spirometry day, refer to [Section 11.2.2.2](#) and [Appendix 5](#).

#### **9.4. Treatment Compliance**

Records of treatment compliance for each subject will be assessed by reviewing the subject diary, the dose indicator of Spiriva® Respimat® (as applicable), or counting of study drug ampules (as applicable), and will be documented. Clinical Research Associates will review treatment compliance during site visits and at the completion of the study.

#### **9.5. Treatment of Investigational Product Overdose**

Treatment of overdosage consists of discontinuation of GSP304 together with institution of appropriate symptomatic and/or supportive therapy.

#### **9.6. Randomization and Blinding**

##### **9.6.1. Allocation to Treatment Groups**

At Screening (Visit 1), each potential subject will be assigned a screening number. Following confirmation of the eligibility criteria as applicable, the subject will enter the Run-in period (Visit 2). After completion of the Run-in period, if the subject is conforming to the applicable eligibility criteria, then he/she will be randomized and allocated a subject randomization number (Visit 3). Subjects who drop out of the study before randomization/run-in period will retain their screening number.

Randomization and investigational product (IP) assignment will occur in the morning of Day 1 after all Screening procedures have been performed, run-in has been completed and eligibility of the subject for the study confirmed. Randomization numbers will be issued centrally using interactive voice response system (IVRS)/interactive web response system (IWRS). Randomized subjects who terminate their study participation for any reason, regardless of whether study drug has been taken or not, will retain their randomization number.

Subjects will be assigned in the ratio of 1:1:1:1:1 to receive treatments with either of double-blind GSP304 at 1 of 3 dose levels, open-label Spiriva® Respimat®, or double-blind GSP304 placebo based on a computer-generated randomization scheme that will be reviewed and approved by a statistician. The randomization scheme will be stored within the IVRS/IWRS database until unblinding of this study is requested. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

##### **9.6.2. Blinding and Unblinding Procedures**

The active GSP304 and GSP304 placebo are double-blind; Spiriva® Respimat® is open-label. Double-blind study drugs (GSP304 and GSP304 placebo) will be supplied in identical packaging, and will be similar in color, smell, and appearance.

The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement. The blind should preferably be broken following discussion, on a case-by-case basis, with the Sponsor Medical Monitor and Pharmacovigilance group.

In the event of a medical emergency, unblinding for a given subject can be performed through the IVRS/TWRS directly by the Investigator or designee. The reason for unblinding, date and time will be required to be entered the appropriate form in the TMF.

If the breaking of the blind was due to an AE, the subject should be followed up until the AE has resolved or stabilized

To enable bioanalysis of tiotropium in plasma and urine samples only from active treatment groups, randomization codes of GSP304 placebo allocated subjects will be shared with a designated person at the bioanalytical site and it will be ensured that this will not unblind the clinical Investigator or Sponsor personnel involved in direct conduct of the study. This process will be documented and filed.

The overall study randomization code will be broken only for study reporting purposes. This will occur once all final clinical data have been entered into the database, all data queries have been resolved, all PK samples have been analyzed, and the database is locked.



## **10. STUDY DRUG MATERIALS AND MANAGEMENT**

### **10.1. Study Drug**

The following treatments will be administered during the treatment period depending on the subject's randomization.

#### **10.1.1. Blinded GSP304**

Test Treatment T1: GSP304 (tiotropium bromide) Inhalation Solution, [REDACTED]

Test Treatment T2: GSP304 (tiotropium bromide) Inhalation Solution, [REDACTED]

Test Treatment T3: GSP304 (tiotropium bromide) Inhalation Solution, [REDACTED]

GSP304 will be administered by oral inhalation [REDACTED] using a nebulizer (provided by the Sponsor).

#### **10.1.2. Blinded GSP304 Placebo**

Test Treatment T4: Placebo to match GSP304.

GSP304 placebo will be administered by oral inhalation [REDACTED] using a nebulizer (provided by the Sponsor).

#### **10.1.3. Open-label Spiriva® Respimat®**

Test Treatment T5 (Reference Treatment): Marketed Spiriva® Respimat® (see [Appendix 4](#) for further details).

### **10.2. Study Drug Packaging and Labeling**

The investigational product will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

### **10.3. Study Drug Storage**

The investigational product (GSP304/GSP304 placebo) should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F, see USP Controlled Room Temperature). Avoid freezing.

Spiriva® Respimat® should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F, see USP Controlled Room Temperature). Avoid freezing.

### **10.4. Study Drug Preparation**

Not applicable.

### **10.5. Administration**

On days where subject visits are scheduled, subjects will bring all used and unused study drug (GSP304/GSP304 placebo or Spiriva® Respimat®) and rescue medication containers to each study visit, along with the nebulizer, if required for treatment administration, per randomization

group, EXCEPT on Day 20 when subjects will be requested to take the study medication at home as instructed by the study staff.

On all other days, subjects will be requested to take the study medication at home as instructed by the study staff.

Subjects will receive the first dose of the allocated study medication in the morning on Day 1 (Visit 3) at the clinic. Study medication (GSP304/GSP304 placebo or Spiriva® Respimat®) will be dispensed to the subjects at Visit 3 (at first dose on Day 1) to support the treatment for 3 weeks. At clinic check-in on Day 20, subjects will also be requested to bring any remaining full ampules of study medication and all empty ampules of study medication to the study site.

GSP304 and GSP304 placebo will be administered (morning) by oral inhalation via a nebulizer. Refer to [Appendix 3](#) for detailed instructions for use of the nebulizer.

Spiriva® Respimat® will be administered QD (morning) by oral inhalation. For the instructions for use, refer to [Appendix 4](#).

The time interval between daily doses should be approximately 24 hours.

#### **10.5.1. Rescue Medication**

Open-label rescue medication (albuterol/salbutamol MDI) will be dispensed to the subjects at Visit 2 or at the start of washout (if the subject requires washout) and at subsequent scheduled visits as required, for self-administration as needed, at home. Albuterol/salbutamol MDI will be sourced from local commercial stock.

#### **10.6. Study Drug Accountability**

The Principal Investigator (or designee) is responsible for IP accountability at the site and its documentation. The Principal Investigator must also ensure that the dispensing and recording of IP is done only by authorized personnel. The IP records must be readily available for inspection by the study monitor and/or auditor/regulatory agency personnel.

#### **10.7. Study Drug Handling and Disposal**

No medication (used or unused) can be returned to the Sponsor or disposed of at the investigational site until the Sponsor's clinical monitor has verified/reconciled the accuracy of the study medication records at the site and indicated whether the medication should be destroyed at the site or returned to the Sponsor. The clinical monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

## **11. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS**

### **11.1. Study Endpoints**

#### **11.1.1. Primary Endpoints**

- The PK endpoints for tiotropium in plasma to assess the relative bioavailability are:
  - Peak concentrations during the dosing interval at steady-state ( $C_{\max SS}$ )
  - Area under the plasma concentration-time curve over the dosing interval at steady state ( $AUC_{0-\tau SS}$ )
- Change from baseline in trough  $FEV_1$  at 24 hours after the last dose of treatment on Day 21 in comparison to GSP304 placebo

#### **11.1.2. Secondary Endpoints**

- Amount ( $A_{\tau}$ ) and fraction of dose of tiotropium ( $F_e$ ) excreted in urine over the dosing interval on Day 1 and Day 21
- Peak concentrations during the dosing interval ( $C_{\max}$ ) on Day 1
- Area under the plasma concentration-time curve over the dosing interval ( $AUC_{0-\tau}$ ) on Day 1
- Time of peak drug concentration over the dosing interval ( $t_{\max}$ ) on Day 1 and Day 21
- Average concentration during a dosing interval at steady state ( $C_{av SS}$ ) on Day 21
- Accumulation ratio ( $R_{ac}$ )
- Change from baseline in peak  $FEV_1$  within 12 hours post-dose on Day 1 and Day 21
- Change from baseline in FVC on Day 1 and Day 21
- Change from baseline in time-normalized area under the curve for  $FEV_1$  measured over 12 hours on Day 1 and Day 21

#### **11.1.3. Safety Endpoints**

- Vital signs, laboratory parameters, 12-lead ECG
- Incidence of all AEs

#### **11.1.4. Appropriateness of Measurements**

All clinical assessments described in the proposed study are standard measurements commonly used in studies of subjects with COPD.

Collection of blood and urine samples pre-dose and at scheduled time points post-dose for determination of individual subject plasma tiotropium concentrations is appropriate to assess the co-primary objective of this study, which is to compare the relative bioavailability of GSP304

(tiotropium bromide) Inhalation Solution at dose levels of [REDACTED] compared with Spiriva® Respimat® inhalation (5 µg QD) in subjects with COPD.

Pre-dose FEV<sub>1</sub> and FVC will be assessed, in addition to serial spirometry to record FEV<sub>1</sub> on Day 1 and Day 21. These PD assessments are appropriate to assess the co-primary objective of this study, which is to characterize the dose response of GSP304 at dose levels of [REDACTED] and [REDACTED] with respect to PD.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

## **11.2. Efficacy Assessments**

### **11.2.1. Spirometry**

The following assessments will be performed in this study:

#### *FEV<sub>1</sub>*

FEV<sub>1</sub> is the volume of air forcibly exhaled in one second as measured by a spirometer.

#### *Pre-dose trough FEV<sub>1</sub>*

It is defined as the mean of FEV<sub>1</sub> values obtained -45 minutes and -15 minutes pre-morning dose at Day 1.

#### *Peak FEV<sub>1</sub>*

It is defined as the maximum FEV<sub>1</sub> over the period of 12 hours post-morning dose.

#### *Trough FEV<sub>1</sub>*

It is defined as the mean FEV<sub>1</sub> obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.

#### *Baseline FEV<sub>1</sub>*

It is defined as the average of the pre-dose FEV<sub>1</sub> measured at -45 minutes and -15 minutes at Day 1

#### *FVC*

FVC is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.

#### *Baseline FVC*

It is defined as the average of the pre-dose FVC measured at -45 minutes and -15 minutes at Day 1.

For a description of FEV<sub>1</sub> and FVC procedures, refer to [Section 11.2.2.2 Pharmacodynamic Assessments](#).

## **11.2.2. Pharmacokinetic, Biomarker, and Pharmacogenomic Assessments**

### **11.2.2.1. Pharmacokinetic Assessments**

The following PK parameters of tiotropium bromide will be evaluated:



**Plasma:** AUC<sub>0-tauSS</sub>; C<sub>maxSS</sub>; C<sub>minSS</sub>; C<sub>avSS</sub>; C<sub>max</sub> on Day 1; t<sub>max</sub> on Day 1 and Day 14; AUC<sub>0-tau</sub> on Day 1; R<sub>ac</sub>

**Urine:** A<sub>etau</sub> and F<sub>e</sub>

Additional parameters may be evaluated depending on the data obtained during the study.

#### 11.2.2.1.1. Blood Sample Collection

Blood samples (approximately 6 mL) will be collected in dipotassium ethylenediaminetetraacetic acid (EDTA) coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and at 2, 4, 6, 10, 15, 30, and 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. Blood samples for PK should not be drawn or processed in the same room that the subject was dosed with study medication. All post-dose timings are relative to the end of dosing (ie, end of nebulization of GSP304/GSP304 placebo or after the second actuation of Spiriva® Respimat®). The pre-dose sample on Day 1 should be collected within 30 minutes prior to dosing while on Days 7, 14, and 21 the pre-dose sample should be collected within 10 minutes prior to the morning dose. On Day 1 and Day 21, blood samples collected within the following collection windows:

- For the 2 minute sample, within a window of ±30 seconds
- For the 4, 6, 10, 15, and 30 minute samples, within a window of ± 1 minute
- For the 45, 60, 75, 90 minute, and 2.0 hour samples, within a window of ± 2 minutes
- For the 4, 6, 8, 12, 16, 20, and 24 hour samples, within a window of ± 5 minutes.

The collected PK blood samples should be placed immediately on an ice bath and centrifuged under refrigeration at 2°C to 8°C within 30 minutes to separate the plasma. The entire plasma (approximately 3 mL) will be transferred into 2 approximately equal aliquots (approximately 1.5 mL each) and stored at -20°C or below and then sent to the bioanalytical site as specified in a separate instruction manual.

Plasma concentrations of tiotropium will be quantified by a validated liquid chromatography-mass spectrometry (LC/MS/MS) method. Only samples from active treatment groups will be analyzed. Details of bioanalysis will be described in a separate bioanalytical plan.

A PK blood sample will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

#### 11.2.2.1.2. Urine Sample Collection

Urine will be collected into pre-weighed containers at pre-dose (within 1 hour prior to dosing), and at the following intervals post-dose from 0-6, 6-12, and 12–24 hours on Day 1 and Day 21. In each urine container, approximately 5 mL of 1M citric acid must be added prior to the start of collection. During each collection period, the containers will be stored in refrigerators at 2°C to 8°C. Collection time intervals and the accurate weights of containers before and after collection of urine for each interval will be noted. Weight of urine (weight of container with urine – weight of empty container) will be converted to volume using a nominal specific gravity of 1.018. Two representative aliquots of equal volume (approximately 20 mL each, estimated) will be taken from each collection interval and shipped to the bioanalytical laboratory as specified in a



separate instruction manual. The remaining volume will be discarded upon confirmation by the Sponsor PK representative.

Urine concentrations of tiotropium will be quantified by a validated LC/MS/MS method. Only samples from active treatment groups will be analyzed for tiotropium concentrations. Details of bioanalysis will be described in a separate bioanalytical plan.

#### **11.2.2.2. Pharmacodynamic Assessments**

In addition to screening, pre-dose FEV<sub>1</sub> and FVC will be assessed at -45 minutes and -15 minutes prior to dosing on Day 1, Day 7, Day 14, and Day 21. Trough FEV<sub>1</sub> will be assessed on Day 22 (ie, 24-hours after the Day 21 dose).

On Day 1 and Day 21, FEV<sub>1</sub> will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes ( $\pm 3$  minutes), 15 minutes ( $\pm 2$  minutes), 30 minutes ( $\pm 5$  minutes), 60 minutes, 90 minutes, and 2 hours (120 minutes); and post-dose at 4, 6, 8, 10, 12, 23 hours 15 minutes and 23 hours 45 minutes. All post-dose timings are relative to the end of dosing (ie, end of nebulization of GSP304/GSP304 placebo or after the second actuation of Spiriva® RespiMat®). The window for 1-hour spirometry and thereafter is  $\pm 5$  minutes. When multiple procedures (eg, PK, spirometry, ECG) conflict at a point of time, PK should be performed first, followed by spirometry, then ECG.

Centralized spirometry will be conducted using equipment meeting or exceeding American Thoracic Society (ATS)/European Respiratory Society (ERS) minimal performance recommendations, with all sites using standardized equipment provided by a vendor. Spirometry testing is to be performed according to the procedure detailed in [Appendix 5](#). The start time of the first spirometry effort will be used for all spirometry time points recorded. For FEV<sub>1</sub> and FVC, at least 3 (and no more than 8) acceptable efforts will be obtained; the largest FEV<sub>1</sub> and FVC from the 3 acceptable efforts will be recorded, regardless of whether the FEV<sub>1</sub> and FVC are from the same effort. Repeatable FEV<sub>1</sub> and FVC will be obtained according to the ATS/ERS recommendations in [Appendix 5](#). Albuterol/salbutamol rescue medication is to be withheld for at least 6 hours. For screening spirometry at Visit 1, COPD medications must be withheld as specified in the exclusion criteria/[Appendix 1](#). At Visit 3 through Visit 6, dosing of the study drug must be withheld until baseline or trough spirometry, as applicable, has been conducted.

#### **11.2.2.3. Diary Assessments**

Subjects will be provided a diary at Visit 1 and trained to record symptoms of exacerbation, frequency and time of rescue medication and/or other new concomitant medications and any AE experienced. In addition, frequency and time of administration of study drug at home will be recorded in the diary by the subject during the treatment period. Investigator or responsible study staff will review the diary at scheduled visits for compliance check, exacerbation reporting and/or AE reporting.

#### **11.2.2.4. Biomarker Assessments**

Not applicable.

**11.2.2.5. Pharmacogenomic Assessments**

Not applicable.

## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in the Schedule of Procedures and Assessments ([Table 2](#)).

Stopping/discontinuation/withdrawal criteria are listed in [Section 7.6](#) and [Section 8.3](#).

In case of premature discontinuation, the reason and their cause must be documented. All appropriate assessments applicable for Visit 7 should be conducted at the Early Withdrawal visit and should be scheduled as soon as possible after a subject withdraws from the study (See [Section 8.3](#) for details). If the withdrawal is due to an AE, the AE should be monitored until it is resolved or it has returned to a status that was prior to the AE.

#### **12.1.1. Demographic/Medical History**

Subject demography information will be collected at the Screening visit. Demography information includes date of birth (or age), sex and race/ethnicity. Other study-specific demography information may be included.

Medical and surgical history, current medical conditions and smoking status will be recorded at the Screening visit. All relevant medical and surgical history must be noted in source documents and in the Medical & Surgical History form of the eCRF.

#### **12.1.2. Vital Signs**

Examination of vital signs will be performed as designated on the Schedule of Procedures and Assessments ([Table 2](#)).

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse rate [beats per minute], respiratory rate [per minute] and temperature [degrees in Centigrade]) will be obtained at the visits designated on the Schedule of Procedures and Assessments ([Table 2](#)) by standard methods. Blood pressure and pulse will be measured after the subject has been sitting or lying down for 5 minutes. Blood pressure can be taken in the same manner (ie, seated or supine position) at every study visit. All BP measurements should be performed on the same arm, and preferably performed by the same person at the study site.

Documentation of the vital signs will be included in the source documentation at the site. Significant findings at the Screening visit will be recorded in the Medical & Surgical History form of the eCRF. Changes from screening/baseline examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### **12.1.3. Weight and Height**

Bodyweight, height and BMI will be assessed at screening visit only.

**12.1.4. Physical Examination**

Physical examinations (comprehensive or symptom directed/targeted examination) will be performed as designated on the Schedule of Procedures and Assessments ([Table 2](#)). A comprehensive physical examination will include general appearance, skin/subcutaneous tissue, head and neck (including thyroid gland), eyes, ears, nose and throat, mouth, abdomen, lymph nodes, musculoskeletal, thorax, lungs/respiratory, heart/cardiovascular, urogenital, anal/rectal, extremities and a brief neurological/psychiatric examination. Urogenital and anal/rectal examinations are optional and sign/symptom-directed examination might be performed as per the Investigator's discretion.

Documentation of the physical examination will be included in the physical examination section of the eCRF and source documentation at the site if applicable. Significant findings at the Screening visit will be recorded on the Medical & Surgical History eCRF. Changes from screening/baseline examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

**12.1.5. Electrocardiogram (ECG)**

Electrocardiograms will be obtained as designated on the Schedule of Procedures and Assessments ([Table 2](#)). Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see [Section 12.2](#)) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

For ECG abnormalities meeting criteria of an SAE (see [Section 12.2.5](#)), the site must fax or email the SAE report including the ECG report (with Subject ID only, and subject's name masked) to the Sponsor using the SAE form (see Regulatory Reporting Requirements for SAEs [[Section 12.2.5.1](#)]).

**12.1.6. Laboratory Assessments**

Clinical laboratory tests to be performed, including hematology, blood chemistry and urinalysis, are summarized in [Appendix 2](#).

Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures and Assessments ([Table 2](#)) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

A central laboratory should usually be used to measure laboratory parameters that are to be assessed as part of the safety analyses for the clinical study report. Local laboratories may be used in cases of a safety concern during the study, in which case the blood sample would be split (or 2 samples collected) to allow both a local laboratory and a central laboratory analysis. In such cases, the local laboratory result(s) will be considered part of the source documentation only and the central laboratory result will be entered into the clinical database. Local laboratory reports from non-split samples generated to follow safety concerns will be contained in the source documentation.



**12.1.6.1. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs**

Any abnormal laboratory test results (hematology, blood chemistry or urinalysis) or other safety assessments (eg, ECGs, vital signs measurements), including those that worsen from baseline, and considered to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

**12.1.6.2. Virus Serology**

Virus serology to be performed at Screening are summarized in [Appendix 2](#).

**12.1.6.3. Drug Screen**

A standard urine drug screening for drugs of abuse and urine cotinine will be performed at Screening and at each clinic check-in (Day-1, Day 20).

**12.1.6.4. Pregnancy Testing**

For all female subjects, serum pregnancy testing will be performed at Screening and urine pregnancy testing will be performed at Day -1 (clinic check in) and End of Study (Follow-up).

**12.1.6.5. Follicle-Stimulating Hormone Screening**

For all female subjects, FSH screening will be performed at screening to confirm non-childbearing potential (FSH >40 IU/L).

**12.2. Adverse and Serious Adverse Events**

The Investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

**12.2.1. Assessment of Adverse Events**

The Reference Safety Information for this study is the Investigator's Brochure section on Guidance for Investigators, Undesirable Effects.

The Reference Safety Information for the comparator product will be the comparator product (Spiriva® Respimat®) USPI sections on Warnings and Precautions and Contraindications.<sup>10</sup>

**12.2.2. Adverse Event**

An AE is defined as any untoward medical occurrence in a subject administered study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of the study drug, whether or not related to the study drug. An AE includes any event, regardless of the presumed causality between the event and the study drug.

Events that, while not necessarily meeting the definition of AEs, should be treated as such because they may be reportable to Regulatory Authorities according to AE reporting regulations, whether or not considered causally associated with IP, include the following:



- Study drug overdose, whether accidental or intentional
- Study drug abuse
- An event occurring from study drug withdrawal
- Any failure of expected pharmacological action
- Inadvertent or accidental study drug exposure (eg, product leaking or being spilled onto a subject or care-giver)
- Unexpected therapeutic or clinical benefit from the study drug
- Medication errors (ie, incorrect route of administration, incorrect dosage, use of incorrect product).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. Note that significant worsening (ie, requiring systemic steroids, antibiotics, or hospitalization, as described in Section 8.3) will be reported as an AE.

### **12.2.3. Assessment of Severity of Adverse Events**

The severity of AEs is classified as follows:

- Mild:
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate:
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequelae.
- Severe:
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
- The AE produces sequelae, which require (prolonged) therapeutic intervention.

The criteria for assessing severity are different from those used for seriousness (see [Section 12.2.5](#) for the definition of an SAE).

#### **12.2.4. Assessment of Relationship to Study Medication**

The relationship of AEs to study medication is classified as follows:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

For each AE, the Investigator should answer the following question with Yes or No:

- Was there a reasonable possibility (evidence) that the drug caused the AE?

A reasonable possibility means that there are facts (evidence) or arguments to suggest a causal relationship.

NOTE: For subjects that have not started receiving study medication, or run-in phase medications the answer must be no.

#### **12.2.5. Serious Adverse Events**

A SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

#### **12.2.5.1. Regulatory Reporting Requirements for SAEs**

Prompt notification of SAEs by the Investigator to GLENMARK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GLENMARK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GLENMARK will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigators.

All SAEs must be reported to the Sponsor immediately or within 24 hours of the Investigator or their staff becoming aware of them. Reporting should be performed by recording as much information as is available at the time on the SAE Form and sending it to the contact information provided below:

Fax: + 44 1923 251137

Email: [GlobalClinicalSAE@glenmarkpharma.com](mailto:GlobalClinicalSAE@glenmarkpharma.com)

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information. Follow-up reports must be submitted to the Sponsor until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

Additional information will be requested by the Sponsor as necessary.



**12.2.6. Pregnancy**

The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy form, immediately or within 24 hours of the Investigator learning of its occurrence. The report should contain as much information as possible and should be sent to:

Fax: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the Pregnancy Report Form should be updated with all new information and reported immediately via the same contact information above. The Pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, and this information must be sent to the Sponsor as above. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Additional information will be requested by the Sponsor as necessary.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study drug, must be promptly reported to the Sponsor.

**12.2.7. Collection and Recording of AEs and SAEs****12.2.7.1. Collection of AEs**

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of signing the informed consent form (ICF) until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (eg, study drug, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication that is a Glenmark product, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to the Sponsor within 24 hours, as indicated in [Section 12.2.5.1](#).

The Investigator will enquire about the occurrence of AEs/SAEs at every visit throughout the study (including Follow-up and Early Withdrawal visits where applicable), by asking the following non-leading verbal question of the subject (or care-giver, where appropriate):

- "Have you had any medical problems since your last visit?"

All AEs not resolved by the end of the study or that have not resolved upon the subject's discontinuation in the study must be followed until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

#### **12.2.8. Recording of AEs**

All AEs, regardless of the seriousness, severity or relationship to the study medication must be recorded on the AE CRF.

Adverse events that meet the definition of a SAE must be reported on the SAE Form provided for this study.

Adverse events must be documented in clear, unambiguous medical language. Do not use abbreviations or acronyms.

For each AE record only the diagnosis, do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available record each sign and symptom as an AE, when a diagnosis becomes available, update the AE CRF, to record the relevant diagnosis only.

In general abnormal findings at screening should be recorded in the subject's Medical History or in the Concurrent Conditions section in the CRF. However if, in the Investigators opinion, the finding is clinically significant and represents a condition that was not present at signing of informed consent, then the finding must be reported as an AE.



### **13. STATISTICS**

A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized before the database lock at the latest. Any changes from the analyses planned in the SAP will be justified in the clinical study report.

All analyses will be performed using SAS®. PK analyses will be performed using appropriate software.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation (SD), minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

#### **13.1. Sample Size**

A sample size of 28 subjects per treatment arm will have 90% power to detect a difference in mean change from baseline in trough FEV<sub>1</sub> of 150 mL between GSP304 and GSP304 placebo assuming a 2-sided alpha of 5% and a SD of 170 mL. These assumptions are based on available literature from similar studies conducted for Spiriva® Respimat®.<sup>30</sup>

Given the overall 1:1:1:1 study treatment allocation ratio, 140 subjects are required for the analysis of the primary endpoint. Assuming a dropout rate of approximately 10%, a total of 155 subjects (31 subjects per treatment arm) will be randomized.

This sample size is also considered to be sufficient for the relative bioavailability endpoint.

#### **13.2. Analysis Sets**

##### **13.2.1. Full Analysis Set (FAS)**

This will include all subjects who are randomized, have received at least 1 dose of study medication and have at least 1 post-baseline PD assessment. This analysis set will be the primary analysis set for the PD endpoints.

##### **13.2.2. Safety Analysis Set (SAF)**

This will include all subjects who are randomized and received at least 1 dose of study medication. All safety endpoints will use the SAF unless otherwise specified.

##### **13.2.3. Per Protocol Analysis Set (PP)**

This will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have exclusionary major protocol deviations. Major and exclusionary protocol deviations will be defined in the SAP and by clinical review prior to unblinding.

##### **13.2.4. PK Analysis Set (PKAS)**

This will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have exclusionary major protocol deviations. The PKAS will be used to analyze the PK endpoints unless otherwise specified in the SAP.

Major and exclusionary protocol deviations will be defined in the SAP and by clinical review prior to unblinding.

### **13.3. Subject Disposition**

Number and percentage of subjects who were screened for the study (enrolled subjects, ie, those who signed informed consent) and reasons for screen failure will be summarized. The number of subjects randomized per treatment arm and the numbers and percentages of subjects in each of the FAS, SAF, PP, and PKAS will be summarized. In addition, the number and percentage of subjects who completed study treatment and discontinued study treatment before Day 21 will be summarized, along with the reason.

### **13.4. Demographics, Baseline Characteristics and Concomitant Medications**

### **13.5. Efficacy Analyses**

Refer to Section 13.6 below.

### **13.6. Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic/ Pharmacogenetic Analyses**

#### **13.6.1. Pharmacokinetic Analyses**

Pharmacokinetic analysis will be performed using the PKAS.

Individual subject plasma PK parameters will be determined from plasma concentrations using non-compartmental methods for each subject using appropriate software. Actual collection times will be used for the analyses.

The amount and fraction of dose of tiotropium excreted in urine during the collected time interval in individual subjects will be estimated. Actual collection times and urine volumes will be used for the estimation.

Additional parameters may be evaluated depending on the data obtained during the study.

The derived PK parameters will be listed by subject and summarized by treatment. Wherever appropriate, data will be visualized by means of graphical representations. For the summaries, descriptive statistics for all relevant PK parameters will include: n, mean, SD, coefficient of variation (%CV), minimum, median, maximum, geometric mean and geometric mean %CV.

The plasma concentrations and amount in urine of tiotropium will also be listed by subject, summarized by treatment, and presented graphically as mean plots, and individual plots.

#### **Statistical Analysis of Pharmacokinetic Parameters**

An analysis of variance (ANOVA) will be performed on the ln-transformed PK parameters  $AUC_{0-\tau_{SS}}$ , and  $C_{maxSS}$ . The ANOVA model will include treatment as fixed effect. The results from the model will be back-transformed and the adjusted geometrics means for each treatment and the estimated treatment ratios for the treatment comparisons will be presented together with 90% CIs.

The ratios and corresponding 90% CIs will be expressed as a percentage.

The following comparisons will be made:

- Test Treatment T1 versus Reference Treatment
- Test Treatment T2 versus Reference Treatment
- Test Treatment T3 versus Reference Treatment

More detail will be provided in the SAP.

For GSP304, dose-proportionality of tiotropium  $C_{maxSS}$  and  $AUC_{0-tauSS}$  parameters will be assessed using a power model (linear regression relating log-transformed  $C_{maxSS}$  and  $AUC_{0-tauSS}$  to the log transformed dose). Estimates of the mean slopes of log-transformed dose will be reported along with corresponding 90% CIs. Dose proportionality will also be assessed based on amount of tiotropium excreted in urine. More detail will be provided in the SAP.

### **13.6.2. Pharmacodynamic Analyses**

The PD comparisons will be made between each dose of GSP304 and GSP304 placebo.

#### **Analysis of Primary Pharmacodynamic Endpoint**

Change from baseline in trough  $FEV_1$  at 24-hours after the last dose of treatment on Day 21 in comparison to GSP304 placebo.

The primary endpoint measures the change from baseline in trough  $FEV_1$  at 24 hours after the last dose of treatment on Day 21. This will be analyzed using a Mixed-effect Model Repeated Measure (MMRM) model to produce treatment differences for each dose of GSP304 vs GSP304 placebo. The MMRM model will include pre-dose data from all visits (Days 7, 14, 21 and 22) and fixed terms for treatment, visit, baseline, center, treatment by visit and baseline by visit interactions. The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 95% CIs. Multiple imputation-based methods will be considered as a sensitivity analysis for missing data, with further detail provided in the SAP.

The primary endpoint will be analyzed using the FAS and primary inference will be based at Day 21. A sensitivity analysis will be based on the PP Analysis Set.

#### **Analyses of Secondary Pharmacodynamic Endpoints**

Analyses of secondary PD endpoints will be performed on the FAS.

- Change from baseline in peak  $FEV_1$  within 12 hours post dose on Day 1 and Day 21: This endpoint measures the peak  $FEV_1$  from the serial readings taken through 12 hours post-dose and then calculates the change from baseline. The change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 vs GSP304 placebo.
- Change from baseline in FVC on Day 1 and Day 21: The change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 vs GSP304 placebo.



- Change from baseline in time-normalized area under the curve for FEV<sub>1</sub> measured over 12 hours on Day 1 and Day 21: The endpoint measures a series of FEV<sub>1</sub> readings taken within 12 hours of dosing. The trapezoidal rule will be used to calculate AUC<sub>0-12h</sub> and then normalized to the length of time. The change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 vs GSP304 placebo.

All PD data will also be displayed in summaries and listings.

### **13.6.3. Biomarker Analyses**

Not applicable.

### **13.6.4. Pharmacogenomic/Pharmacogenetic Analyses**

## **13.7. Safety Analyses**

All safety analyses will be performed on the SAF and will be presented by the study treatment. Safety data will be summarized descriptively. Data describing quantitative measures will be summarized as mean, SD, median and range (minimum and maximum). Qualitative variables will be presented as counts and percentages.

All safety data will also be displayed in listings.

### **13.7.1. Extent of Exposure**

The extent of exposure in each treatment group will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed.

### **13.7.2. Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be displayed in listings.

### **13.7.3. Laboratory Values**

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts in laboratory tests relative to normal ranges from baseline to each time point during treatment will also be tabulated. All laboratory data will be displayed in listings.

### **13.7.4. Vital Signs**

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. All vital signs data will be displayed in listings.

**13.7.5. Electrocardiograms**

ECG assessments are to be performed at visits as described in Schedule of Procedures and Assessments ([Table 2](#)). Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group and time point.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit.

**13.7.6. Other Safety Analyses**

Physical examination results including baseline bodyweight, height and BMI will be summarized and will be displayed in listings.

**13.8. Interim Analysis**

No interim analysis is planned for this study.



## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

### **14.2. Audits and Inspections**

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB)**

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

## **15. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, The Sponsor may conduct a quality assurance audit. Please see [Section 14.2](#) for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### **16.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the Sponsor's policy on Bioethics.

### **16.3. Written Informed Consent**

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

### **17.2. Retention of Records**

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

### **17.3. Financing and Insurance**

The Sponsor will provide clinical study insurance for any subjects participating in the study in accordance with all applicable laws and regulations.



**18. PUBLICATION POLICY**

The Sponsor recognizes and supports the publication and dissemination of scientific information as a means of furthering knowledge. The general strategy regarding publication of the study (what, when, where, etc.) will be mutually agreed upon by the Investigator and Sponsor.

However, in order to protect its commercial interests, the Sponsor reserves the right to manage the publication of all study results. The Investigator agrees that oral and written communication to third parties of any procedures or results from the study is subject to prior written consent of the Sponsor. Presentation material and/or manuscript(s) for publication will be reviewed by Sponsor prior to submission for publication. This review will be completed within 30 days of receiving presentation material and 60 days of receiving the manuscript from the Investigator. Alterations in the material will only be made in agreement between the Investigator and the Sponsor.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

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**APPENDIX 1. LIST OF MEDICATIONS EXCLUDED DURING ACTIVE TREATMENT PERIODS**

<b>Medication</b>	<b>No use within the following time intervals prior to Screening (Visit 1) Spirometry and thereafter at any time during the study</b>
Inhaled short acting muscarinic antagonist (ipratropium or ipratropium/salbutamol combination product)	6 hours
Inhaled short acting beta <sub>2</sub> -agonists	6 hours
Oral beta <sub>2</sub> -agonists	48 hours
Inhaled long-acting beta <sub>2</sub> -agonists (salmeterol, formoterol, etc.)	48 hours
Xanthines preparations	48 hours
Cromolyn and nedocromil inhalers	24 hours
Zafirlukast, montelukast, zileuton	48 hours
Inhaled LAMA (tiotropium etc.)	7 days
Inhaled corticosteroid or inhaled corticosteroids/LABA combination	7 days
Oral PDE-4 inhibitors	7 days
Oral or parenteral corticosteroids	6 weeks
Any other investigational medication	30 days or 5 drug half-lives of the investigational drug (whichever is longer)
Depot corticosteroids	3 months
Antibiotics (for lower respiratory tract infection)	6 weeks
Systemic cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (eg, indinavir, nelfinavir, ritonavir, saquinavir, atazanavir); imidazole and triazole anti-fungals (eg, ketoconazole, itraconazole, voriconazole); clarithromycin, telithromycin, troleandomycin, mibefradil, cyclosporin, nefazodone	6 weeks

LABA = long-acting beta<sub>2</sub>-agonist; LAMA = long-acting muscarinic antagonist; PDE-4 = phosphodiesterase 4



**APPENDIX 2. LIST OF CLINICAL LABORATORY TESTS**

<b>Blood Chemistry Parameters</b>	<b>Hematology Parameters</b>
Blood glucose	Erythrocyte count
Total protein	Hemoglobin
Albumin	Packed cell volume
Albumin to globulin ratio	Activated partial thromboplastin time and prothrombin time
Serum cholesterol (total)	Mean corpuscular volume
Serum triglycerides	Mean corpuscular hemoglobin
Serum creatinine	Mean corpuscular hemoglobin concentration
Blood urea nitrogen	Red cell distribution width
Sodium	Total and differential leucocyte count (absolute and percents)
Potassium	Platelet count
Bicarbonate	
Glomerular filtration rate (GFR); GFR will be estimated by the Cockcroft-Gault formula utilizing serum creatinine values, age, weight, and gender, from the screening visit.	
<b>Liver Function Parameters</b>	<b>Urinalysis</b>
Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST)	Color, appearance, pH
Serum glutamic-pyruvic transaminase (SGPT)/alanine aminotransferase (ALT)	Microscopy
Gamma-glutamyl transferase	Specific gravity
Alkaline phosphatase	Glucose
Bilirubin (total, direct and indirect)	Protein
	Ketones
<b>Screening for</b>	Blood
HBsAg and HCV antibody	Bilirubin
Thyroid stimulating hormone	Leukocyte Esterase
Follicle stimulating hormone	Nitrite

**APPENDIX 3. INSTRUCTIONS FOR THE USE OF GSP304 OR GSP304  
PLACEBO NEBULIZER**

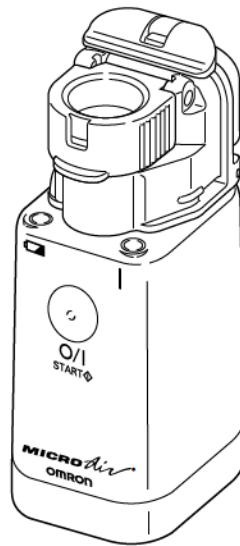
# OMRON

## INSTRUCTION MANUAL

### **MICRO** *Air*®

## VIBRATING MESH NEBULIZER

### Model **NE-U22V**



Español

Français

English

**CAUTION:** Federal law restricts this device to sale by or on the order of a physician and/or licensed healthcare practitioner.

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## INTRODUCTION

Thank you for purchasing the Omron® NE-U22V MICROAir® Vibrating Mesh Nebulizer.

Fill-in for future reference

DATE PURCHASED: \_\_\_\_\_

SERIAL NUMBER: \_\_\_\_\_

Staple your purchase receipt here.

Omron Healthcare has moved forward in the development of electronic nebulizer technology with the introduction of the NE-U22V MICROAir® Vibrating Mesh Nebulizer. Focusing on patient convenience and compliance as its goal, this device offers ultimate portability for wherever you go and revolutionary vibrating mesh technology that provides a precise, powerful and effective treatment every time.

The MICROAir® is a vibrating mesh nebulizer system designed to aerosolize liquid medications for inhalation by the patient. The device may be used with pediatric and adult patients in the home, hospital, and sub-acute care settings.

Your NE-U22V MICROAir® comes with the following components:

- Main Unit
- Unit Cover
- Medication Bottle
- Mesh Cap
- Mask and Mouthpiece Adapter
- Mouthpiece
- Storage Case
- Instruction Manual
- Instructional DVD

The following are optional accessories sold separately:

- AC Adapter
- Child Mask



*The MICROAir® is a prescription medical device. Operate this device only as instructed by your physician and/or licensed healthcare practitioner.*

**SAVE THESE INSTRUCTIONS**











## SAFETY INFORMATION

To assure the correct use of the product basic safety measures should always be followed including the warnings and cautions listed in this instruction manual.

SAFETY ICONS USED IN THIS INSTRUCTION MANUAL	
 <b>WARNING</b>	Indicates a potentially hazardous situation which, if not avoided, could result in death or serious injury
 <b>CAUTION</b>	Indicates a potentially hazardous situation which, if not avoided, may result in minor or moderate injury to the user or patient or damage to the equipment or other property.

### OPERATING THE DEVICE

-  Read all the information in the instruction book and any other literature included in the box before using the unit.
-  For type, dose, and regimen of medication follow the instructions of your physician and/or licenced healthcare practitioner.
-  Pentamidine is not an approved medication for use with this device.
-  Do not use tap or mineral water in the nebulizer for nebulizing purposes.
-  Clean and disinfect the Medication Bottle, Mesh Cap, Mask, Mouthpiece and Mask and Mouthpiece Adapter before using the device for the first time after purchase.
-  If the device has not been used for a long period of time, clean and disinfect the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter before using them.
-  Always dispose of any remaining medication in the medication cup after each use. Use fresh medication each time you use the device.
-  Do not leave the device or its parts where it will be exposed to extreme temperatures or changes in humidity, such as leaving the device in a vehicle during warm or hot months, or where it will be exposed to direct sunlight.

## IMPORTANT SAFETY NOTES

### OPERATING THE DEVICE (continued)

- ⚠ Provide close supervision when this device is used by, on, or near infants, children or compromised individuals.
- ⚠ Inspect the main unit and the nebulizer parts each time before using the device. Make sure no parts are damaged, the device is assembled properly, and the device operates normally.
- ⚠ To prevent damage to the device, add the medication slowly. Do not allow the medication to overflow the Medication Port.
- ⚠ Do not add more than 7 mL of medication to the medication cup.
- ⚠ To prevent damage to the device, make sure that the Mesh Cap is correctly in place. If the Mesh Cap is not properly closed, medication will leak.
- ⚠ Do not operate the device at temperatures greater than +104° F (+40° C).
- ⚠ Do not subject the device or any of the components to strong shocks, such as dropping on the floor.
- ⚠ This device is approved for human use only.
- ⚠ Do not disassemble or attempt to repair the device or components.
- ⚠ Operate the device only as intended. Do not use the device for any other purpose.
- ⚠ Dispose of the device, components and optional accessories according to applicable local regulations. Unlawful disposal may cause environmental pollution.
- ⚠ Use only Omron authorized parts and accessories. Parts and accessories not approved for use with the device may damage the unit.
- ⚠ Changes or modifications not approved by Omron Healthcare will void the user warranty.

### RISK OF ELECTRICAL SHOCK WHEN USING THE AC ADAPTER

- ⚠ Do not plug or unplug the power cord into the electrical outlet with wet hands.
- ⚠ Use only the AC adapter designed by Omron for this device. Use of any other AC adapter may damage the device.

## IMPORTANT SAFETY NOTES

### RISK OF ELECTRICAL SHOCK WHEN USING THE AC ADAPTER (continued)

- ⚠ Do not overload power outlets. Plug the device into the appropriate voltage outlet.
- ⚠ Do not use extension cords. Plug the power cord directly into the electrical outlet.
- ⚠ Unplug the power cord from the electrical outlet after using the device.
- ⚠ Unplug the power cord from the electrical outlet before cleaning the device.

### MAINTENANCE AND STORAGE

- ⚠ Keep the device out of the reach of unsupervised infants and children. The device may contain small parts that can be swallowed.
- ⚠ Do not immerse the main unit in water or other liquid.
- ⚠ Do not use or store the device in humid locations, such as a bathroom. Use the device within the operating temperature and humidity.
- ⚠ Do not leave the cleaning solution in the nebulizer parts. Rinse the nebulizer parts with distilled water after disinfecting.
- ⚠ Rinse the nebulizer parts after each use. Dry the parts immediately after washing.
- ⚠ Store the device and the components in a clean, safe location.
- ⚠ To prevent damage to the device, do not carry or leave the Medication Bottle filled with medication or distilled water.
- ⚠ Do not place or attempt to dry the device or any of its parts in a microwave oven.
- ⚠ To prevent damage to the device, do not rinse or immerse the Main Unit in any liquid, do not wash or rinse any of the parts under strong running water, and do not touch the mesh with your hand or any object.
- ⚠ Do not use household bleach. The mesh will rust and the Mesh Cap cannot be used.
- ⚠ To prevent damage to the device, do not clean the Main Unit using abrasive cleaners or any type of chemical, and do not allow any moisture to contact the electrodes or the AC Adapter jack on the Main Unit.
- ⚠ Do not put the AC Adapter in the Storage Case. The Storage Case is not intended to carry the AC Adapter.

## KNOW YOUR UNIT

### Main Unit

#### Electrode

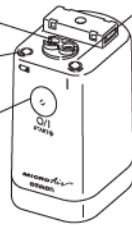
Power conductor from the Main Unit to the vibrator on the Medication Bottle

#### Battery Low Indicator

An orange light blinks when the batteries are worn

#### ON/OFF Button

Turns the power for the Main Unit on and off



#### Power Indicator

The green light shows the power is on

#### Bottom of Main Unit

#### Battery Cover

Push lever to remove cover

#### Electrode

Power conductor from the Main Unit to the AC Adapter Connection Stand



### Medicine Bottle



#### Bottle Cap Locking Lever

Opens the Medication Bottle for cleaning

#### Medication Bottle

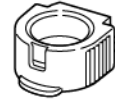
Holds maximum capacity of 7mL for treatment

#### Medication Port

Add the medicine to the bottle

### Mesh Cap

Metal Alloy Mesh creates high efficiency aerosol



### Mask and Mouthpiece Adapter



Holds the Mouthpiece or Mask securely on the device

### Mouthpiece



Patient Interface

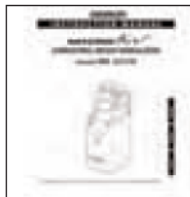
### Main Unit Cover



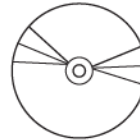
Protects the Main Unit with the attached Medication Bottle and Mesh Cap during storage

## KNOW YOUR UNIT

### Instruction Manual



### Instructional DVD



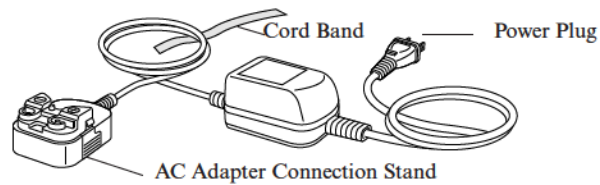
### Storage Case



Case holds the Main Unit, Medication Bottle, Mask and Mouthpiece Adapter

## Optional Accessory

### AC Adapter Model No. U22-5



## Optional Accessory

### Child Mask Model No. C922



Patient Interface  
for pediatric use

## Replacement Parts

	Model No.
BATTERY COVER	U22-8
MAIN UNIT COVER	U22-9
MASK AND MOUTHPIECE ADAPTER	U22-2
MEDICATION BOTTLE	U22-3
MESH CAP	U22-4
MOUTHPIECE	U22-1
STORAGE CASE	U22-7



## PREPARING THE NEBULIZER FOR USE



### WARNING

Read all the information in the instruction book and any other literature included in the box before using the unit.



### WARNING

Clean and disinfect the Medication Bottle, Mesh Cap, Mask, Mouthpiece and Mask and Mouthpiece Adapter before using the device for the first time after purchase.



### WARNING

If the device has not been used for a long period of time, clean and disinfect the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter before using them.

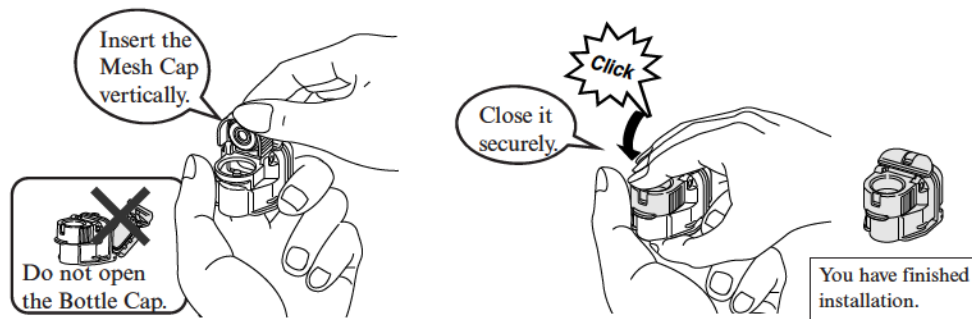
For directions on cleaning and disinfecting go to page 16 and 17 under Care and Maintenance.

**The device must be assembled before it is used.**

### General Information

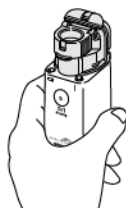
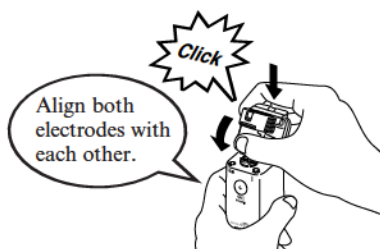
- Components may fit tightly since they are made to prevent the medication from leaking.
- Hold the device securely with both hands.
- Install the parts securely. You may hear a click sound as you install some of the parts.

#### 1. Attach the Mesh Cap to the Medication Bottle.



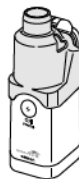
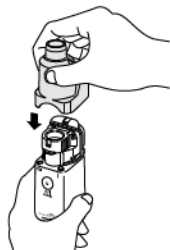
## PREPARING THE NEBULIZER FOR USE

2. Attach the Medication Bottle to the Main Unit.



You have finished installation.

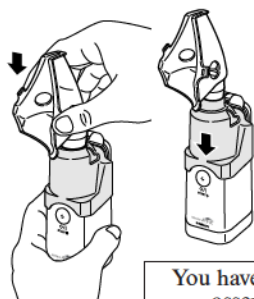
3. Attach the Mask and Mouthpiece Adapter to the Main Unit.



You have finished installation.

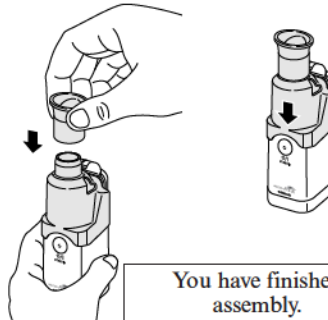
4. Attach the Mouthpiece or the Child Mask to the Mask and Mouthpiece Adapter.

• How to attach the Child Mask



You have finished assembly.

• How to attach the Mouthpiece



You have finished assembly.

## BATTERY INSTALLATION

This device operates using two (2) AA alkaline batteries or two (2) NiMH AA rechargeable batteries.



### CAUTION

Do not install worn and new batteries together.  
Do not use different types of batteries together.  
Remove the batteries if the device will not be used  
for three months or longer.

#### 1. Remove the Battery Cover.

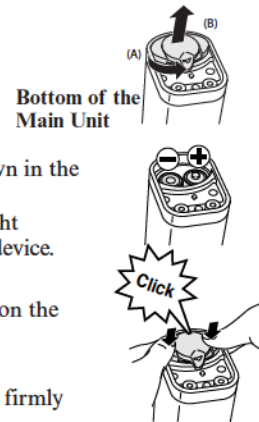
- (A) Rotate the Battery Cover lever in the direction of the arrow as shown in the illustration.
- (B) Remove the Battery Cover. The Battery Cover may appear to be tight fitting since it was designed to prevent fluids from getting into the device.

#### 2. Insert the batteries.

Correctly align the polarities (+ and -) with the battery indication marks on the device.

#### 3. Replace the Battery Cover.

Use your thumbs to push on both ends of the Battery Cover Press down firmly until you hear both tabs click into place.



### Battery Life and Battery Replacement

#### Alkaline Batteries

- The device can be used for approximately 8 days if operating for 30 minutes a day.
- The Battery Low Indicator (orange light) flashes to signal the batteries are low. Replace both batteries with new ones.
- The Battery Low Indicator (orange light) turns on to signal the batteries are worn out. The device will not nebulize. Immediately replace both batteries with new ones.

#### NiMH Rechargeable Batteries

- The device can be used for approximately 8 days if operating for 30 minutes a day when the batteries are fully charged.
- The Battery Low Indicator (orange light) flashes to signal the rechargeable batteries have little or no residual power remaining. If the device will not nebulize immediately recharge the batteries.
- Recharge the batteries using a commercially available battery charger suitable for the batteries used in the device.
- The AC Adapter does not function as a battery charger.

## USING THE AC ADAPTER

The device is designed not to draw power from the batteries when the AC Adapter is used. The AC Adapter is not a battery charger.



### **WARNING**

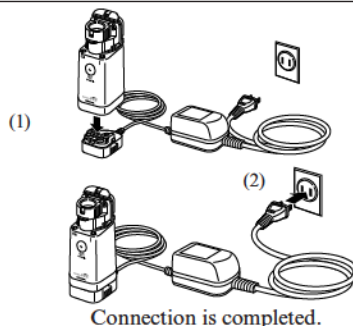
Use only the AC adapter designed by Omron for this device. Use of any other AC adapter may damage the device.

### **To connect the AC Adapter to the Main Unit**

- (1) Place the Main Unit on the AC Adapter Connection Stand as shown in the illustration below.

**NOTE:** It will click and lock to the stand.

- (2) Insert the AC Adapter Power Plug into a 120V electrical outlet.



### **WARNING**

Do not plug or unplug the power cord into the electrical outlet with wet hands.



### **CAUTION**

Do not overload power outlets. Plug the device into the appropriate voltage outlet.



### **CAUTION**

Do not use extension cords. Plug the power cord directly into the electrical outlet.



### **CAUTION**

Unplug the power cord from the electrical outlet before cleaning the device.

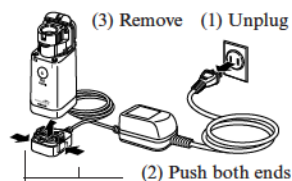
### **To remove the AC Adapter from the Main Unit**

- (1) Disconnect the AC Adapter Power Plug from the electrical outlet.
- (2) Push on both sides of the Connection Stand to unlock the Main Unit.
- (3) Remove the Main Unit



### **CAUTION**

Unplug the power cord from the electrical outlet after using the device.



## FILLING THE MEDICATION BOTTLE

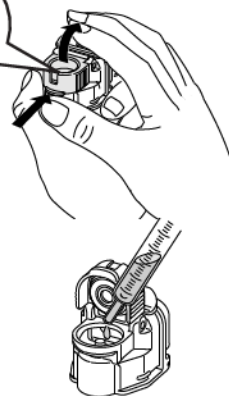
Remove the Mouthpiece or Mask and the Mask and Mouthpiece Adapter from the Main Unit.

### 1. Open the Mesh Cap.

Hold the device securely in your hand.



Lift up the mesh cap while pressing your thumb upward on the brim.



Check that the Mesh Cap is closed.

### 2. Fill the Medication Bottle.



#### **WARNING**

Pentamidine is not an approved medication for use with this device.



#### **WARNING**

Do not use tap or mineral water in the nebulizer for nebulizing purposes.

Be careful to prevent the Mesh Cap from closing as shown in the illustration.

The maximum capacity of the Medication Bottle is 7mL.



#### **CAUTION**

Do not add more than 7 mL of medication to the medication cup.



#### **CAUTION**

To prevent damage to the device, add the medication slowly. Do not allow the medication to overflow the medication port.

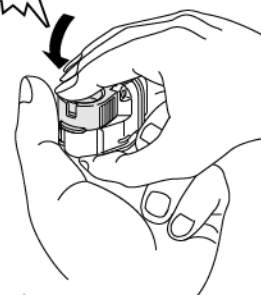


### 3. Close the Mesh Cap.



#### **CAUTION**

To prevent damage to the device, make sure that the Mesh Cap is correctly in place. If the Mesh Cap is not properly closed, medication will leak.



### 4. Attach the Mask and Mouthpiece Adapter to the Main Unit

Attach the Mouthpiece or the Child Mask to the Mask and Mouthpiece Adapter.

**NOTE:** For instructions on attaching the Mask and Mouthpiece Adapter return to Unit Assembly on Page 10.



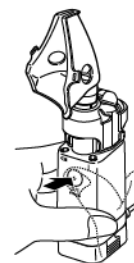
## SELECTING THE NEBULIZATION MODE

This device operates in the Continuous Nebulization Mode or in the Manual Nebulization Mode.

- **Continuous Nebulization Mode**

To start the device using the continuous nebulization mode press and hold the ON/OFF Button down for 1 second.

Press the ON/OFF Button again to stop nebulization.



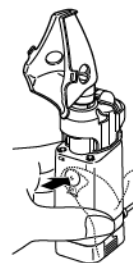
- **Manual Nebulization Mode**

In the Manual Nebulization Mode the device will nebulize only when you press and hold the ON/OFF Button down. You can inhale on demand using this mode.

To start the device using manual nebulization press and hold the ON/OFF Button down for at least 2 seconds.

Press and hold the ON/OFF Button to start nebulization.

Press and hold the ON/OFF Button down with your finger for 1 second.



**NOTE:** The power indicator (green light) illuminates during nebulization.

Press and hold the ON/OFF Button down with your finger for 2 seconds.

## USING THE DEVICE



### **WARNING**

For type, dose, and regimen of medication follow the instructions of your healthcare provider.



### **WARNING**

Always dispose of any remaining medication in the medication cup after each use. Use fresh medication each time you use the device.



### **CAUTION**

Provide close supervision when this device is used by, on, or near infants, children or compromised individuals.



### **CAUTION**

Inspect the Main Unit and the nebulizer parts each time before using the device. Make sure no parts are damaged, the device is assembled properly, and the device operates normally.



### **CAUTION**

Do not operate the device at temperatures greater than +104°F (+40°C).



### **CAUTION**

This device is approved for human use only.

1. Slightly tilt the Main Unit toward yourself to immerse the Vibrating Mesh Cap in the medication.

**NOTE:** If the vibrator is not immersed in the medication, the device will not nebulize.

2. Start inhalation in a relaxed position.
3. Place your lips lightly around the mouthpiece. If using the Child Mask position the mask lightly against the face.
4. Start the treatment as directed by your healthcare provider.
5. Press the ON/OFF Button to turn off the device when finished with your treatment.

**NOTE:** The device has a built-in timer to turn off the power approximately 30 minutes after the power is turned on.

When the AC Adapter is used, remove the power plug from the electrical outlet.

## CLEANING AFTER EACH USE

Following the cleaning instructions after each use will prevent any remaining medication in the bottle from drying, adhering to the mesh cap, and resulting in the device not nebulizing effectively.

**Wash the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter after each use.**



### **WARNING**

Rinse the nebulizer parts after each use. Dry the parts immediately after washing.



### **CAUTION**

To prevent damage to the device:

- Do not rinse or immerse the Main Unit in any liquid.
  - Do not wash or rinse any of the parts under strong running water.
  - Do not touch the mesh with your hand or any other object.
1. Remove the Mouthpiece or Mask and the Mask and Mouthpiece Adapter from the Main Unit.
  2. Remove the Medication Bottle from the Main Unit.
  3. Open the Medication Bottle and discard any remaining medication.
  4. Attach the Medication Bottle to the Main Unit. Open the Mesh Cap.
  5. Pour a small amount of distilled water into the Medication Bottle and close the Mesh Cap.
  6. Turn on the device to nebulize the distilled water for 1 to 2 minutes to remove residual medication from the mesh holes.
  7. Turn off the device and remove the Medication Bottle from the Main Unit.
  8. Remove the Mesh Cap from the Medication Bottle and discard any remaining distilled water from the Medication bottle.
  9. Rinse the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter with distilled water.
  10. Gently wipe off excess water with a soft clean cloth or allow the parts to air dry in a clean environment.
  11. Assemble the device. Store the device in the Storage Case or in a clean environment.

## DAILY DISINFECTING

Disinfect the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter after the last treatment of each day.

### CAUTION

To prevent damage to the device:

- Do not rinse or immerse the Main Unit in any liquid.
- Do not wash or rinse any of the parts under strong running water.
- Do not touch the mesh with your hand or any other object.

1. Make a solution using one of the following solutions: Vinegar (1 part white vinegar and 3 parts distilled water), OR mild detergent soap (dishwashing soap in distilled water).

### CAUTION

Do not use household bleach. The mesh will rust and the Mesh Cap cannot be used.

2. Lift open the Mesh Cap and pour a small amount of disinfecting solution into the Medication Bottle.
3. Turn on the device to nebulize the disinfecting solution for 1 to 2 minutes.
4. Turn off the device and remove the Medication Bottle from the Main Unit.
5. Remove the Mesh Cap from the Medication Bottle and discard any remaining disinfecting solution from the Medication Bottle.
6. Soak the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter in the disinfecting solution for 10 to 15 minutes.
7. Rinse the Medication Bottle, Mesh Cap, Mask, Mouthpiece, and Mask and Mouthpiece Adapter in distilled water.

### WARNING

Do not leave the cleaning solution in the nebulizer parts. Rinse the nebulizer parts with distilled water after disinfecting.

8. Gently wipe off excess water with a soft clean cloth or allow the parts to air dry in a clean environment.
9. Assemble the device. Store the device in the Storage Case or in a clean environment.

## CARING FOR THE DEVICE

To keep your device in the best condition and protect the unit from damage follow these directions:

- ⚠ Keep the device out of the reach of unsupervised infants and children. The device may contain small parts that can be swallowed.
- ⚠ Store the device and the components in a clean, safe location.
- ⚠ Do not use or store the device in humid locations, such as a bathroom. Use the device within the operating temperature and humidity.
- ⚠ Do not leave the device or its parts where it will be exposed to extreme temperatures or changes in humidity, such as leaving the device in a vehicle during warm or hot months, or where it will be exposed to direct sunlight.
- ⚠ Do not subject the device or any of the components to strong shocks, such as dropping on the floor.
- ⚠ Do not disassemble or attempt to repair the device or components.
- ⚠ Use only Omron authorized parts and accessories. Parts and accessories not approved for use with the device may damage the unit.
- ⚠ Operate the device only as intended. Do not use the device for any other purpose.
- ⚠ Changes or modifications not approved by Omron Healthcare will void the user warranty.
- ⚠ Dispose of the device, components, and optional accessories according to applicable local regulations. Unlawful disposal may cause environmental pollution.
- ⚠ Remove the batteries if the device will not be used for three months or longer. Always replace all the batteries with new ones at the same time. Do not use different types of batteries together.



## CARING FOR THE DEVICE

### Cleaning the Main Unit

To clean the casing of the main unit moisten a soft cloth with water or a mild detergent. Wipe the casing and immediately dry using a soft clean cloth.

#### CAUTION

Do not place or attempt to dry the device or any of its parts in a microwave oven.

#### CAUTION

To prevent damage to the device:

- Do not rinse or immerse the Main Unit in any liquid.
- Do not clean the Main Unit using abrasive cleaners or any type of chemical.
- Do not allow any moisture to contact the electrodes or the AC Adapter Jack on the Main Unit or AC Adapter connection stand.

### Carrying the device in the Storage Case

Assemble the device by attaching the Mesh Cap and the Medication Bottle to the Main Unit. Place the Main Unit Cover on the device.

Position the device in the Storage Case as shown in the illustration.

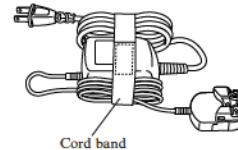
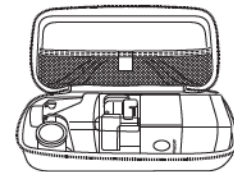
The Mouthpiece and Mask Adapter can be easily placed in the Storage Case to carry with the Main Unit.

#### CAUTION

To prevent damage to the device

- Do not carry or leave the nebulizer with medication or distilled water in the Medicine Bottle.
- Do not put the AC Adapter in the Storage Case. The Storage Case is not intended to carry the optional AC Adapter.

To carry the AC Adapter bundle the power cord of the AC Adapter and fasten it to the Main Unit of the AC Adapter with the cord band as shown in the illustration.



## TROUBLESHOOTING GUIDE

PROBLEM	CAUSE	SOLUTION
The power indicator does not illuminate.	The AC Adapter is not plugged into an electrical outlet.	Turn the power switch off. Plug the power plug into an electrical outlet. Turn the device on.
	The connection stand is not attached to the Main Unit.	Make sure Main Unit has been clicked onto the Connection Stand.
	The batteries have not been inserted properly. The batteries are low in charge.	Reinsert the batteries. Replace both worn batteries immediately. Recharge NiMH batteries with a commercially available charger.
	Residual medication has dried on the components and accessories.	Clean and disinfect the components and accessories.
	The mesh cap needs to be replaced.	Replace the Mesh Cap.
The power indicator is illuminated but the unit does not nebulize.	The batteries are low in charge.	Replace same type batteries with new alkaline or charged NiMH batteries.
	The Medication Bottle has too much medication in it.	Fill the Medication Bottle with the proper amount of prescribed medication. Max is 7 mL.
	Liquid may have collected around the electrodes of the Main Unit.	Absorb any moisture with a soft cloth.
	There is liquid on top of the Mesh Cap.	Remove visible liquid with a soft cloth and a very light touch so as not to damage the mesh.
	The medication has not come in contact with the nebulizing parts.	Slightly slant the Main Unit towards you with the ON/OFF button pointing down.

## TROUBLESHOOTING GUIDE

PROBLEM	CAUSE	SOLUTION
The unit is on; however, it nebulizes weakly, or is taking too long for treatment.	The Medication Bottle is not properly installed.	Make sure the Medication Bottle is properly installed.
	The unit needs to be cleaned.	Follow directions for cleaning after each use.
	The unit needs to be disinfected.	Follow directions for disinfecting.
	The batteries are low in charge.	Replace the batteries per installation instructions.
	Nebulization rates vary based on the medication used.	Treatment times may vary among medications and patients.

## WARRANTY INFORMATION

### LIMITED WARRANTIES

Your NE-U22V Nebulizer, excluding the mesh cap and accessories, is warranted to be free from defects in materials and workmanship appearing within 2 years from date of purchase, when used in accordance with the instructions provided with your device. The above warranty extends only to the original retail purchaser.

We will, at our option, repair or replace without charge your Omron Nebulizer. Repair or replacement is our only responsibility and your only remedy under the above warranties.

To obtain warranty service, contact Omron Healthcare's Customer Service by calling 1-800-634-4350 for the address of the repair location and the return shipping and handling fee. Information for warranty service is available on our website at [www.omronhealthcare.com](http://www.omronhealthcare.com).

Enclose the Proof of Purchase. Include a letter, with your name, address, phone number, and description of the specific problem. Pack the product carefully to prevent damage in transit. Because of possible loss in transit, we recommend insuring the product with return receipt requested.

**ALL IMPLIED WARRANTIES, INCLUDING BUT NOT LIMITED TO THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR PARTICULAR PURPOSE, ARE LIMITED TO THE DURATION OF THE APPLICABLE WRITTEN WARRANTY ABOVE.** Some states do not allow limitations on how long an implied warranty lasts, so the above limitation may not apply to you.

**OMRON SHALL NOT BE LIABLE FOR LOSS OF USE OR ANY OTHER INCIDENTAL, CONSEQUENTIAL OR INDIRECT COSTS, EXPENSES OR DAMAGES.** Some states do not allow the exclusion or limitation of incidental or consequential damages, so the above exclusions may not apply to you.

This warranty gives you specific legal rights, and you may also have other rights, which may vary from state to state.

### FOR CUSTOMER SERVICE (US and CANADA)

Visit our web site at: [www.omronhealthcare.com](http://www.omronhealthcare.com)  
Call toll free: 1-800-634-4350

## FCC STATEMENT

**Note:**

**POTENTIAL FOR RADIO/TELEVISION INTERFERENCE (for U.S.A. only)**

This product has been tested and found to comply with the limits for a Class B digital device, pursuant to part 15 of the FCC rules.

These limits are designed to provide reasonable protection against harmful interference in a residential installation. The product generates, uses, and can radiate radio frequency energy and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If the product does cause harmful interference to radio or television reception, which can be determined by turning the product on and off, the user is encouraged to try to correct the interference by one or more of the following measures:

- Reorient or relocate the receiving antenna.
- Increase the separation between the product and the receiver.
- Connect the product into an outlet on a circuit different from that to which the receiver is connected.
- Consult the dealer or an experienced radio/TV technician for help.

**POTENTIAL FOR RADIO/TELEVISION INTERFERENCE (for Canada only)**

This digital apparatus does not exceed the Class B limits for radio noise emissions from digital apparatus as set out in the interference-causing equipment standard entitled “Digital Apparatus”, ICES-003 of the Canadian Department of Communications.

Cet appareil numérique respecte les limites de bruits radioélectriques applicables aux appareils numériques de Classe B prescrites dans la norme sur le matériel brouilleur: “Appareils Numériques”, ICES-003 édictée par le ministre des communications.

Changes or modifications not expressly approved by the party responsible for compliance could void the user's authority to operate the equipment.



## SPECIFICATIONS

<b>Model:</b>	<b>Omron NE-U22V Nebulizer with V.M.T.®</b>
<b>Power Source:</b>	DC 3V AC 120V 60 Hz (with AC adapter)
<b>Power Consumption:</b>	1.5 W
<b>Nebulization Rate:</b>	0.25 mL/min minimum
<b>Particle Size Range:</b>	MMD approximately 5µm
<b>Medication Capacity:</b>	7 mL maximum
<b>Operating Temperature/Humidity:</b>	+50°F to +104°F (+10°C to +40°C) / 30% to 85% RH
<b>Storage Temperature/Humidity/Air Pressure:</b>	-4°F to +140°F (-20°C to +60°C) / 10% to 95% RH / 700hPa to 1060 hPa
<b>Vibration Frequency:</b>	180 kHz
<b>Dimensions:</b>	1.5" (l) x 2.1" (w) x 4.1" (h) (38mm x 51mm x 104mm)
<b>Weight:</b>	3.4 oz. (97 g)
<b>Battery:</b>	2 "AA" Alkaline or NiMH Rechargeable (not included)
<b>Contents:</b>	Main unit, medication bottle, carrying case, mouthpiece, mesh cap, mask and mouthpiece adapter, video and instruction manual
<b>UPC Code:</b>	0 73796 45122 6

- Subject to technical modification without prior notice

Cascade Impactor Testing at 13 lpm:

	<b>Pulmicort®</b>	<b>Intal®</b>	<b>Salubutamol®</b>
<b>MMD (micron)</b>	6.76µ	6.43µ	5.79µ
<b>GSD (geometric standard deviation)</b>	2.08	2.56	2.75
<b>Respirable fraction (%mass 0.52 to 6 µ)</b>	65.0%	66.0%	73.4%

Treatment time 5 minutes for 2ml.

- Please note that specifications may vary with medication type used.

## NOTES

Made in Japan

Distributed by:  
**OMRON HEALTHCARE, INC.**

1200 Lakeside Drive  
Bannockburn, Illinois 60015

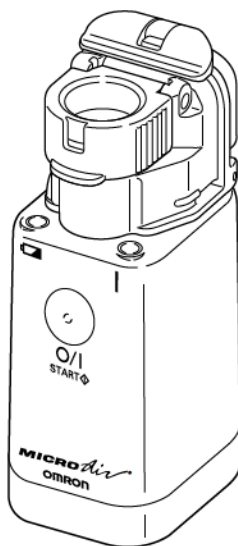
[www.omronhealthcare.com](http://www.omronhealthcare.com)

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# OMRON

## GUIDE DE L'UTILISATEUR

### **MICRO** *Air*® **NÉBULISEUR À FILTRE VIBRANT** Modèle **NE-U22V**



Français

**MISE EN GARDE:** En vertu de la loi américaine, la vente de cet appareil n'est permise que sur ordonnance d'un médecin ou d'un professionnel de la santé autorisé.

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## INTRODUCTION

Nous vous remercions d'avoir acheté le nébuliseur à filtre vibrant MICROAir® modèle NE-U22V d'Omron®.

Veuillez inscrire les renseignements demandés à des fins de référence

DATE D'ACHAT : \_\_\_\_\_

NUMÉRO DE SÉRIE : \_\_\_\_\_

Agrafez votre reçu d'achat ici.

Omron Healthcare va de l'avant dans le développement de la technologie des nébuliseurs électroniques avec son nouveau nébuliseur à filtre vibrant MICROAir® modèle NE-U22V. Ayant pour objectifs la commodité pour le patient et la conformité, cet appareil offre une portabilité unique où que vous alliez ainsi que la technologie révolutionnaire des filtres vibrants qui procure un traitement précis, puissant et efficace en tout temps.

Le système MICROAir® est un nébuliseur à filtre vibrant conçu pour transformer en aérosol les médicaments liquides pour permettre au patient de les inhaler. L'appareil peut être utilisé par les enfants et les adultes à la maison, à l'hôpital et dans les établissements de soins subaigus.

Votre MICROAir® modèle NE-U22V est livré avec les composants suivants :

- Unité principale
- Couvercle de l'appareil
- Réservoir de médicament
- Bouchon-filtre
- Adaptateur pour masque et embout buccal
- Embout buccal
- Étui de rangement
- Guide de l'utilisateur
- DVD d'instructions

Les accessoires suivants sont en option et vendus séparément :

- Adaptateur c.a.
- Masque pour enfant



*Le MICROAir® est un appareil médical de prescription. Utilisez cet appareil uniquement tel que prescrit par votre médecin ou votre professionnel de la santé autorisé.*

**CONSERVEZ CES DIRECTIVES**









## RENSEIGNEMENTS SUR LA SÉCURITÉ

Il est important de toujours respecter les mesures de sécurité de base ainsi que les avertissements et les mises en garde de ce guide de l'utilisateur afin d'assurer une utilisation appropriée du produit.

### SYMBOLES DE SÉCURITÉ UTILISÉS DANS CE GUIDE DE L'UTILISATEUR

 <b>AVERTISSEMENT</b>	Indique une situation potentiellement dangereuse qui, si elle n'est pas évitée, pourrait causer la mort ou une blessure grave.
 <b>MISE EN GARDE</b>	Indique une situation potentiellement dangereuse qui, si elle n'est pas évitée, pourrait causer une blessure mineure ou modérée à l'utilisateur ou au patient ou bien endommager l'équipement ou d'autres objets.

### UTILISATION DE L'APPAREIL

-  Lisez tous les renseignements fournis dans le guide de l'utilisateur et dans tout document inclus dans la boîte avant d'utiliser l'appareil.
-  Utilisez toujours le type, la dose et le régime posologique des médicaments prescrits par votre médecin ou votre professionnel de la santé autorisé.
-  L'utilisation de la pentamidine avec cet appareil n'est pas approuvée.
-  N'utilisez pas l'eau du robinet ou de l'eau minérale dans le nébuliseur dans le but de la pulvériser.
-  Nettoyez et désinfectez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal avant la première utilisation de l'appareil après l'achat.
-  Si l'appareil n'a pas servi pendant une longue période, nettoyez et désinfectez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal avant de les utiliser.
-  Jetez toujours tout reste de médicament qui se trouve dans le réservoir à médicament après chaque utilisation. Utilisez un médicament frais à chaque utilisation de l'appareil.
-  Ne laissez pas l'appareil ni ses composants dans un endroit où ils pourraient être exposés à des températures extrêmes ou à des changements d'humidité, par exemple en les laissant dans un véhicule pendant les mois chauds, où ils seront exposés aux rayons directs du soleil.

## CONSIGNES DE SÉCURITÉ IMPORTANTES

### UTILISATION DE L'APPAREIL (suite)

- ⚠ Assurez une supervision étroite quand cet appareil est utilisé par ou sur des bébés, des enfants ou des personnes à risque ou en présence de ceux-ci.
- ⚠ Inspectez l'unité principale et les pièces du nébuliseur avant chaque utilisation de l'appareil. Assurez-vous qu'aucune pièce n'est endommagée, que l'appareil est bien assemblé et que l'appareil fonctionne normalement.
- ⚠ Ajoutez le médicament lentement pour éviter d'endommager l'appareil. Assurez-vous que le médicament ne déborde pas de l'orifice d'admission du médicament.
- ⚠ Ne mettez pas plus de 7 ml de médicament dans le réservoir à médicament.
- ⚠ Pour éviter d'endommager l'appareil, assurez-vous que le bouchon-filtre est bien en place. Si le bouchon-filtre n'est pas bien fermé, le médicament se renversera.
- ⚠ N'utilisez pas l'appareil à des températures supérieures à +104 °F (+40 °C)
- ⚠ Ne soumettez pas l'appareil ni les autres composants à un grand choc, tel que le laisser tomber sur le plancher.
- ⚠ Cet appareil est approuvé uniquement pour utilisation par des humains.
- ⚠ Ne démontez et ne tentez pas de réparer l'appareil ou ses composants.
- ⚠ Utilisez l'appareil uniquement pour la fonction pour laquelle il est destiné. Ne l'utilisez pas à d'autres fins.
- ⚠ Jetez l'appareil, les composants et les accessoires en option conformément aux règlements locaux applicables. La disposition illégale peut causer de la pollution environnementale.
- ⚠ Utilisez uniquement les pièces et les accessoires Omron autorisées. Les pièces et accessoires non approuvés pour l'utilisation avec l'appareil pourraient endommager l'appareil.
- ⚠ Tout changement ou altération non approuvés par Omron Healthcare entraînera l'annulation de la garantie.

### RISQUE DE CHOC ÉLECTRIQUE LORS DE L'UTILISATION DE L'ADAPTATEUR C.A.

- ⚠ Ne branchez ou ne débranchez pas le cordon d'alimentation dans une prise de courant lorsque vous avez les mains mouillées.
- ⚠ N'utilisez que l'adaptateur c.a. conçu par Omron pour cet appareil. L'utilisation de tout autre adaptateur c.a. pourrait endommager l'appareil.

## CONSIGNES DE SÉCURITÉ IMPORTANTES

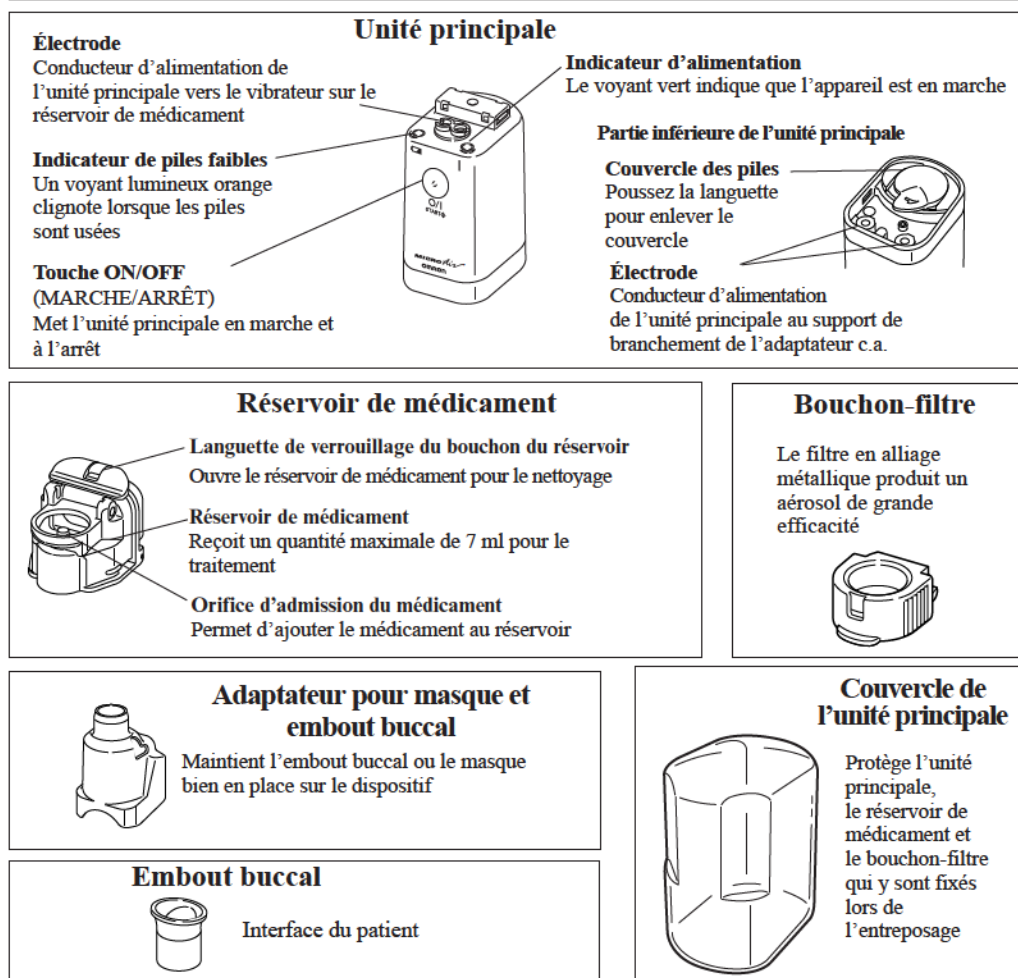
### RISQUE DE CHOC ÉLECTRIQUE LORS DE L'UTILISATION DE L'ADAPTATEUR C.A. (suite)

- ⚠ Ne surchargez pas les prises de courant. Branchez l'appareil dans une prise à la tension appropriée.
- ⚠ N'utilisez pas de rallonges électriques. Branchez le cordon d'alimentation directement dans la prise de courant.
- ⚠ Débranchez le cordon d'alimentation de la prise de courant après avoir utilisé l'appareil.
- ⚠ Débranchez le cordon d'alimentation de la prise de courant avant de nettoyer l'appareil.

### ENTRETIEN ET ENTREPOSAGE

- ⚠ Gardez l'appareil hors de la portée des bébés ou des enfants sans surveillance. L'appareil peut contenir de petites pièces qui peuvent être avalées.
- ⚠ N'immergez pas l'unité principale dans l'eau ou un autre liquide.
- ⚠ N'utilisez ou n'entrez pas l'appareil dans un endroit humide, comme la salle de bain. Utilisez l'appareil dans les conditions de température et d'humidité recommandées.
- ⚠ Ne laissez pas de solution nettoyante dans les pièces du nébuliseur. Rincez les pièces du nébuliseur à l'eau chaude du robinet après les avoir désinfectées.
- ⚠ Rincez les pièces du nébuliseur après chaque usage. Asséchez les pièces immédiatement après les avoir lavées.
- ⚠ Rangez l'appareil et ses composants dans un endroit sûr et sec.
- ⚠ Pour éviter d'endommager l'appareil, ne transportez et ne laissez pas le réservoir de médicament rempli de médicament ou d'eau distillée.
- ⚠ N'essayez pas de sécher ou de mettre l'appareil ou l'une de ses pièces au four à micro-ondes.
- ⚠ Pour éviter d'endommager l'appareil, ne rincez pas l'unité principale ou ne l'immergez pas dans aucun liquide, ne lavez ni ne rincez aucune pièce à grande eau et ne touchez pas au bouchon-filtre avec la main ou un objet.
- ⚠ N'utilisez pas de javellisant ménager. Le filtre rouillera et le bouchon-filtre ne sera plus utilisable.
- ⚠ Pour éviter d'endommager l'appareil, ne nettoyez pas l'unité principale à l'aide de nettoyants abrasifs ou de tout autre produit chimique et ne laissez pas l'humidité toucher les électrodes ou la prise d'adaptateur c.a. de l'unité principale.
- ⚠ Ne placez pas l'adaptateur c.a. dans l'étui de rangement. L'étui de rangement n'est pas conçu pour transporter l'adaptateur c.a..

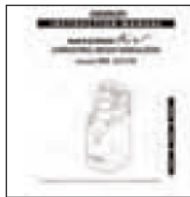
## FAMILIARISEZ-VOUS AVEC L'APPAREIL



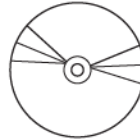


## FAMILIARISEZ-VOUS AVEC L'APPAREIL

### Guide de l'utilisateur



### DVD d'instructions



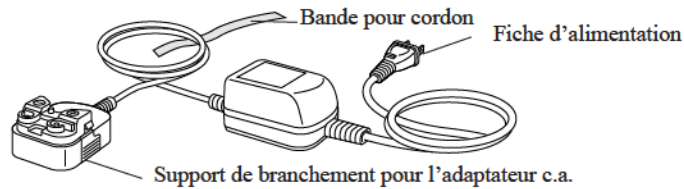
### Étui de rangement



Contient l'unité principale, le réservoir de médicament ainsi que l'adaptateur pour masque et embout buccal

### Accessoire en option

#### Adaptateur c.a., modèle no U22-5



### Accessoire en option

#### Masque pour enfant modèle no C922



Interface du patient  
à usage pédiatrique

### Pièces de rechange

	No de modèle
COUVERCLE DES PILES	U22-8
COUVERCLE DE L'UNITÉ PRINCIPALE	U22-9
ADAPTATEUR POUR MASQUE ET	
EMBOUT BUCCAL	U22-2
RÉSERVOIR DE MÉDICAMENT	U22-3
BOUCHON-FILTRE	U22-4
EMBOUT BUCCAL	U22-1
ÉTUI DE RANGEMENT	U22-7

## PRÉPARATION DU NÉBULISEUR POUR L'UTILISATION

### ⚠ AVERTISSEMENT

Lisez tous les renseignements fournis dans le guide de l'utilisateur et dans tout document inclus dans la boîte avant d'utiliser l'appareil.

### ⚠ AVERTISSEMENT

Nettoyez et désinfectez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal avant la première utilisation de l'appareil après l'achat.

### ⚠ AVERTISSEMENT

Si l'appareil n'a pas servi pendant une longue période, nettoyez et désinfectez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal avant de les utiliser.

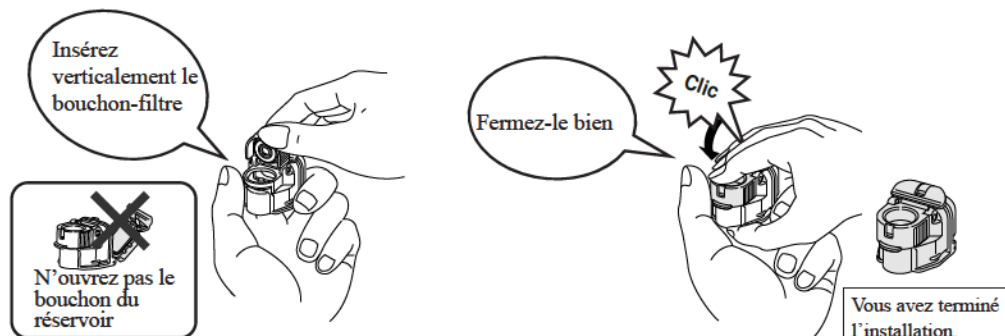
Pour des directives sur le nettoyage et la désinfection, consultez la section Entretien et nettoyage aux pages 16 et 17.

**L'appareil doit être assemblé avant son utilisation.**

### Renseignements généraux

- Les composants peuvent s'ajuster bien serrés puisqu'ils sont prévus pour empêcher le médicament de couler.
- Tenez bien l'appareil des deux mains.
- Fixez bien les pièces. Il se peut que vous entendiez un cliquement lorsque vous installez certaines pièces.

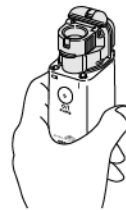
1. Fixez le bouchon-filtre au réservoir de médicament.



F9

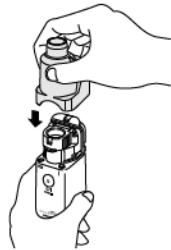
## PRÉPARATION DU NÉBULISEUR POUR L'UTILISATION

2. Fixez le réservoir de médicament à l'unité principale.



Vous avez terminé l'installation.

3. Fixez l'adaptateur pour masque et embout buccal à l'unité principale.

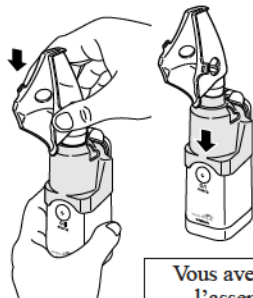


Vous avez terminé l'installation.

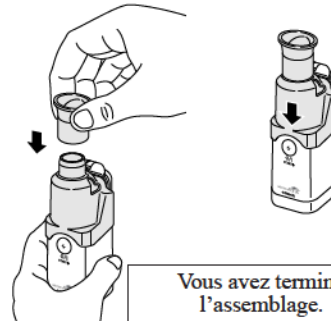
4. Fixez l'embout buccal ou le masque pour enfant à l'adaptateur pour masque et embout buccal.

• Comment fixer le masque pour enfant

• Comment fixer l'embout buccal



Vous avez terminé l'assemblage.



Vous avez terminé l'assemblage.

## INSTALLATION DES PILES

Cet appareil fonctionne à l'aide de deux (2) piles alcalines AA ou de deux (2) piles AA NiMH rechargeables.

### ⚠ MISE EN GARDE

N'utilisez pas une pile usée et une pile neuve ensemble.  
N'utilisez pas différents types de piles.  
Retirez les piles lorsque vous prévoyez que l'appareil ne sera pas utilisé pendant au moins trois mois.

#### 1. Ouvrez le couvercle des piles.

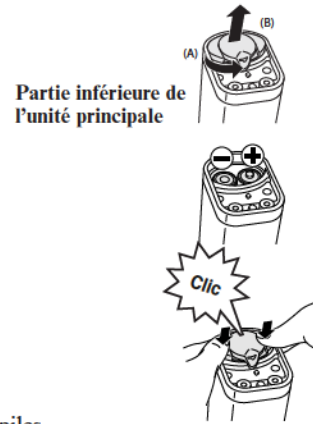
- (A) Faites tourner le couvercle des piles dans le sens de la flèche comme le montre l'illustration.
- (B) Ouvrez le couvercle des piles. Le couvercle des piles peut sembler s'ajuster serré puisqu'il est prévu pour éviter que les liquides pénètrent dans l'appareil.

#### 2. Insérez les piles.

Alignez correctement les polarités (+ et -) avec les repères des piles sur l'appareil.

#### 3. Fermez le couvercle des piles.

À l'aide de vos pouces, poussez les deux extrémités du couvercle des piles. Appuyez fermement jusqu'à ce que vous entendiez les deux languettes cliquer en place.



### Durée et remplacement des piles

#### Piles alcalines

- L'appareil peut être utilisé environ 8 jours à raison de 30 minutes par jour.
- L'indicateur de piles faibles (voyant orange) clignote pour signaler que les piles sont usées. Remplacez les deux piles par des neuves.
- L'indicateur de piles faibles (voyant orange) s'allume pour signaler que les piles sont à plat. L'appareil ne nébulisera pas. Remplacez immédiatement les deux piles par des neuves.

#### Piles NiMH rechargeables

- L'appareil peut être utilisé environ 8 jours à raison de 30 minutes par jour lorsque les piles sont complètement chargées.
- L'indicateur de piles faibles (voyant orange) clignote pour signaler que les piles rechargeables sont à plat ou presque à plat. Si l'appareil ne nébulise pas immédiatement, rechargez les piles.
- Rechargez les piles au moyen d'un chargeur de piles disponible sur le marché et adapté aux piles utilisées dans cet appareil.
- L'adaptateur c.a. ne sert pas de chargeur de piles.

## UTILISATION DE L'ADAPTATEUR c.a.

L'appareil est conçu de façon à ne pas consommer la puissance des piles lorsque l'adaptateur c.a. est utilisé. L'adaptateur c.a. n'est pas un chargeur de piles.

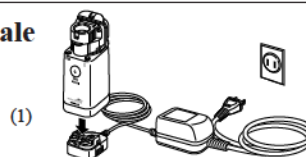


### AVERTISSEMENT

Utilisez uniquement l'adaptateur c.a. conçu par Omron pour cet appareil.  
L'utilisation d'un autre adaptateur c.a. pourrait endommager l'appareil.

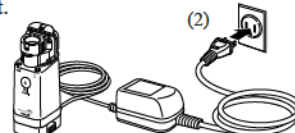
### Pour brancher l'adaptateur c.a. à l'unité principale

- (1) Placez l'unité principale sur le support de branchement de l'adaptateur c.a. tel qu'illustré ci-dessous.



**REMARQUE :** Il émettra un clic et s'enclenchera au support.

- (2) Insérez la fiche d'alimentation de l'adaptateur c.a. dans une prise de courant de 120 V.



Le branchement est terminé.



### AVERTISSEMENT

Ne branchez ou ne débranchez pas le cordon d'alimentation dans une prise de courant lorsque vous avez les mains mouillées.



### MISE EN GARDE

Ne surchargez pas les prises de courant. Branchez l'appareil dans une prise à la tension appropriée.



### MISE EN GARDE

N'utilisez pas de rallonges électriques. Branchez le cordon d'alimentation directement dans la prise de courant.

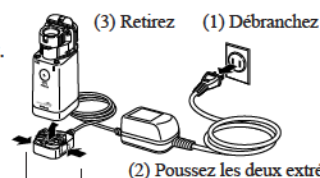


### MISE EN GARDE

Débranchez le cordon d'alimentation de la prise de courant avant de nettoyer l'appareil.

### Pour retirer l'adaptateur c.a. de l'unité principale

- (1) Débranchez la fiche de l'adaptateur c.a. de la prise de courant.
- (2) Poussez les deux côtés du support de branchement pour débloquer l'unité principale.
- (3) Retirez l'unité principale.



### MISE EN GARDE

Débranchez le cordon d'alimentation de la prise de courant après l'utilisation de l'appareil.



## REPLISSAGE DU RÉSERVOIR DE MÉDICAMENT

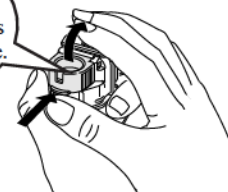
Retirez l'embout buccal ou le masque ainsi que l'adaptateur pour masque et embout buccal de l'unité principale.

### 1. Ouvrez le bouchon-filtre.

Tenez le dispositif fermement dans votre main.



Soulevez le bouchon-filtre en poussant le bord vers le haut avec le pouce.



### 2. Remplissez le réservoir de médicament.



#### AVERTISSEMENT

L'utilisation de la pentamidine avec cet appareil n'est pas approuvée.



#### AVERTISSEMENT

N'utilisez pas l'eau du robinet ou de l'eau minérale dans le nébuliseur dans le but de la pulvériser.

Prenez garde que le bouchon-filtre ne se ferme comme le montre l'illustration.  
La capacité maximale du réservoir de médicament est de 7 ml.



#### MISE EN GARDE

Ne mettez pas plus de 7 ml de médicament dans le réservoir à médicament.



#### MISE EN GARDE

Ajoutez le médicament lentement pour éviter d'endommager le dispositif. Assurez-vous que le médicament ne déborde pas de l'orifice d'admission du médicament.



Vérifiez si le bouchon-filtre est fermé.



### 3. Fermez le bouchon-filtre.



#### MISE EN GARDE

Pour éviter d'endommager l'appareil, assurez-vous que le bouchon-filtre est bien en place. Si le bouchon-filtre n'est pas bien fermé, il y aura fuite de médicament.

### 4. Fixez l'adaptateur pour masque et embout buccal à l'unité principale

Fixez l'embout buccal ou le masque pour enfant à l'adaptateur pour masque et embout buccal.

**REMARQUE:** Pour des directives sur la façon de fixer l'adaptateur pour masque et embout buccal, retournez la section Assemblage de l'unité à page 10.

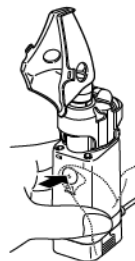
## SÉLECTION DU MODE DE NÉBULISATION

Ce dispositif fonctionne en mode de nébulisation continue ou en mode de nébulisation manuelle.

### • Mode de nébulisation continue

Pour démarrer l'appareil en mode de nébulisation continue, appuyez sur la touche ON/OFF (MARCHE/ARRÊT) en la maintenant enfoncée pendant 1 seconde.

Appuyez à nouveau sur la touche ON/OFF (MARCHE/ARRÊT) pour arrêter la nébulisation.



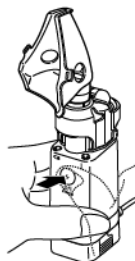
Appuyez sur la touche ON/OFF (MARCHE/ARRÊT) en la maintenant enfoncée pendant 1 seconde

### • Mode de nébulisation manuelle

En mode de nébulisation manuelle, l'appareil nébulise seulement si vous appuyez sur la touche ON/OFF (MARCHE/ARRÊT) en la maintenant enfoncée. Ce mode permet l'inhalation sur demande.

Pour démarrer l'appareil en mode de nébulisation manuelle, appuyez sur la touche ON/OFF (MARCHE/ARRÊT) et maintenez-la enfoncée pendant au moins 2 secondes.

Appuyez sur la touche ON/OFF (MARCHE/ARRÊT) en la maintenant enfoncée pour commencer la nébulisation.



Appuyez sur la touche ON/OFF (MARCHE/ARRÊT) et maintenez-la enfoncée pendant 2 secondes.

**REMARQUE :** Le voyant d'alimentation (voyant vert) s'allume pendant la nébulisation.

## UTILISATION DE L'APPAREIL



### AVERTISSEMENT

Utilisez toujours le type, la dose et le régime posologique des médicaments prescrits par votre fournisseur de soins de santé.



### AVERTISSEMENT

Jetez toujours tout reste de médicament qui se trouve dans le réservoir à médicament après chaque utilisation. Utilisez un médicament frais à chaque utilisation de l'appareil.



### MISE EN GARDE

Assurez une supervision étroite quand cet appareil est utilisé par ou en présence des bébés, des enfants ou des personnes à risque ou en présence de ceux-ci.



### MISE EN GARDE

Inspectez l'unité principale et les pièces du nébuliseur avant chaque utilisation de l'appareil. Assurez-vous qu'aucune pièce n'est endommagée, que l'appareil est bien assemblé et que l'appareil fonctionne normalement.



### MISE EN GARDE

N'utilisez pas l'appareil à des températures plus élevées que +104 °F (+40 °C).



### MISE EN GARDE

Cet appareil est approuvé uniquement pour utilisation par des humains.

1. Inclinez légèrement l'unité principale vers vous pour immerger le bouchon-filtre vibrant dans le médicament.

**REMARQUE :** Si le vibreur n'est pas immergé dans le médicament, l'appareil ne nébulisera pas.

2. Commencez l'inhalation dans une position détendue.
3. Placez vos lèvres autour de l'embout buccal sans serrer. Si le masque pour enfant est utilisé, positionnez-le délicatement contre le visage.
4. Commencez le traitement comme votre fournisseur de soins de santé vous l'a indiqué.
5. Appuyez sur la touche ON/OFF (MARCHE/ARRÊT) pour éteindre l'appareil lorsque vous avez terminé votre traitement.

**REMARQUE :** L'appareil est muni d'une minuterie intégrée qui met l'appareil hors tension environ 30 minutes après la mise sous tension.

Lorsque vous utilisez l'adaptateur c.a., retirez la fiche d'alimentation de la prise de courant.

## NETTOYAGE APRÈS CHAQUE UTILISATION

Respecter les directives de nettoyage après chaque utilisation évitera que du médicament restant dans le flacon s'assèche et adhère au bouchon-filtre, ce qui aurait pour résultat que l'appareil ne nébulise plus efficacement.

**Lavez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal après chaque utilisation.**



### AVERTISSEMENT

Rincez les pièces du nébuliseur après chaque usage. Asséchez les pièces immédiatement après les avoir lavées.



### MISE EN GARDE

Pour éviter d'endommager l'appareil :

- Ne rincez ou n'immergez pas l'unité principale dans aucun liquide.
  - Ne lavez ou ne rincez aucune pièce sous un jet d'eau puissant.
  - Ne touchez pas au filtre avec la main ou tout autre objet.
1. Retirez l'embout ou le masque ainsi que l'adaptateur pour masque et embout buccal de l'unité principale.
  2. Retirez le réservoir de médicament de l'unité principale.
  3. Ouvrez le réservoir de médicament et jetez tout reste de médicament.
  4. Fixez le réservoir de médicament à l'unité principale. Ouvrez le bouchon-filtre.
  5. Versez une petite quantité d'eau distillée dans le réservoir de médicament et fermez le bouchon-filtre.
  6. Mettez l'appareil en marche pour nébuliser l'eau distillée pendant 1 à 2 minutes et enlevez les restes de médicament du filtre.
  7. Éteignez l'appareil et retirez le réservoir de médicament de l'unité principale.
  8. Retirez le bouchon-filtre du réservoir de médicament et jetez toute l'eau distillée qui reste dans le réservoir de médicament.
  9. Rincez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal à l'eau distillée.
  10. Essuyez délicatement l'excès d'eau à l'aide d'un chiffon doux et propre ou laissez les pièces sécher à l'air libre dans un endroit propre.
  11. Assemblez l'appareil. Rangez l'appareil dans l'étui de rangement ou dans un endroit propre.

## DÉSINFECTION QUOTIDIENNE

Désinfectez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal chaque jour après le dernier traitement.

### MISE EN GARDE

Pour éviter d'endommager l'appareil :

- Ne rincez ou n'immergez pas l'unité principale dans aucun liquide.
- Ne lavez ou ne rincez aucune pièce sous un jet d'eau puissant.
- Ne touchez pas au filtre avec la main ou tout autre objet.

1. Préparez l'une des deux solutions suivantes : Vinaigre (1 partie de vinaigre blanc pour 3 parties d'eau distillée) OU savon détergent doux (savon à vaisselle dans de l'eau distillée).

### MISE EN GARDE

N'utilisez pas de javellisant ménager. Le filtre rouillera et le bouchon-filtre ne sera plus utilisable.

2. Ouvrez le bouchon-filtre en le soulevant et versez une petite quantité de solution désinfectante dans le réservoir de médicament.
3. Mettez l'appareil en marche pour nébuliser la solution désinfectante pendant 1 à 2 minutes.
4. Éteignez l'appareil et retirez le réservoir de médicament de l'unité principale.
5. Retirez le bouchon-filtre du réservoir de médicament et jetez le reste de la solution désinfectante du réservoir de médicament.
6. Faites tremper le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal dans la solution désinfectante pendant 10 à 15 minutes.
7. Rincez le réservoir de médicament, le bouchon-filtre, le masque, l'embout buccal et l'adaptateur pour masque et embout buccal à l'eau distillée.

### AVERTISSEMENT

Ne laissez pas de solution nettoyante dans les pièces du nébuliseur. Rincez les pièces du nébuliseur à l'eau distillée après les avoir désinfectées.

8. Essuyez délicatement l'excès d'eau à l'aide d'un chiffon doux et propre ou laissez les pièces sécher dans un endroit propre.
9. Assemblez l'appareil. Rangez l'appareil dans l'étui de rangement ou dans un endroit propre.

## ENTRETIEN DE L'APPAREIL

**Afin de garder votre appareil dans le meilleur état possible et de bien le protéger, suivez les directives ci-dessous :**

- ⚠ Gardez l'appareil hors de la portée des bébés ou des enfants sans surveillance. L'appareil peut contenir de petites pièces qui peuvent être avalées.
- ⚠ Rangez l'appareil et ses composants dans un endroit sûr et sec.
- ⚠ N'utilisez ou n'entrez pas l'appareil dans un endroit humide, comme la salle de bain. Utilisez l'appareil dans les conditions de température et d'humidité recommandées.
- ⚠ Ne laissez pas l'appareil ni ses composants dans un endroit où ils pourraient être exposés à des températures extrêmes ou à des changements d'humidité, par exemple en les laissant dans un véhicule pendant les mois chauds, où ils seront exposés aux rayons directs du soleil.
- ⚠ Ne soumettez l'appareil ni les autres composants à un grand choc, tel que le laisser tomber sur le plancher.
- ⚠ Ne démontez et ne tentez pas de réparer l'appareil ou ses composants.
- ⚠ Utilisez uniquement les pièces et les accessoires Omron autorisés. Les pièces et accessoires non approuvés pour l'utilisation avec l'appareil pourraient endommager l'appareil.
- ⚠ Utilisez l'appareil uniquement pour la fonction pour laquelle il est destiné. Ne l'utilisez pas à d'autres fins.
- ⚠ Tout changement ou altération non approuvés par Omron Healthcare entraînera l'annulation de la garantie.
- ⚠ Jetez l'appareil, les composants et les accessoires en option conformément aux règlements locaux applicables. La disposition illégale peut causer de la pollution environnementale.
- ⚠ Retirez les piles lorsque vous prévoyez que l'appareil ne sera pas utilisé pendant au moins trois mois. Remplacez toujours toutes les piles en même temps par des piles neuves. N'utilisez pas différents types de piles.



## ENTRETIEN DE L'APPAREIL

### Nettoyage de l'unité principale

Nettoyez le boîtier de l'unité principale à l'aide d'un chiffon doux humidifié avec de l'eau ou un détergent doux. Essuyez le boîtier et séchez-le immédiatement à l'aide d'un chiffon doux et propre.



#### MISE EN GARDE

N'essayez pas de sécher ou de mettre l'appareil ou l'une de ses pièces au four à micro-ondes.



#### MISE EN GARDE

Pour éviter d'endommager l'appareil :

- Ne rincez ou n'immergez pas l'unité principale dans un liquide.
- Ne nettoyez pas l'unité principale à l'aide de nettoyeurs abrasifs ou de tout autre produit chimique.
- Ne laissez pas l'humidité entrer en contact avec les électrodes ou la prise de l'adaptateur c.a. sur l'unité principale ou le support de branchement de l'adaptateur c.a.

### Transport de l'appareil dans l'étui de rangement

Assemblez l'appareil en fixant le bouchon-filtre et le réservoir de médicament à l'unité principale. Placez le couvercle de l'unité principale sur l'appareil.

Placez l'appareil dans l'étui de rangement tel qu'illustré.

L'embout buccal et l'adaptateur pour masque se placent facilement dans l'étui de rangement avec l'unité principale.



#### MISE EN GARDE

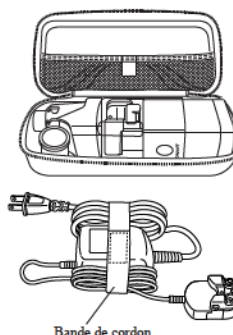
Pour éviter d'endommager l'appareil

- Ne transportez pas et ne laissez pas le nébuliseur lorsqu'il reste du médicament ou de l'eau distillée dans le réservoir de médicament.



- Ne placez pas l'adaptateur c.a. dans l'étui de rangement. L'étui de rangement n'est pas conçu pour le transport de l'adaptateur c.a. en option.

Pour transporter l'adaptateur c.a., enroulez le cordon d'alimentation de l'adaptateur c.a. et fixez-le à l'unité principale de l'adaptateur c.a. à l'aide de la bande pour cordon, tel qu'illustré.



## GUIDE DE DÉPANNAGE

PROBLÈME	CAUSE	SOLUTIONS
Le voyant d'alimentation ne s'éclaire pas.	L'adaptateur c.a. n'est pas branché dans une prise de courant. Le support de branchement n'est pas fixé à l'unité principale. Les piles n'ont pas été insérées correctement. Les piles sont presque déchargées.	Éteignez en appuyant sur la touche ON/OFF (MARCHÉ/ARRÊT). Branchez le cordon d'alimentation dans une prise de courant. Mettez l'appareil sous tension. Assurez-vous que l'unité principale est bien fixée au support de branchement. Réinsérez les piles. Remplacez immédiatement les deux piles usagées. Rechargez les piles NiMH à l'aide d'un chargeur disponible sur le marché.
	Des résidus de médicament ont séché sur les composants et les accessoires.	Nettoyez et désinfectez les composants et les accessoires.
	Le bouchon-filtre doit être remplacé.	Remplacez le bouchon-filtre.
Le voyant d'alimentation s'éclaire, mais l'appareil ne nébulise pas.	Les piles sont presque déchargées.	Remplacez les quatre piles du même type par des piles neuves alcalines ou NiMH chargées.
	Le réservoir de médicament contient trop de médicament.	Remplissez le réservoir de médicament avec la quantité prescrite de médicament. La quantité maximale est de 7 ml.
	Il se peut que du liquide se soit accumulé autour des électrodes de l'unité principale.	Absorbez le liquide à l'aide d'un chiffon doux.
	Il y a du liquide sur le bouchon-filtre.	Enlevez le liquide délicatement à l'aide d'un chiffon doux de manière à ne pas endommager le filtre.
	Le médicament n'est pas entré en contact avec les pièces du nébuliseur.	Inclinez légèrement l'unité principale vers vous alors que la touche ON/OFF (MARCHÉ/ARRÊT) pointe vers le bas.

## GUIDE DE DÉPANNAGE

PROBLÈME	CAUSE	SOLUTIONS
L'appareil est en marche; toutefois, il nébulise faiblement ou met trop de temps pour le traitement.	Le réservoir de médicament n'est pas bien installé.	Assurez-vous que le réservoir de médicament est bien installé.
	L'unité doit être nettoyée.	Suivez les directives de nettoyage après chaque utilisation.
	L'unité doit être désinfectée.	Suivez les directives de désinfection.
	Les piles sont presque déchargées.	Remplacez les piles en suivant les directives d'installation.
	La vitesse de nébulisation peut varier selon le médicament utilisé.	La durée du traitement peut varier selon les médicaments et les patients.

## RENSEIGNEMENTS SUR LA GARANTIE

### GARANTIES RESTREINTES

Votre nébuliseur NE-U22, à l'exclusion du bouchon-filtre et des accessoires, est garanti contre tout défaut de matériaux et de fabrication apparaissant dans les 2 années suivant la date d'achat, lorsqu'il est utilisé selon les directives fournies avec l'appareil. La garantie ci-dessus n'est offerte qu'à l'acheteur au détail original.

À notre discrétion, nous réparerons ou remplacerons sans frais votre nébuliseur Omron. La réparation ou le remplacement est notre seule responsabilité et votre seul recours en vertu des garanties ci-dessus.

Pour obtenir du service en vertu de cette garantie, communiquez avec le Service à la clientèle d'Omron Healthcare en composant le 1 800 634-4350 pour obtenir l'adresse de l'emplacement pour la réparation ainsi que les frais d'expédition de retour et de manutention. Les renseignements relatifs au service en vertu de la garantie sont disponibles sur notre site Web à l'adresse [www.omronhealthcare.com](http://www.omronhealthcare.com).

Veuillez joindre une preuve d'achat. Veuillez également joindre une lettre dans laquelle vous indiquez vos nom, adresse, numéro de téléphone, et une description du problème spécifique. Emballez le produit avec soin afin d'éviter tout risque de dommages supplémentaires durant le transport. En raison des risques de perte lors du transport, nous vous recommandons d'assurer le produit et de demander un avis de réception.

**TOUTES GARANTIES IMPLICITES INCLUANT, SANS S'Y LIMITER, LES GARANTIES LIMITÉES DE QUALITÉ MARCHANDE ET D'ADAPTABILITÉ À DES FINS PARTICULIÈRES, SONT LIMITÉES À LA DURÉE DE LA GARANTIE ÉCRITE APPLICABLE CI-DESSUS.** Certaines provinces/états ne permettent pas de limites quant à la durée de la garantie implicite; il se peut donc que les limites ci-dessus ne s'appliquent pas à vous.

**OMRON NE SERA PAS TENUE RESPONSABLE DES PERTES DÉCOULANT DE L'UTILISATION OU D'AUTRES DOMMAGES INDIRECTS OU ACCESSOIRES OU DE COÛTS INDIRECTS, DÉPENSES OU DOMMAGES.** Certaines provinces ne permettent pas d'exclusions ou de limites de dommages indirects; il se peut donc que les exclusions ci-dessus ne s'appliquent pas à vous.

Cette garantie vous donne des droits précis reconnus par la loi, et vous pouvez également avoir d'autres droits qui varient d'une province à l'autre.

### POUR LE SERVICE À LA CLIENTÈLE (É.-U. et CANADA)

Visitez notre site Web au : [www .omronhealthcare.com](http://www.omronhealthcare.com)  
Téléphonez sans frais au : 1 800 634-4350

## CONFORMITÉ FCC

**Remarque :**

INTERFÉRENCES POTENTIELLES POUR LA RADIO/TÉLÉVISION  
(pour les É.-U. seulement)

Ce produit a été testé et déclaré conforme aux limites de la section 15 du règlement FCC, applicables aux appareils numériques de classe B.

Ces limites sont conçues pour fournir une protection satisfaisante contre les interférences dans les installations résidentielles. Ce produit génère, utilise et émet des ondes de fréquence radio et, s'il n'est pas installé conformément aux directives, les ondes risquent de provoquer des interférences avec les communications radio. Il est cependant impossible de garantir que des interférences ne surviendront pas dans une installation particulière. Si ce produit est la cause d'interférences gênant la réception de programmes radio ou télévisés, ce qui peut être déterminé en mettant l'appareil hors tension et de nouveau sous tension, l'utilisateur doit tenter de remédier au

problème en prenant une ou plusieurs des mesures suivantes:

- Réorienter ou relocaliser l'antenne de réception.
- Augmenter la distance séparant l'équipement et le récepteur.
- Brancher l'équipement à une prise de courant ou à un circuit différent de celui auquel le récepteur est branché.
- Contacter votre revendeur ou un technicien radio/TV qualifié.

INTERFÉRENCES POTENTIELLES POUR LA RADIO/TÉLÉVISION  
(pour le Canada seulement)

Cet appareil numérique respecte les limites de bruits radioélectriques applicables aux appareils numériques de Classe B prescrites dans la norme sur le matériel brouilleur : « Appareils numériques », ICES-003 édictée par le ministère des Communications.

Les changements ou modifications non approuvés expressément par l'autorité responsable de la conformité peuvent annuler l'autorisation accordée à l'utilisateur de faire fonctionner cet équipement.

## SPÉCIFICATIONS

<b>Modèle :</b>	<b>Nébuliseur Omron NE-U22V avec V.M.T.®</b>
Source d'alimentation :	CC : 3 V, c.a. : 120 V, 60 Hz (avec adaptateur c.a.)
Consommation d'énergie :	1,5 W
Débit de nébulisation :	0,25 ml/min. minimum
Plage de taille des particules :	DMM environ 5µm
Capacité du réservoir de médicament :	7 ml maximum
Température/humidité d'utilisation :	+50 °F à +104 °F (+10 °C à +40 °C) / 30 % à 85 % HR
Température/humidité d'entreposage/pression d'air :	-4 °F à +140 °F (-20 °C à +60 °C) / 10 % à 95 % RH / 700 hPa à 1 060 hPa
Fréquence des vibrations :	180 kHz
Dimensions :	1,5 po (L.) x 2,1 po (l.) x 4,1 po (H.) (38 mm x 51 mm x 104 mm)
Poids :	3.4 oz (97 g)
Pile :	2 piles « AA » ou NiMH rechargeables (non comprises)
Contenu :	Unité principale, réservoir de médicament, étui de transport, embout buccal, bouchon-filtre, adaptateur pour masque et embout buccal, vidéo et guide de l'utilisateur
Code CUP :	0 73796 45122 6

• Sujet à des modifications techniques sans préavis

Essai de l'impacteur en cascade à 13 lpm:

	<b>Pulmicort®</b>	<b>Intal®</b>	<b>Salubutamol®</b>
DMM (microns)	6,76 µ	6,43 µ	5,79 µ
ETG (écart type géométrique)	2,08	2,56	2,75
Fraction inhalable (% masse : 0,52 à 6 µ)	65,0 %	66,0 %	73,4 %

Durée du traitement: 5 minutes pour 2 ml

• Veuillez noter que les spécifications peuvent varier selon le type de médicament utilisé.



## REMARQUES

Fabriqué au Japon

Distribué par :  
**OMRON HEALTHCARE, INC.**

1200, Lakeside Drive  
Bannockburn, Illinois 60015

[www.omronhealthcare.com](http://www.omronhealthcare.com)

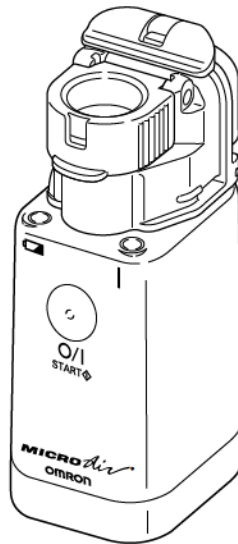
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# OMRON

## MANUAL DE INSTRUCCIONES

### **MICRO** *Air*® **NEBULIZADOR VIBRADOR CON MALLA** Modelo **NE-U22V**

Español



**PRECAUCIÓN:** Conforme a las leyes federales de los Estados Unidos, este dispositivo sólo se puede vender a pedido de un médico.

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## INTRODUCCIÓN

Gracias por adquirir el nebulizador vibrador con malla Omron® NE-U22V MICROAir®.

Complete los siguientes datos para futuras consultas

FECHA DE COMPRA: \_\_\_\_\_

NÚMERO DE SERIE: \_\_\_\_\_

Abroche aquí su recibo de compra.

Omron Healthcare ha progresado en el desarrollo de la tecnología de nebulizadores electrónicos con la introducción del nebulizador vibrador con malla NE-U22V MICROAir®. Con el objetivo de brindar comodidad al paciente y cumplir con la normativa vigente, este dispositivo ofrece la máxima portabilidad dondequiera que vaya y una revolucionaria tecnología de malla vibradora que proporciona un tratamiento preciso, poderoso y efectivo cada vez que lo utiliza.

El MICROAir® es un sistema nebulizador vibrador con malla diseñado para convertir medicamentos líquidos en aerosol para que los pacientes puedan inhalarlo. El dispositivo se puede usar con pacientes pediátricos y adultos, en el hogar, en nosocomios y en entornos de cuidados subagudos.

Su nebulizador NE-U22V MICROAir® cuenta con los siguientes componentes:

- Unidad principal
- Cubierta de la unidad
- Depósito para el medicamento
- Tapa de la malla
- Adaptador para la mascarilla y la boquilla
- Boquilla
- Estuche
- Manual de instrucciones
- DVD instructivo

Los siguientes accesorios son opcionales y se venden por separado:

- Transformador de CA
- Mascarilla para niños



*El MICROAir® es un dispositivo médico. Utilícelo únicamente según las indicaciones del médico o del profesional autorizado.*

**GUARDE ESTAS INSTRUCCIONES**









## INFORMACIÓN DE SEGURIDAD

Para asegurar el uso correcto del producto, siempre se deben tomar medidas de seguridad básicas, entre ellas las advertencias y precauciones que se describen en este manual de instrucciones.

### ÍCONOS DE SEGURIDAD USADOS EN ESTE MANUAL DE INSTRUCCIONES

 <b>ADVERTENCIA</b>	Indica una situación potencialmente peligrosa que, si no se evita, puede provocar la muerte o lesiones graves.
 <b>PRECAUCIÓN</b>	Indica una situación potencialmente peligrosa que, si no se evita, puede provocar lesiones leves o moderadas al usuario o al paciente o puede provocar daños al equipo o a otros bienes.

### FUNCIONAMIENTO DEL DISPOSITIVO

-  Antes de utilizar la unidad, lea toda la información del manual de instrucciones y cualquier otro material impreso que se incluya en la caja.
-  Para el tipo, la dosis y el régimen de medicamento, siga las instrucciones del médico y/o del profesional médico autorizado.
-  La pentamidina no es un medicamento aprobado para usar con este dispositivo.
-  No use agua mineral o agua corriente en el nebulizador para fines de nebulización.
-  Limpie y desinfecte el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y la boquilla antes de utilizar el dispositivo por primera vez después de la compra.
-  Si el dispositivo no se ha utilizado durante un tiempo prolongado, limpie y desinfecte el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y la boquilla antes de utilizarlos.
-  Siempre deseche el medicamento que queda en el recipiente después de cada uso. Utilice medicamento nuevo cada vez que use el dispositivo.
-  No deje el dispositivo ni sus piezas en un lugar donde esté expuesto a extremas o a cambios en la humedad, por ejemplo, no deje el dispositivo en un vehículo durante los meses de temperatura cálida o alta o donde quede expuesto a la luz directa del sol.



## INFORMACIÓN DE SEGURIDAD IMPORTANTE

### FUNCIONAMIENTO DEL DISPOSITIVO (continuación)

- ⚠ Supervise atentamente el uso del dispositivo cuando sea utilizado por , en o cerca de bebés, niños o personas enfermas.
- ⚠ Inspeccione la unidad principal y las piezas del nebulizador antes de usar el dispositivo. Asegúrese de que las piezas no estén dañadas, de que el dispositivo esté armado correctamente y de que el dispositivo funcione normalmente.
- ⚠ Para evitar que el dispositivo se dañe, agregue el medicamento lentamente. No permita que el medicamento se derrame por el orificio del depósito para el medicamento.
- ⚠ No agregue más de 7 ml de medicamento en el recipiente del medicamento.
- ⚠ Para evitar que el dispositivo se dañe, asegúrese de que la tapa de la malla esté ubicada correctamente. Si la tapa de la malla no está bien cerrada, el medicamento se derramará.
- ⚠ No haga funcionar el dispositivo a temperaturas superiores a los +104 °F (+40 °C).
- ⚠ No someta al dispositivo ni a ninguno de los componentes a golpes fuertes como, por ejemplo, dejarlo caer al suelo.
- ⚠ Este dispositivo está aprobado para uso en seres humanos solamente.
- ⚠ No desarme ni trate de reparar el dispositivo ni los componentes.
- ⚠ Sólo haga funcionar el dispositivo para el fin para el que está diseñado. No use el dispositivo para ningún otro fin.
- ⚠ Al desechar el dispositivo, los componentes y los accesorios opcionales, siga las normas locales vigentes. Violar las normas establecidas para su eliminación puede provocar contaminación ambiental.
- ⚠ Use sólo las piezas y los accesorios autorizados por Omron. Las piezas y los accesorios que no hayan sido aprobados para ser usados con el dispositivo pueden causar daños en la unidad.
- ⚠ Los cambios o las modificaciones que no hayan sido aprobados por Omron Healthcare anularán la garantía del usuario.

### RIESGO DE CHOQUES ELÉCTRICOS MIENTRAS SE USA EL TRANSFORMADOR DE CA

- ⚠ No enchufe ni desenchufe el cable de alimentación en el tomacorrientes con las manos mojadas.
- ⚠ Use sólo el transformador de CA diseñado por Omron para este dispositivo. El uso de cualquier otro transformador de CA puede dañar el dispositivo.

## INFORMACIÓN DE SEGURIDAD IMPORTANTE

### RIESGO DE CHOQUES ELÉCTRICOS MIENTRAS SE USA EL TRANSFORMADOR DE CA (Continuación)

- ⚠ No sobrecargue los tomacorrientes. Enchufe el dispositivo en un tomacorriente con el voltaje adecuado.
- ⚠ No use cables prolongadores. Enchufe el cable de alimentación directamente en el tomacorriente.
- ⚠ Desenchufe el cable de alimentación del tomacorriente después de usar el dispositivo.
- ⚠ Desenchufe el cable de alimentación del tomacorriente antes de limpiar el dispositivo.

### MANTENIMIENTO Y ALMACENAMIENTO

- ⚠ Mantenga el dispositivo fuera del alcance de los bebés y niños si no están bajo estricta supervisión. El dispositivo puede contener piezas pequeñas que se pueden tragar .
- ⚠ No sumerja la unidad principal en agua u otro líquido.
- ⚠ No use ni guarde el dispositivo en lugares húmedos como, por ejemplo, el baño. Use el dispositivo teniendo en cuenta los límites de temperatura y humedad de funcionamiento.
- ⚠ No deje solución de limpieza en las piezas del nebulizador . Enjuague las piezas del nebulizador con agua destilada después de desinfectar .
- ⚠ Enjuague las piezas del nebulizador después de cada uso. Seque las piezas inmediatamente después de lavarlas.
- ⚠ Guarde el dispositivo y los componentes en un lugar limpio y seguro.
- ⚠ Para evitar que el dispositivo se dañe, no transporte ni deje el depósito para el medicamento con medicamento o agua destilada.
- ⚠ No coloque ni trate de secar el dispositivo o alguna de sus piezas en un horno de microondas.
- ⚠ Para evitar que el dispositivo se dañe, no enjuague ni sumerja la unidad principal en ningún líquido, no lave ni enjuague ninguna de las piezas con un chorro de agua de alta presión y no toque la malla con la mano ni con cualquier otro objeto.
- ⚠ No utilice un blanqueador de uso doméstico. La malla se oxidará y la tapa de la malla no se podrá usar .
- ⚠ Para evitar que el dispositivo se dañe, no limpie la unidad principal con limpiadores abrasivos ni con ningún tipo de químicos, y no permita que la humedad entre en contacto con los electrodos o el enchufe del transformador de CA en la unidad principal.
- ⚠ No coloque el transformador de CA en el estuche. El estuche no está diseñado para transportar el transformador de CA.

## CONOZCA SU UNIDAD

### Unidad principal

#### Electrodo

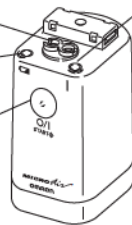
Conductor eléctrico desde la unidad principal hasta el vibrador del depósito para el medicamento

#### Indicador de pilas descargadas

Una luz anaranjada titila cuando las pilas están gastadas

#### Botón ENCENDIDO/APAGADO

Enciende y apaga la unidad principal



#### Indicador de encendido

La luz verde indica que el dispositivo está en funcionamiento

#### Parte inferior de la unidad principal

#### Tapa del compartimiento de las pilas

Presione la palanca para quitar la tapa



#### Electrodo

Conductor eléctrico que transporta corriente desde la unidad principal hasta la base de conexión del transformador de CA

### Depósito para el medicamento



#### Palanca de bloqueo de la tapa del depósito

Abre el depósito para el medicamento para limpiarlo

#### Depósito para el medicamento

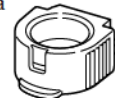
Tiene una capacidad máxima de 7 ml por tratamiento

#### Orificio para el medicamento

Agregue aquí el medicamento para el depósito

### Tapa de la malla

La malla de aleación metálica produce un aerosol de gran eficacia



### Adaptador para la mascarilla y boquilla



Mantiene la boquilla o la mascarilla conectada firmemente al dispositivo

### Boquilla



Pieza de contacto con el paciente

### Cubierta de la unidad principal



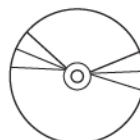
Protege la unidad principal, el depósito para el medicamento y la tapa de la malla mientras está almacenado

## CONOZCA SU UNIDAD

### Manual de instrucciones



### DVD instructivo



### Estuche



El estuche está diseñado para almacenar la unidad principal, el depósito para el medicamento y el adaptador para la mascarilla y boquilla

### Accesorio opcional

#### Transformador de CA, modelo N.º U22-5



### Accesorio opcional

#### Mascarilla para niños Modelo N.º C922



Pieza de contacto con el paciente para uso pediátrico

### Piezas de repuesto

#### Modelo N.º

TAPA DEL COMPARTIMIENTO PARA PILAS	U22-8
TAPA DE LA UNIDAD PRINCIPAL	U22-9
ADAPATADOR PARA LA	
MASCARILLA Y BOQUILLA	U22-2
DEPÓSITO PARA EL MEDICAMENTO	U22-3
TAPA DE LA MALLA	U22-4
BOQUILLA	U22-1
ESTUCHE U22-7	

## PREPARACIÓN DEL NEBULIZADOR PARA SU USO



### ADVERTENCIA

Antes de utilizar la unidad, lea toda la información del manual de instrucciones y toda otra información que se incluya en la caja.



### ADVERTENCIA

Antes de utilizar el dispositivo por primera vez después de su compra, limpie y desinfecte el depósito para el medicamento, la tapa de la malla, la mascarilla y el adaptador para la mascarilla y la boquilla.



### ADVERTENCIA

Si el dispositivo no se ha utilizado durante un tiempo prolongado, limpie y desinfecte el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y boquilla antes de utilizarlos.

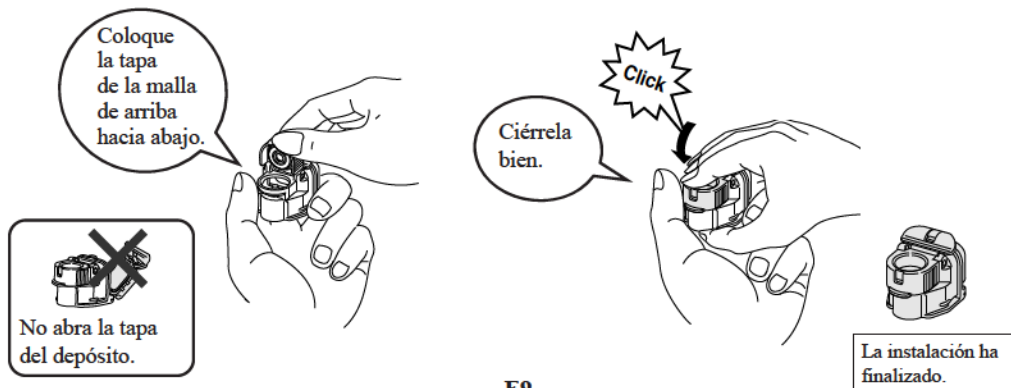
Para obtener instrucciones acerca de la limpieza y desinfección, consulte las páginas 16 y 17 de la sección Cuidado y mantenimiento.

### El dispositivo debe armarse antes de su uso.

#### Información general

- Los componentes encajan herméticamente ya que están diseñados para evitar que el medicamento se derrame.
- Sostenga firmemente el dispositivo con las dos manos.
- Coloque las piezas correctamente. Es probable que escuche un clic cuando instala alguna de las piezas.

1. Coloque la tapa de la malla en el depósito para el medicamento.



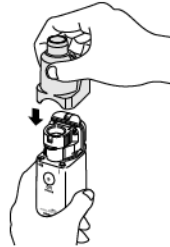
## PREPARACIÓN DEL NEBULIZADOR PARA SU USO

2. Conecte el depósito para el medicamento a la unidad principal.



La instalación ha finalizado.

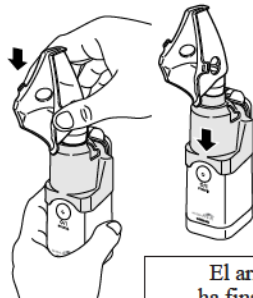
3. Conecte el adaptador para la mascarilla y boquilla a la unidad principal.



La instalación ha finalizado.

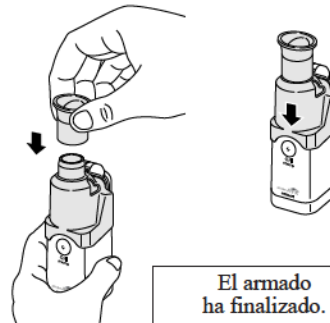
4. Conecte la boquilla o la mascarilla para niños al adaptador para la mascarilla y boquilla.

• Cómo conectar la mascarilla para niños



El armado ha finalizado.

• Cómo conectar la boquilla



El armado ha finalizado.



## INSTALACIÓN DE LAS PILAS

Este dispositivo funciona con dos (2) pilas alcalinas AA o dos (2) pilas recargables NiMH AA.

### PRECAUCIÓN

No instale pilas gastadas junto con pilas nuevas.  
No combine diferentes tipos de pilas.  
Quite las pilas si no se va a utilizar el dispositivo durante tres meses o más.

#### 1. Retire la tapa del compartimiento de las pilas.

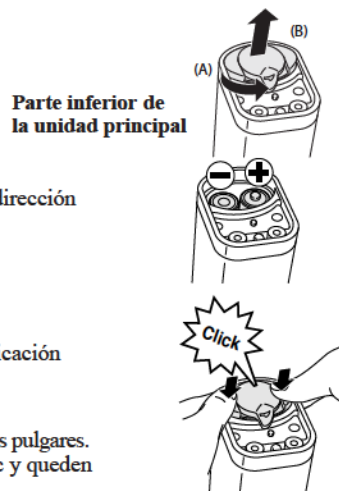
- Gire la palanca de la tapa del compartimiento de las pilas en la dirección de la flecha, como se indica en el dibujo.
- Retire la tapa del compartimiento de las pilas. Esta tapa puede parecer que está demasiado ajustada, ya que fue diseñada para impedir que ingresen líquidos dentro del dispositivo.

#### 2. Coloque las pilas.

Alinee de forma correcta las polaridades (+ y -) con las marcas de indicación de las pilas que están en el dispositivo.

#### 3. Vuelva a colocar la tapa.

Presione ambos extremos de la tapa del compartimiento de las pilas con los pulgares. Presione firmemente hasta que escuche que ambas pestañas hagan clic y queden correctamente trabadas.



### Vida útil y recambio de las pilas

#### Pilas alcalinas

- El dispositivo se puede utilizar durante aproximadamente 8 días si se lo hace funcionar durante 30 minutos por día.
- El indicador de pilas descargadas (luz anaranjada) titila para indicar que las pilas tienen poca carga. Cambie las dos pilas por pilas nuevas.
- El indicador de pilas descargadas (luz anaranjada) se enciende para indicar que las pilas están agotadas. El dispositivo no funcionará. Reemplace inmediatamente las dos pilas por otras nuevas.

#### Pilas NiMH recargables

- El dispositivo se puede utilizar durante aproximadamente 8 días si se lo hace funcionar durante 30 minutos por día cuando las pilas están totalmente cargadas.
- El indicador de pilas descargadas (luz anaranjada) titila para indicar que las pilas recargables tienen poca o casi nada de carga. Si el dispositivo no nebuliza, recargue inmediatamente las pilas.
- Recargue las pilas con un cargador que esté disponible en el mercado y que sea adecuado para las pilas que se utilizan en el dispositivo.
- El transformador de CA no funciona como un cargador de batería.

## USO DEL TRANSFORMADOR DE CA

El dispositivo está diseñado para no tomar energía de las pilas mientras se usa el transformador de CA. El transformador de CA no es un cargador de pilas.



### ADVERTENCIA

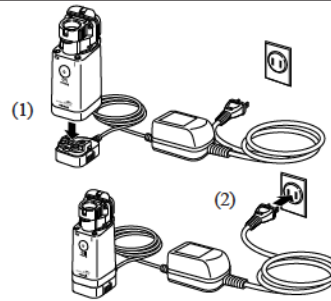
Use sólo el transformador de CA diseñado por Omron para este dispositivo.  
El uso de cualquier otro transformador de CA puede dañar el dispositivo.

### Para conectar el transformador de CA a la unidad principal

- (1) Coloque la unidad principal en la base de conexión del transformador de CA, tal como se indica en la siguiente figura.

**NOTA:** Se escuchará un clic y quedará sujeta a la base.

- (2) Conecte el enchufe del transformador de CA a un tomacorriente de 120V.



La conexión se completó.



### ADVERTENCIA

No enchufe ni desenchufe el cable de alimentación del tomacorriente con las manos mojadas.



### PRECAUCIÓN

No sobrecargue los tomacorrientes. Enchufe el dispositivo en un tomacorriente con el voltaje adecuado.



### PRECAUCIÓN

No use cables prolongadores. Enchufe el cable de alimentación directamente en el tomacorriente.



### PRECAUCIÓN

Desenchufe el cable de alimentación del tomacorriente antes de limpiar el dispositivo.

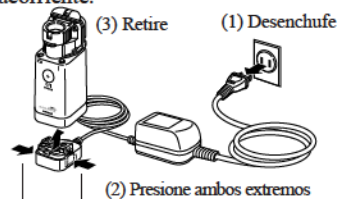
### Para quitar el transformador de CA de la unidad principal

- (1) Desconecte el enchufe del transformador de CA del tomacorriente.
- (2) Presione ambos lados de la base de conexión para desbloquear la unidad principal.
- (3) Retire la unidad principal.



### PRECAUCIÓN

Desenchufe el cable de alimentación del tomacorriente después de usar el dispositivo.



## LLENADO DEL DEPÓSITO PARA EL MEDICAMENTO

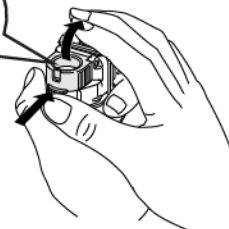
Quite la boquilla o la mascarilla y el adaptador para la mascarilla y boquilla de la unidad principal.

### 1. Abra la tapa de la malla.

Sostenga el dispositivo firmemente con las manos.



Levante la tapa de la malla mientras presiona el borde hacia arriba con el pulgar.



### 2. Llene el depósito para el medicamento.



#### ADVERTENCIA

La pentamidina no es un medicamento aprobado para usar con este dispositivo.



#### ADVERTENCIA

No use agua mineral o agua corriente en el nebulizador para fines de nebulización.

Tenga cuidado y evite que la tapa de la malla se cierre como se indica en el dibujo. La capacidad máxima del depósito para el medicamento es de 7 ml.



#### PRECAUCIÓN

No agregue más de 7 ml de medicamento en el recipiente de medicamento.



#### PRECAUCIÓN

Para evitar que el dispositivo se dañe, agregue el medicamento lentamente. No permita que el medicamento se derrame por el orificio del depósito para el medicamento.



Verifique que la tapa de la malla esté cerrada.



### 3. Cierre la tapa de la malla.



#### PRECAUCIÓN

Para evitar que el dispositivo se dañe, asegúrese de que la tapa de la malla esté colocada correctamente. De lo contrario, el medicamento se derramará.

### 4. Conecte el adaptador para la mascarilla y boquilla a la unidad principal.

Conecte la boquilla o la mascarilla para niños al adaptador para la mascarilla y boquilla.

**NOTA:** Para obtener instrucciones acerca de cómo conectar el adaptador para la mascarilla y boquilla, consulte la página 10 de la sección Armado de la unidad.

## SELECCIÓN DEL MODO DE NEBULIZACIÓN

Este dispositivo funciona en modo de nebulización continua o en modo de nebulización manual.

### • Modo de nebulización continua

Para utilizar el dispositivo en modo de nebulización continua, mantenga presionado el botón de APAGADO/ENCENDIDO durante 1 segundo.

Pulse el botón de ENCENDIDO/APAGADO nuevamente para detener la nebulización.



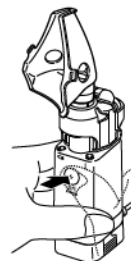
Presione y mantenga presionado el botón de ENCENDIDO/APAGADO con el dedo durante 1 segundo.

### • Modo de nebulización manual

En el modo de nebulización manual, el dispositivo sólo funcionará cuando presione y mantenga presionado el botón de ENCENDIDO/APAGADO. En este modo, puede inhalar el tiempo que necesite.

Para utilizar el dispositivo en modo de nebulización manual, mantenga presionado el botón de ENCENDIDO/APAGADO durante por lo menos 2 segundos.

Presione y mantenga presionado el botón de ENCENDIDO/APAGADO para iniciar la nebulización.



Presione y mantenga presionado el botón de ENCENDIDO/APAGADO con el dedo durante 2 segundos.

**NOTA:** El indicador de encendido (luz verde) estará encendido durante la nebulización.

## USO DEL DISPOSITIVO



### ADVERTENCIA

Para el tipo, la dosis y el régimen de medicamento, siga las instrucciones del médico.



### ADVERTENCIA

Siempre deseche el medicamento que queda en el recipiente después de cada uso. Utilice medicamento nuevo cada vez que use el dispositivo.



### PRECAUCIÓN

Se requiere una supervisión estricta cuando este dispositivo es usado por , o cerca de bebés, niños o personas enfermas.



### PRECAUCIÓN

Inspeccione la unidad principal y las piezas del nebulizador antes de usar el dispositivo. Asegúrese de que las piezas no estén dañadas, de que el dispositivo esté armado correctamente y de que el dispositivo funcione normalmente.



### PRECAUCIÓN

No haga funcionar el dispositivo a temperaturas superiores a los +104 °F (+40 °C).



### PRECAUCIÓN

Este dispositivo está aprobado para uso en seres humanos solamente.

1. Inclínele levemente la unidad principal hacia usted para sumergir la tapa de la malla vibradora en el medicamento.

**NOTA:** Si el vibrador no está sumergido en el medicamento, el dispositivo no nebulizará.

2. Comience a inhalar en una posición relajada.
3. Coloque los labios ligeramente alrededor de la boquilla. Si utiliza la mascarilla para niños, colóquela ligeramente contra la cara.
4. Comience el tratamiento según las indicaciones del médico.
5. Pulse el botón de ENCENDIDO/APAGADO para apagar el dispositivo cuando termine el tratamiento.

**NOTA:** El dispositivo cuenta con un temporizador incorporado que lo apaga aproximadamente 30 minutos después de que ha sido encendido.

Cuando utilice el transformador de CA, quite el enchufe del tomacorriente.

## LIMPIEZA DESPUÉS DE CADA USO

Si sigue las instrucciones de limpieza después de cada uso, evitará que cualquier medicamento que haya quedado en el depósito se seque y se adhiera a la tapa de la malla, lo que afectaría la efectividad de la nebulización.

**Lave el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y boquilla después de cada uso.**



### ADVERTENCIA

Enjuague las piezas del nebulizador después de cada uso. Seque las piezas inmediatamente después de lavarlas.



### PRECAUCIÓN

Para evitar que el dispositivo se dañe:

- No enjuague ni sumerja la unidad principal en ningún líquido.
- No lave ni enjuague ninguna de las piezas con un chorro de agua de alta presión.
- No toque la malla con la mano ni con ningún otro objeto.

1. Quite la boquilla o la mascarilla y el adaptador para la mascarilla y boquilla de la unidad principal.
2. Retire el depósito para el medicamento de la unidad principal.
3. Abra el depósito para el medicamento y elimine cualquier resto que pudiera quedar.
4. Conecte el depósito para el medicamento a la unidad principal. Abra la tapa de la malla.
5. Vierta una pequeña cantidad de agua destilada en el depósito para el medicamento y cierre la tapa de la malla.
6. Encienda el dispositivo para nebulizar el agua destilada durante 1 ó 2 minutos para eliminar los restos de medicamento que pudieran quedar en los orificios de la malla.
7. Apague el dispositivo y quite el depósito para el medicamento de la unidad principal.
8. Quite la tapa de la malla del depósito para el medicamento y elimine cualquier resto de agua destilada que pudiera quedar en el depósito.
9. Enjuague con agua destilada el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y boquilla.
10. Seque cuidadosamente el exceso de agua con un paño suave y limpio o deje que las piezas se sequen solas en un ambiente limpio.
11. Arme el dispositivo. Guarde el dispositivo en el estuche o en un lugar limpio.



## DESINFECCIÓN DIARIA

Desinfecte el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y boquilla después del último tratamiento de cada día.

### PRECAUCIÓN

Para evitar que el dispositivo se dañe:

- No enjuague ni sumerja la unidad principal en ningún líquido.
- No lave ni enjuague ninguna de las piezas con un chorro de agua de alta presión.
- No toque la malla con la mano ni con ningún otro objeto.

1. Prepare una solución con alguna de las siguientes soluciones: Vinagre (1 parte de vinagre blanco y 3 partes de agua destilada) O detergente o jabón suave (jabón para lavavajillas en agua destilada).

### PRECAUCIÓN

No utilice un blanqueador de uso doméstico. La malla se oxidará y la tapa de la malla no se podrá usar.

2. Levante la tapa de la malla y vierta una pequeña cantidad de solución desinfectante dentro del depósito para el medicamento.
3. Encienda el dispositivo para nebulizar la solución desinfectante durante 1 ó 2 minutos.
4. Apague el dispositivo y quite el depósito para el medicamento de la unidad principal.
5. Quite la tapa de la malla del depósito para el medicamento y elimine cualquier resto de solución desinfectante que pudiera quedar en el depósito.
6. Enjuague el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y boquilla en la solución desinfectante durante 10 ó 15 minutos.
7. Enjuague con agua destilada el depósito para el medicamento, la tapa de la malla, la mascarilla, la boquilla y el adaptador para la mascarilla y boquilla.

### ADVERTENCIA

No deje solución de limpieza en las piezas del nebulizador. Enjuague las piezas del nebulizador con agua destilada después de desinfectar.

8. Seque cuidadosamente el exceso de agua con un paño suave y limpio o deje que las piezas se sequen solas en un ambiente limpio.
9. Arme el dispositivo. Guarde el dispositivo en el estuche o en un lugar limpio.

## CUIDADO DEL DISPOSITIVO

**Para mantener el dispositivo en buen estado y proteger la unidad para que no se dañe, siga estas instrucciones:**

- ⚠ Mantenga el dispositivo fuera del alcance de los bebés y niños si no están bajo estricta supervisión. El dispositivo puede contener piezas pequeñas que se pueden tragar.
- ⚠ Guarde el dispositivo y los componentes en un lugar limpio y seguro.
- ⚠ No use ni guarde el dispositivo en lugares húmedos como, por ejemplo, el baño. Use el dispositivo dentro de los límites de temperatura y humedad de funcionamiento.
- ⚠ No deje el dispositivo ni sus piezas en lugares que estén expuestos a temperaturas extremas o cambios en la humedad, como por ejemplo en un vehículo durante los meses de calor o donde quede expuesto a la luz directa del sol.
- ⚠ No someta al dispositivo ni a ninguno de los componentes a golpes fuertes como, por ejemplo, dejarlo caer al suelo.
- ⚠ No desarme ni trate de reparar el dispositivo ni los componentes.
- ⚠ Use sólo las piezas y los accesorios autorizados por Omron. Las piezas y los accesorios que no están aprobados para ser usados con el dispositivo pueden causar daños en la unidad.
- ⚠ Sólo haga funcionar el dispositivo para el fin para el que está diseñado. No use el dispositivo para ningún otro fin.
- ⚠ Los cambios o las modificaciones que no hayan sido aprobados por Omron Healthcare dejarán sin efecto la garantía del usuario.
- ⚠ Respete las normas locales vigentes al desechar el dispositivo, los componentes y los accesorios opcionales. Violar las normas establecidas para su eliminación puede provocar contaminación ambiental.
- ⚠ Retire las pilas si no va a utilizar la unidad durante tres meses o un período más prolongado. Siempre reemplace todas las pilas por pilas nuevas al mismo tiempo. No utilice diferentes tipos de pilas al mismo tiempo.

## CUIDADO DEL DISPOSITIVO

### Limpieza de la unidad principal

Limpie la carcasa de la unidad principal con un paño suave humedecido con agua o detergente suave. Limpie la carcasa y séquela inmediatamente con un paño suave y limpio.



#### PRECAUCIÓN

No coloque ni trate de secar el dispositivo o alguna de sus piezas en un horno de microondas.



#### PRECAUCIÓN

Para evitar que el dispositivo se dañe:

- No enjuague ni sumerja la unidad principal en ningún líquido.
- No limpie la unidad principal con limpiadores abrasivos ni con ningún tipo de producto químico.
- No permita que la humedad entre en contacto con los electrodos o con la entrada del transformador de CA en la unidad principal o en la base de conexión del transformador de CA.

### Transporte del dispositivo en el estuche

Arme el dispositivo, colocando la tapa de la malla y el depósito para el medicamento en la unidad principal. Coloque la cubierta de la unidad principal en el dispositivo.

Coloque el dispositivo en el estuche, como se indica en el dibujo.

El adaptador para la boquilla y la mascarilla se puede colocar fácilmente en el estuche para transportarlo junto con la unidad principal.

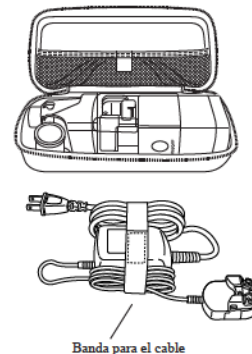


#### PRECAUCIÓN

Para evitar que el dispositivo se dañe

- No transporte ni deje el nebulizador con medicamento o agua destilada en el depósito para el medicamento.
- No coloque el transformador de CA en el estuche.  
El estuche no está diseñado para transportar el transformador de CA opcional.

Para transportar el transformador de CA, enrolle el cable de alimentación del transformador de CA y sujételo a la unidad principal del adaptador de CA con la banda para el cable, como se indica en el dibujo.



## GUÍA PARA LA SOLUCIÓN DE PROBLEMAS

PROBLEMA	CAUSA	SOLUCIONES
El indicador de encendido no se enciende.	El transformador de CA no está conectado a un tomacorriente. La base de conexión no está conectada a la unidad principal. Las pilas no se instalaron correctamente. Las pilas tienen poca carga.	Apague la unidad con el interruptor. Conecte el enchufe de alimentación a un tomacorriente. Encienda el dispositivo. Asegúrese de que la unidad haya encajado en la base de conexión. Vuelva a colocar las pilas. Reemplace ambas pilas gastadas de forma inmediata. Recargue las pilas NiMH con un cargador que esté disponible en el mercado.
	Hay restos de medicamento seco en los componentes y accesorios.	Limpie y desinfecte los componentes y accesorios.
	Se debe reemplazar la tapa de la malla.	Reemplace la tapa de la malla.
El indicador de encendido está prendido, pero la unidad no nebuliza.	Las pilas tienen poca carga.	Reemplace el mismo tipo de pilas con pilas alcalinas nuevas o cargue las pilas NiMH.
	El depósito para el medicamento tiene mucha cantidad de medicamento.	Llene el depósito para el medicamento con la cantidad correcta de medicamento recetado. La cantidad máxima es 7 ml.
	Se puede haber acumulado líquido alrededor de los electrodos de la unidad principal.	Absorba toda la humedad con un paño suave.
	Hay líquido en la parte superior de la tapa de la malla.	Quite el líquido visible con un paño suave, con cuidado, para no dañar la malla.
	El medicamento no ha tenido contacto con las piezas de nebulización.	Incline ligeramente la unidad principal hacia usted con el botón de ENCENDIDO/APAGADO apuntando hacia abajo.

## GUÍA PARA LA SOLUCIÓN DE PROBLEMAS

PROBLEMA	CAUSA	SOLUCIONES
La unidad está encendida; sin embargo, nebuliza de forma suave o demora mucho tiempo por cada tratamiento.	El depósito para el medicamento no está colocado correctamente.	Asegúrese de que el depósito para el medicamento esté colocado correctamente.
	Se debe limpiar la unidad.	Siga las instrucciones de limpieza después de cada uso.
	Se debe desinfectar la unidad.	Siga las instrucciones para la desinfección.
	Las pilas tienen poca carga.	Reemplace las pilas según las instrucciones de instalación.
	Las velocidades de nebulización varían en base al medicamento que se utiliza.	Los tiempos de duración de un tratamiento pueden variar según los medicamentos y los pacientes.

## INFORMACIÓN SOBRE LA GARANTÍA

### GARANTÍAS LIMITADAS

Su Nebulizador NE-U22V, salvo la tapa de la malla y los accesorios, estará garantizado contra defectos de materiales y mano de obra que surjan dentro de los 2 años a partir de la fecha de compra, si se usa de acuerdo con las instrucciones suministradas con el dispositivo. La garantía a la que se hace referencia anteriormente se extiende sólo al comprador minorista original.

Nos comprometemos a reparar o reemplazar sin cargo y según nuestro criterio su nebulizador Omron. La reparación o el reemplazo son nuestra única responsabilidad y su único recurso conforme a las garantías anteriormente mencionadas.

Para recibir el servicio de garantía, póngase en contacto con el servicio de atención al cliente de Omron Healthcare llamando al 1-800-634-4350 para obtener la dirección donde se realizan las reparaciones y las tarifas de envío y manipulación. Para obtener información relativa al servicio de garantía, visite nuestro sitio Web en: [www.omronhealthcare.com](http://www.omronhealthcare.com).

Adjunte el comprobante de compra. Incluya una carta con su nombre, dirección, número de teléfono y la descripción del problema específico. Empaque el producto cuidadosamente para evitar que se dañe durante el traslado. Dado que existe la posibilidad de pérdida durante el traslado, le recomendamos que asegure el producto con solicitud de acuse de recibo.

**TODAS LAS GARANTÍAS IMPLÍCITAS, INCLUIDAS, ENTRE OTRAS, LAS GARANTÍAS IMPLÍCITAS DE COMERCIALIZACIÓN Y APTITUD PARA UN PROPÓSITO EN PARTICULAR, SE LIMITAN A LA DURACIÓN DE LA GARANTÍA ESCRITA PERTINENTE QUE APARECE ANTERIORMENTE.** Algunos estados no aceptan limitaciones en cuanto a la duración de una garantía implícita, de modo que es posible que la limitación anteriormente mencionada no se aplique en su caso.

**OMRON NO SERÁ RESPONSABLE DE LA PÉRDIDA DE USO O CUALQUIER OTRO COSTO, GASTO O DAÑO INCIDENTAL, INDIRECTO O RESULTANTE.** Algunos estados no aceptan la exclusión o limitación de los daños incidentales o resultantes, de modo que es posible que las exclusiones anteriores no se aplique en su caso.

Esta garantía le otorga derechos legales específicos, y es posible que también le correspondan otros derechos que pueden variar de un estado a otro.

### SERVICIO DE ATENCIÓN AL CLIENTE (EE.UU. y CANADÁ)

Visite nuestro sitio Web en: [www.omronhealthcare.com](http://www.omronhealthcare.com)

Llame sin cargo al: 1-800-634-4350



## DECLARACIÓN DE LA FCC

**Nota:**

**POTENCIAL DE INTERFERENCIA DE RADIO/TELEVISIÓN (para EE.UU. solamente)**

Este producto ha sido probado y cumple con los límites de un dispositivo digital de Clase B, de acuerdo con la parte 15 de las normas de la FCC.

Estos límites fueron diseñados para proporcionar una protección razonable contra interferencias perjudiciales cuando se utilice el equipo en una instalación residencial. El producto genera, utiliza y puede irradiar energía de radiofrecuencia y, si no se instala y utiliza de acuerdo con las instrucciones, puede provocar interferencias perjudiciales en las comunicaciones por radio. Sin embargo, no se puede garantizar que no se producirán interferencias en una instalación en particular. Si el producto provoca interferencias perjudiciales en la recepción de radio o televisión, lo que se puede determinar encendiendo y apagando el equipo, se sugiere que el usuario intente corregir la interferencia a través de una o más de las siguientes medidas:

- Reoriente o reubique la antena receptora
- Aumente la distancia entre el equipo y el receptor.
- Conecte el equipo a un tomacorrientes que esté en un circuito distinto de aquél al que se encuentra conectado el receptor.
- Consulte al distribuidor o a un técnico experimentado en radio/TV para obtener más información.

**POTENCIAL DE INTERFERENCIA DE RADIO/TELEVISIÓN (para Canadá solamente)**

Este aparato digital no excede los límites de Clase B para las emisiones de ruido de radio de los dispositivos digitales tal como se establece en la norma con respecto a equipos que causan interferencia denominada "Dispositivos digitales", ICES-003 del Departamento Canadiense de Comunicaciones.

Cet appareil numérique respecte les limites de bruits radioélectriques applicables aux appareils numériques de Classe B prescrites dans la norme sur le matériel brouilleur: "Appareils Numériques", ICES-003 édictée par le ministre des communications.

Todo cambio o modificación que no esté expresamente aprobado por la parte responsable encargada del cumplimiento podrá anular la autoridad del usuario para operar el equipo.

## ESPECIFICACIONES

<b>Modelo:</b>	<b>Nebulizador Omron NE-U22V con V.M.T.*</b>
Fuente de alimentación:	CC 3V CA 120V 60 Hz (con adaptador de CA)
Consumo eléctrico:	1.5 W
Velocidad de nebulización:	0.25 ml/min. mínimo
Tamaño de las partículas:	MMD aproximadamente 5µm
Capacidad de medicamento:	7 ml máximo
Temperatura/Humedad de funcionamiento:	+50 °F a +104 °F (+10 °C a +40 °C) / 30% a 85% HR
Temperatura/Humedad/ Presión de aire de almacenamiento:	-4 °F a +140 °F (-20 °C a +60 °C) / 10% a 95% HR / 700hPa a 1060 hPa
Frecuencia de vibración:	180 kHz
Dimensiones:	1.5" (largo) x 2.1" (ancho) x 4.1" (alto) (38 mm x 51 mm x 104 mm)
Peso:	3.4 onzas (97 gramos)
Pilas:	2 pilas alcalinas "AA" o pilas recargables NiMH (no incluidas)
Contenido:	Unidad principal, depósito para el medicamento, estuche para transportar el dispositivo, tapa de la malla, adaptador para mascarilla y boquilla, video y manual de instrucciones.
Código UPC:	0 73796 45122 6

- Sujeto a modificaciones técnicas sin previo aviso.

Impactador de cascada probado a 13 Ipm (pulgadas por minutos):

	<b>Pulmicort®</b>	<b>Intal®</b>	<b>Salubutamol®</b>
MMD (micrón)	6.76µ	6.43µ	5.79µ
Desviación Estándar Geométrica (GSD, por sus siglas en inglés)	2.08	2.56	2.75
Fracción respirable (% de masa 0.52 a 6 µ)	65.0%	66.0%	73.4%

Tiempo que dura el tratamiento: 5 minutos para 2 ml.

- Tenga en cuenta que las especificaciones pueden variar según el tipo de medicamento utilizado.

## NOTAS

Hecho en Japón

Distribuido por:  
**OMRON HEALTHCARE, INC.**  
1200 Lakeside Drive  
Bannockburn, Illinois 60015  
[www.omronhealthcare.com](http://www.omronhealthcare.com)  
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**APPENDIX 4. INSTRUCTIONS FOR THE USE OF SPIRIVA®  
RESPIMAT®**

## Instructions for Use

SPIRIVA® RESPIMAT® (speh REE vah - RES peh mat)  
(tiotropium bromide)  
inhalation spray

### For Oral Inhalation Only

**Do not spray SPIRIVA RESPIMAT into your eyes.**

Read these Instructions for Use before you start using SPIRIVA RESPIMAT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

You will need to use this inhaler **ONCE A DAY**, at the same time each day. Each time you use it take **TWO PUFFS**.

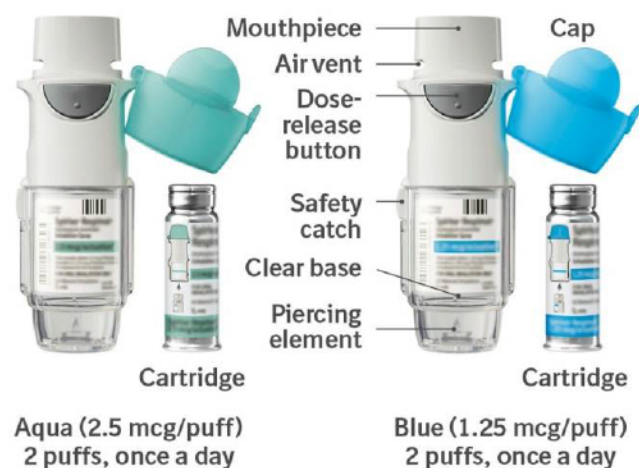
**Use SPIRIVA RESPIMAT exactly as prescribed by your doctor.** Do not change your dose or how often you use SPIRIVA RESPIMAT without talking with your doctor.

**Tell your doctor about all of the medicines you take.** SPIRIVA RESPIMAT may affect the way some medicines work and some other medicines may affect the way SPIRIVA RESPIMAT works. Do not use other inhaled medicines with SPIRIVA RESPIMAT without talking to your doctor.

The SPIRIVA RESPIMAT inhaler has a slow moving mist that helps you inhale the medicine.

**Do not turn the clear base before inserting the cartridge.**

Your SPIRIVA RESPIMAT may have either an aqua or a blue cap, depending on the strength prescribed by your doctor. The steps shown below should be followed.



### How to store your SPIRIVA RESPIMAT inhaler

- Store SPIRIVA RESPIMAT at room temperature 68°F to 77°F (20°C to 25°C).
- Do not freeze your SPIRIVA RESPIMAT cartridge and inhaler.



- If SPIRIVA RESPIMAT has not been used for more than 3 days, release 1 puff towards the ground.
- If SPIRIVA RESPIMAT has not been used for more than 21 days, repeat steps 4 to 6 under the “Prepare for first use” until a mist is visible. Then repeat steps 4 to 6 three more times.
- Keep your SPIRIVA RESPIMAT cartridge and inhaler out of the reach of children.

### How to care for your SPIRIVA RESPIMAT inhaler

Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least once a week. Any minor discoloration in the mouthpiece does not affect your SPIRIVA RESPIMAT inhaler.

### When to get a new SPIRIVA RESPIMAT inhaler

- Your inhaler contains 60 puffs (30 doses) if used as indicated (2 puffs once daily). If you have a sample, your inhaler contains 28 puffs (14 doses) if used as indicated (2 puffs once daily).

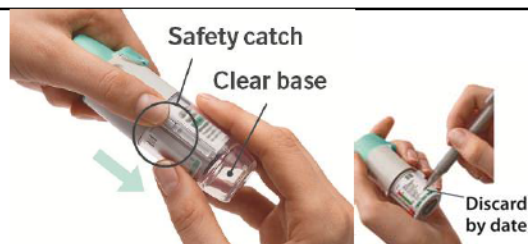






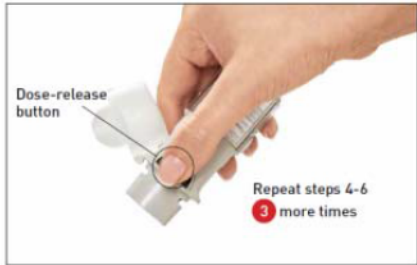
- The dose indicator shows approximately how much medicine is left.
- When the dose indicator enters the red area of the scale you need to get a refill; there is approximately medicine for 7 days left (if you have a sample, there is approximately medicine for 3 days left).
- When the dose indicator reaches the end of the red scale, your SPIRIVA RESPIMAT is empty and automatically locks. At this point, the clear base cannot be turned any further.
- Three months after insertion of cartridge, throw away the SPIRIVA RESPIMAT even if it has not been used, or when the inhaler is locked, or when it expires, whichever comes first.

### Prepare for first use

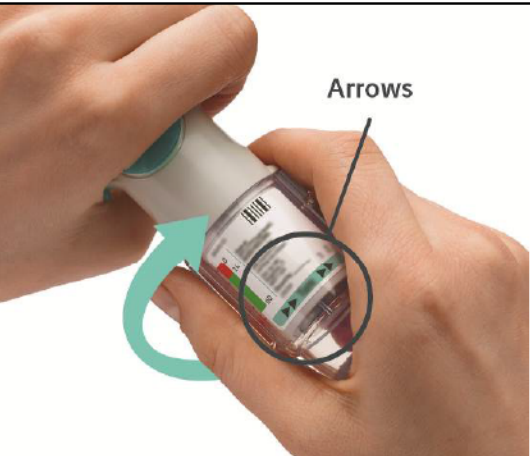
#### 1. Remove clear base


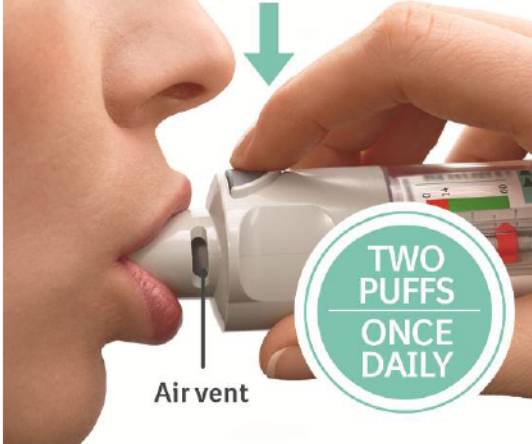
- Keep the cap closed.
- Press the safety catch while firmly pulling off the clear base with your other hand. Be careful not to touch the piercing element.
- Write the discard by date on the label (3 months from the date the cartridge is inserted).



<p><b>2. Insert cartridge</b></p> <ul style="list-style-type: none"> <li>Insert the narrow end of the cartridge into the inhaler.</li> <li>Place the inhaler on a firm surface and push down firmly until it clicks into place.</li> </ul>	 <p>Narrow end</p> <p>"Click"</p>
<p><b>3. Replace clear base</b></p> <ul style="list-style-type: none"> <li>Put the clear base back into place until it clicks.</li> <li>Do not remove the clear base or the cartridge after it has been put together.</li> </ul>	 <p>Clear base</p>
<p><b>4. Turn</b></p> <ul style="list-style-type: none"> <li>Keep the cap closed.</li> <li>Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).</li> </ul>	 <p>Arrows</p>
<p><b>5. Open</b></p> <ul style="list-style-type: none"> <li>Open the cap until it snaps fully open.</li> </ul>	 <p>Cap</p>
<p><b>6. Press</b></p> <ul style="list-style-type: none"> <li>Point the inhaler toward the ground.</li> <li>Press the dose-release button.</li> <li>Close the cap.</li> <li>If you do not see a mist, repeat steps 4 to 6 until a mist is seen.</li> <li><b>After a mist is seen, repeat steps 4 to 6 three more times.</b></li> <li>After complete preparation of your inhaler, it will be ready to deliver the number of puffs on the label.</li> </ul>	 <p>Dose-release button</p> <p>Repeat steps 4-6 3 more times</p>

## Daily use (**I O P**)

<p><b>Turn</b></p> <ul style="list-style-type: none"> <li>Keep the cap closed.</li> <li><b>Turn</b> the clear base in the direction of the arrows on the label until it clicks (half a turn).</li> </ul>	 <p>Arrows</p>
--	--

<p><b>Open</b></p> <ul style="list-style-type: none"> <li>• <b>Open</b> the cap until it snaps fully open.</li> </ul>	
<p><b>Press</b></p> <ul style="list-style-type: none"> <li>• Breathe out slowly and fully.</li> <li>• Close your lips around the mouthpiece without covering the air vents.</li> <li>• Point the inhaler to the back of your throat.</li> <li>• While taking a slow, deep breath through your mouth, <b>Press</b> the dose-release button and continue to breathe in.</li> <li>• Hold your breath for 10 seconds or for as long as comfortable.</li> <li>• Repeat <b>Turn, Open, Press (TOP)</b> for a total of 2 puffs.</li> <li>• Close the cap until you use your inhaler again.</li> </ul>	

## Answers to Common Questions

### It is difficult to insert the cartridge deep enough:

**Did you accidentally turn the clear base before inserting the cartridge?** Open the cap, press the dose-release button, then insert the cartridge.

**Did you insert the cartridge with the wide end first?** Insert the cartridge with the narrow end first.

### I cannot press the dose-release button:

**Did you turn the clear base?** If not, turn the clear base in a continuous movement until it clicks (half a turn).

**Is the dose indicator on the SPIRIVA RESPIMAT pointing to zero?** The SPIRIVA RESPIMAT inhaler is locked after 60 puffs (30 doses). If you have a sample, the SPIRIVA RESPIMAT inhaler is locked after 28 puffs (14 doses). Prepare and use your new SPIRIVA RESPIMAT inhaler.

### I cannot turn the clear base:

**Did you turn the clear base already?** If the clear base has already been turned, follow steps "Open" and "Press" under "Daily use" to get your medicine.

**Is the dose indicator on the SPIRIVA RESPIMAT is pointing to zero?** The SPIRIVA RESPIMAT inhaler is locked after 60 puffs (30 doses). If you have a sample, the SPIRIVA RESPIMAT inhaler is locked after 28 puffs (14 doses). Prepare and use your new SPIRIVA RESPIMAT inhaler.

**The dose indicator on the SPIRIVA RESPIMAT reaches zero too soon:**

**Did you use SPIRIVA RESPIMAT as indicated (2 puffs once daily)?** SPIRIVA RESPIMAT will deliver 60 puffs and last 30 days if used at 2 puffs once daily. If you have a sample, SPIRIVA RESPIMAT will deliver 28 puffs and last 14 days if used at 2 puffs once daily.

**Did you turn the clear base before you inserted the cartridge?** The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.

**Did you spray in the air often to check whether the SPIRIVA RESPIMAT is working?** Once you have prepared SPIRIVA RESPIMAT, no test-spraying is required if used daily.

**Did you insert the cartridge into a used SPIRIVA RESPIMAT?** Always insert a new cartridge into a **NEW** SPIRIVA RESPIMAT.

**What should I do if my SPIRIVA RESPIMAT sprays automatically:**

**Was the cap open when you turned the clear base?** Close the cap, then turn the clear base.

**Did you press the dose-release button when turning the clear base?** Close the cap, so the dose-release button is covered, then turn the clear base.

**Did you stop when turning the clear base before it clicked?** Turn the clear base in a continuous movement until it clicks (half a turn).

**My SPIRIVA RESPIMAT doesn't spray:**

**Did you insert a cartridge?** If not, insert a cartridge.

**Did you repeat Turn, Open, Press (TOP) less than three times after inserting the cartridge?** Repeat Turn, Open, Press (TOP) three times after inserting the cartridge as shown in steps 4 to 6 under "Prepare for first use".

**Is the dose indicator on the SPIRIVA RESPIMAT pointing to 0?** You have used up all your medicine and the inhaler is locked.

For more information about SPIRIVA RESPIMAT or a video demonstration on how to use SPIRIVA RESPIMAT, go to [www.spiriva.com](http://www.spiriva.com), or scan the code below. You may also call 1-800-542-6257 or (TTY) 1-800-459-9906 for further information about SPIRIVA RESPIMAT.



This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877 USA

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## **APPENDIX 5. GUIDANCE FOR SPIROMETRY**

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society / European Respiratory Society Standardization of Spirometry. All spirometers must be calibrated.

### **Preparing the test subject**

On study days when spirometry will be performed, subjects will refrain from the following:

- Coffee, tea, chocolate, cola, other caffeine-containing beverages, foods, ice-cold beverages and heavy meals within 2 hours prior to spirometry. Decaffeinated beverages are acceptable.
- Smoking will not be permitted in 30-minute period prior to spirometry testing. As such smoking will be discouraged for 12 hours prior to spirometry.
- Strenuous activity for 12 hours prior to spirometry testing. Exposure to cold temperatures, environmental smoke, dust or areas with strong odors (eg, perfumes).
- Use of rescue medication within 6 hours prior to spirometry testing.

Prior to Screening spirometry for subject's eligibility, subjects taking prohibited medications should undergo washout for appropriate period as per [Appendix 1](#).

At Visit 3 through Visit 5, dosing of the study drug has to be withheld until baseline or trough spirometry, as applicable, has been conducted.

### **Performing Spirometry**

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry will be conducted with the subject in a seated position and it is preferable that the same trained individual performs the tests for a given subject by using the same spirometer. Spirometry assessments will be initiated between 6:00 AM and 10:00 AM. The start time of the first spirometry effort will be used for all spirometry time points recorded. Spirometry, an effort-dependent test, requires careful instruction to and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

For FEV<sub>1</sub> and FVC, at least 3 (and no more than 8) acceptable maneuvers will be obtained; the largest FEV<sub>1</sub> and FVC from the 3 acceptable maneuvers will be recorded, regardless of whether they are from the same maneuver.

### **Acceptability Criteria of a Maneuver**

An acceptable maneuver has the following characteristics:

- Without unsatisfactory start of expiration, characterized by excessive hesitation or false start extrapolated volume or EV >5% of FVC or 0.150 L, whichever is greater;



- Without cough, especially during the first second of the maneuver, or any other cough that, in the technician's judgment, interferes with the measurement of accurate results;
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further).
- Without Valsalva maneuver (no glottis closure) or obstruction by tongue or dentures or hesitation during the maneuver that causes a cessation of airflow;
- Without a leak;
- Without evidence of an extra breath being taken during the maneuver.

**Repeatability Criteria**

The 2 largest values of FVC must be within 0.150 L of each other.

The 2 largest values of FEV<sub>1</sub> must be within 0.150 L of each other.

If both of these criteria are met, the test session may be concluded.

If both of these criteria are not met:

- Continue testing until both of the criteria are met with analysis of additional acceptable spirograms

Or

- A total of 8 tests have been performed

Or

- The subject cannot or should not continue.

Save, as a minimum, the 3 satisfactory maneuvers.

**Testing for Screening Spirometry**

Screening spirometry will be performed during the screening period prior to Visit 2 after a washout period if applicable (Refer to [Appendix 1](#)). Both pre- and post-bronchodilator spirometry will be performed for subject eligibility. Spirometry will be conducted before and approximately 30 minutes following inhalation of albuterol/salbutamol (400 µg ie, 4 inhalations, approximately 30 seconds apart) from an MDI (100 µg per inhalation).

## **APPENDIX 6. SUMMARY OF CHANGES IN CURRENT PROTOCOL AMENDMENT**

### **PROTOCOL GSP304-201**

#### **PROTOCOL AMENDMENT 2.0 SUMMARY OF CHANGES**

**A DOSE RANGING, PARALLEL GROUP, ACTIVE (SPIRIVA® RESPIMAT®) AND PLACEBO-CONTROLLED STUDY TO ASSESS RELATIVE BIOAVAILABILITY, PHARMACODYNAMICS AND SAFETY OF THREE DOSES OF TIOTROPIUM BROMIDE INHALATION SOLUTION IN SUBJECTS WITH MILD TO MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

#### **PROTOCOL HISTORY**

PROTOCOL VERSION 1.0, 11-Oct-2016  
PROTOCOL VERSION 2.0 (Amendment 1.0), 05-Jan-2017  
PROTOCOL VERSION 3.0 (Amendment 2.0), 11-Apr-2017

### Description of Changes in Protocol Version 3.0 dated 11-Apr-2017

Minor editorial changes for accuracy, clarity, and consistency have been made throughout the document and are not included in the description(s) below.

#### A. Details of Substantial Changes to the Protocol

From Original Protocol Version 2.0, 05-Jan-2017	To Protocol Version 3.0 (Amendment 2.0), 11-Apr-2017	Rationale for Amendment
1. 8.2, Subject Exclusion Criteria, added new exclusion criterion 9		
Used to read: (Not Applicable)	Added: <b>9. Subjects with a screening serum creatinine value &gt;1.5 mg/dL</b> Subsequent exclusion criteria have been renumbered 10 through 30.	PK considerations regarding tiotropium excretion by the renal pathway.
2. 8.2, Subject Exclusion Criteria, former exclusion criterion 22 (now exclusion criterion 23)		
Used to read: 22. Subject has a history or suspected history of abuse of a barbiturate, amphetamine, or narcotic and/or has a positive screening result for any of these substances at study start	Now reads: <b>23. Subject has a positive serum alcohol test during screening. Subjects with a known history of alcohol use may be enrolled in the study if the alcohol use is not indicative of abuse, as considered by the Investigator. Note: Positive drug screening results are not exclusionary for prescription narcotics, amphetamines, or barbiturates, if taken only as prescribed under the supervision of a physician for a well-documented medical indication, without any evidence or suspicion of abuse. However, methadone and cannabinoids are exclusionary for this study even when taken by prescription.</b>	Expanded criterion to include subjects using prescription therapies (that do not affect tiotropium PK) if used for well-documented medical indication. Renumbered due to addition of Exclusion Criterion #9.
3. 8.2, Subject Exclusion Criteria, former exclusion criterion 25 (now exclusion criterion 26)		
Used to read: 25. Subject has received oral anticoagulant therapy within 90 days before screening except use of low dose aspirin (up to 325 mg daily) to prevent heart attack or a stroke.	Now reads: <b>26. Subject has received oral anticoagulant therapy within 90 days before screening except use of low dose aspirin (up to 325 mg daily) to prevent heart attack or a stroke. Certain types of</b>	Elaboration of Exclusion Criterion #26 to allow Medical Monitor discretion to distinguish antiplatelet drugs on a case by case basis. Renumbered due to addition of Exclusion Criterion #9.

	anticoagulant therapy (ie, clopidogrel, prasugrel) may be permitted, but all must be reviewed on a case-by-case basis with the Medical Monitor.	
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## B. Details of Non-substantial Changes to the Protocol

From Original Protocol Version 2.0, 05-Jan-2017	To Protocol Version 3.0 (Amendment 2.0), 11-Apr-2017	Rationale for Amendment
1. Sponsor's Signature		
Used to read: [REDACTED] Vice President, Clinical Sciences, Respiratory Glenmark Pharmaceuticals 750 Corporate Drive, Mahwah, NJ 07430, USA E-mail: [REDACTED]@glenmarkpharma.com	Now reads: [REDACTED] Executive Director, Clinical Sciences, Respiratory Glenmark Pharmaceuticals 750 Corporate Drive, Mahwah, NJ 07430, USA E-mail: [REDACTED]@glenmarkpharma.com	Change of Clinical Lead
2. Synopsis, Pharmacokinetic Assessments		
Used to read: In addition, urine will be collected into pre-weighed containers at pre-dose (within 1 hour prior to dosing), and at the following intervals post-dose from 0-6, 6-12, and 12-24 hours on Day 1 and Day 21. Collection times and the accurate volume of urine will be noted.	Now reads: In addition, urine will be collected into pre-weighed containers at pre-dose (within 1 hour prior to dosing), and at the following intervals post-dose from 0-6, 6-12, and 12-24 hours on Day 1 and Day 21. Collection <del>times</del> <b>time intervals</b> and the accurate <del>volume of urine</del> <b>weights of containers before and after urine collection at each interval</b> will be noted.	Clarification of procedure.
3. Synopsis, Pharmacodynamic, Biomarker, and Pharmacogenomic Assessments; Table 2, Schedule of Assessments Footnote 10; Section 11.2.2.2, Pharmacodynamic Assessments		
Used to read: ... On Day 1 and Day 21, FEV <sub>1</sub> will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes (±1 minute),...	Now reads: ... On Day 1 and Day 21, FEV <sub>1</sub> will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes (± <del>1</del> <b>3</b> minutes),...	Increase of the allowable time window at the 5 minute post-dose time point due to multiple clinical assessments occurring at this time point
4. Synopsis, Statistical Methods; Section 13.2, Analysis Sets		

<p>Used to read: Per Protocol Analysis Set (PP)</p> <p>This will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have any major protocol deviations. Major protocol deviations will be defined in the SAP.</p> <p>PK Analysis Set (PKAS)</p> <p>This will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have any major protocol deviations. The PKAS will be used to analyze the PK endpoints unless otherwise specified in the SAP.</p>	<p>Now reads:</p> <p>This will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have <del>any</del> <b>exclusionary</b> major protocol deviations. Major <del>protocol</del> <b>and exclusionary protocol</b> deviations <b>and PP exclusions</b> will be defined in the SAP <b>and by clinical review prior to unblinding</b>.</p> <p>PK Analysis Set (PKAS)</p> <p>This will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have <del>any major</del> <b>exclusionary major</b> protocol deviations. The PKAS will be used to analyze the PK endpoints unless otherwise specified in the SAP. <b>Major and exclusionary protocol deviations will be defined in the SAP and by clinical review prior to unblinding.</b></p>	<p>To define exclusionary protocol deviations that would exclude subjects from analysis, and to clarify how major and exclusionary protocol deviations will be determined.</p>
5. Table 2, Schedule of Assessments, Footnote 4 added		
<p>Used to read: (Not applicable)</p>	<p>Added:</p> <p>New footnote 4 to 12-lead ECG on Screening Visit within the table.</p> <p>4. Triplicate ECG will be performed at the screening visit.</p> <p>All subsequent footnotes have been renumbered.</p>	<p>Clarification of ECG procedure at Screening visit to align with exclusion criterion number 7.</p>
6. Table 2, Schedule of Assessments, Footnote 8		
<p>Used to read:</p> <p>8. On days on which subject visits are scheduled, subjects will take the study drug at the Investigator site (ie, after any required pre-dose blood samples and pre-dose PD measures have been collected). On all other days, subjects will be requested to take the study medication at home as instructed by the study staff.</p>	<p><b>Now reads:</b></p> <p>8. On days on which subject visits are scheduled, subjects will take the study drug at the Investigator site (ie, after any required pre-dose blood samples and pre-dose PD measures have been collected), <b>EXCEPT on Day 20 when subjects will be requested to take the study medication at home as instructed by the study staff.</b> On all other days, subjects will be requested to take the study medication at home as instructed by the study staff.</p>	<p>Clarification of subject dosing procedure for Day 20.</p>



7. Section 10.5, Administration		
<p>Used to read: On days where subject visits are scheduled, subjects will bring all used and unused study drug (GSP304/GSP304 placebo or Spiriva® Respimat®) and rescue medication containers to each study visit, along with the nebulizer, if required for treatment administration, per randomization group. On all other days, subjects will be requested to take the study medication at home as instructed by the study staff.</p>	<p>Now reads: On days where subject visits are scheduled, subjects will bring all used and unused study drug (GSP304/GSP304 placebo or Spiriva® Respimat®) and rescue medication containers to each study visit, along with the nebulizer, if required for treatment administration, per randomization group <b>EXCEPT on Day 20 when subjects will be requested to take the study medication at home as instructed by the study staff.</b> On all other days, subjects will be requested to take the study medication at home as instructed by the study staff.</p>	<p>Clarification of subject dosing procedure for Day 20.</p>
8. Section 11.2.2.1.1, Blood Sample Collection; Table 2, Footnote 9		
<p>Used to read: Blood samples (approximately 6 mL) will be collected in dipotassium ethylenediaminetetraacetic acid (EDTA) coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and at 2, 4, 6, 10, 15, 30, and 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. ...</p>	<p>Now reads: Blood samples (approximately 6 mL) will be collected in dipotassium ethylenediaminetetraacetic acid (EDTA) coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and at 2, 4, 6, 10, 15, 30, and 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. <b>Blood samples for PK should not be drawn or processed in the same room that the subject was dosed with study medication.</b> ...</p>	<p>Precautionary measure to prevent contamination of the PK plasma.</p>
9. Section 11.2.2.1.2, Urine Sample Collection		
<p>Used to read: ... During each collection period, the containers will be stored in refrigerators at 2°C to 8°C. Collection times and the accurate volume of urine collected for each interval will be noted. Two representative aliquots of equal volume (approximately 20 mL each, estimated using a</p>	<p>Now reads: ... During each collection period, the containers will be stored in refrigerators at 2°C to 8°C. Collection <b>time intervals accurate volume of urine collected for each interval will be noted. Two representative aliquots of equal volume (approximately 20 mL each, estimated using a nominal specific gravity of 1.018)</b> and the</p>	<p>Clarification of procedure.</p>



nominal specific gravity of 1.018) will be taken from each collection interval...	accurate weights of containers before and after collection of urine for each interval will be noted. Weight of urine (weight of container with urine – weight of empty container) will be converted to volume using a nominal specific gravity of 1.018. Two representative aliquots of equal volume (approximately 20 mL each, estimated) will be taken from each collection interval...	
10. Section 11.2.2.2, Pharmacodynamic Assessments		
Used to read: ...Spirometry testing is to be performed according to the procedure detailed in Appendix 5. For FEV <sub>1</sub> and FVC...	Now reads: ...Spirometry testing is to be performed according to the procedure detailed in Appendix 5. <b>The start time of the first spirometry effort will be used for all spirometry time points recorded.</b> For FEV <sub>1</sub> and FVC...	Clarification of spirometry start time.
11. Section 12.1.2, Vital Signs; Table 2, Schedule of Assessments, Footnote 1		
Used to read: Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse rate [beats per minute], respiratory rate [per minute] and oral temperature [degrees in Centigrade])...	Now reads: Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse rate [beats per minute], respiratory rate [per minute] and <del>oral</del> temperature [degrees in Centigrade])...	Allow flexibility in measurement of subject temperature.
12. Section 12.1.2, Vital Signs		
Used to read: Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes.	Now reads: Blood pressure and pulse will be measured after the subject has been sitting <b>or lying down</b> for 5 minutes.	Allow flexibility in measurement of subject vital signs.
13. Appendix 2, List of Clinical Laboratory Tests		
Used to read: (Not applicable)	Added: Glomerular filtration rate (GFR); GFR will be estimated by the Cockcroft-Gault formula utilizing serum creatinine values, age, weight, and gender, from the screening visit.	Added GFR calculation to screening clinical laboratory tests.
14. Appendix 5, Guidance for Spirometry		
Used to read: ...Spirometry assessments will be initiated between 6:00 AM and 10:00 AM. Spirometry, an effort-dependent test, requires careful instruction to and cooperation of the subject. ...	Now reads: ...Spirometry assessments will be initiated between 6:00 AM and 10:00 AM. <b>The start time of the first spirometry effort will be used for all spirometry time points recorded.</b> Spirometry, an	Clarification of spirometry start time.

	effort-dependent test, requires careful instruction to and cooperation of the subject. ...	
15. Appendix 6, title of appendix and content		
Used to read: Appendix 6, Protocol Amendment 1.0 Summary of Changes	Now reads: Appendix 6, Summary of Changes in Current Protocol Amendment	Updated Appendix 6 to show summary of changes in current amendment.