CLINICAL STUDY PROTOCOL

Nebulizer versus Handheld Maintenance Therapy for Patients with COPD

Protocol Name:	**Nebulizer versus Handheld Maintenance Therapy for Patients with COPD**
Abbreviated Name:	**The DELIVERY Study**
Protocol Number:	**2025-DELIVERY**
Protocol Date:	**May 04, 2026**

PROTOCOL SIGNATURE PAGE

Nebulizer versus Handheld Maintenance Therapy for Patients with COPD

Protocol #: 2025-DELIVERY

As an Investigator for this Study, I have read the Clinical Trial Protocol. I agree to make available to the Sponsor, Viatris (or its designee), original source documents and all regulatory documents pertaining to this Study. I agree to cooperate fully with the Sponsor with the conduct of study-related audits.

By my signature below, I agree to conduct this Study in accordance with the Clinical Trial Protocol and current Good Clinical Practice (cGCP) obligations as set forth in Title 21 CPR Parts 812, 54, 56 and 11 (as applicable), and any applicable regulatory laws. I will make no changes to protocol-defined procedures without written pelmission from the Sponsor.

I further agree to treat the results of this Study as confidential information and will not submit the results of the Study for publication without prior written authorization from the Sponsor.

Principal Investigator

Printed name DONALD A. MAHLER, M.D. Signature Donald A Mahler Date 5/20/2026

Viatris

Printed name Seth Woodruff Signature Seth Woodruff Date 05/19/2026

ABBREVIATIONS

BDI	Baseline dyspnea index
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
COPDF	Chronic Obstructive Pulmonary Disease Foundation
CRF	Case report form
DPI	Dry powder inhaler
FEV_1	Forced expiratory volume in 1 second
FDT	Functional Dexterity Test
FVC	Forced Vital Capacity
GOLD	Global initiative for chronic obstructive pulmonary disease
IC	Inspiratory capacity
ICF	Informed consent form
ICS	Inhaled Corticosteroid
IRB	Institutional review board
LABA	Long-acting Beta-2-agonist
LAMA	Long-acting Muscarinic Antagonist
mMRC	Modified Medical Research Council Dyspnea Scale
MMSE	Mini-mental state exam
PIF	Peak inspiratory flow
pMDI	Pressurized meter dose inhaler
SAE	Serious adverse event
TDI	Transition Dyspnea Index

Table of Contents

1. INTRODUCTION 5
2. HYPOTHESIS 5
3. STUDY OBJECTIVES 6
4. STUDY OVERVIEW 6
Visit 0 6
Visit 1 7
Visit 2 8
5. STUDY POPULATION 8
5.1 Study Population 8
5.2 Inclusion criteria 8
5.3 Exclusion criteria 9
6. STUDY PROCEDURES 9
7. RESPONSIBILITIES, STUDY CONDUCT AND MANAGEMENT 13
7.1 Regulatory and Ethical Considerations 13
7.2 Informed Consent Process 13
7.3 Data Infrastructure 14
7.4 Randomization Process 14
7.5 Data Protection 15
7.6 Data Dissemination 15
7.7 Record Retention 15
8. STATISTICAL METHODS 15
8.1 Sample Size 15
8.2 Planned Analyses 16
8.3 Primary Endpoint 16
9. ADVERSE EVENT REPORTING 17
10. APPENDIX 21

Nebulizer versus Handheld Maintenance Therapy for Patients with COPD

The DELIVERY Study

1. INTRODUCTION

There is a paucity of information about the efficacy of inhaled long-acting medications for patients with COPD delivered by nebulization versus handheld devices. In particular, there is only one multi-center, multi-dose randomized trial of long-acting bronchodilator therapy – a once daily muscarinic antagonist - comparing nebulizer (revefenacin) versus handheld (tiotropium dry powder) inhaler delivery in patients with COPD (Mahler DA. Chronic Obstr Pulm Dis 2019; 6:321).

One common reason for health care professionals to prescribe nebulized therapy is that the patient does not experience clinical benefit with handheld therapy. The rationale for this study is to examine whether delivery of similar long-acting, maintenance medications via nebulization achieves greater symptom relief compared to continuing handheld therapy in patients with COPD who remain symptomatic despite maintenance therapy delivered by handheld device(s).

2. HYPOTHESIS

In stable out-patients with an established diagnosis of severe to very severe COPD the hypothesis is that delivery of similar long-acting, maintenance medications via a breath-enhanced jet nebulizer provides significant improvements in ratings of dyspnea and health status compared with continuing therapy with handheld device(s). This hypothesized benefit could be due to:

► Patients with severe to very severe COPD may not consistently use their handheld inhaler(s) correctly every day and therefore not achieve optimal bronchodilation/symptom benefit; and/or

► A breath-enhanced jet nebulizer can deliver smaller size particles and a greater fine particle fraction (< 5 μm) than handheld therapy in patients with COPD using Acceptable technique.

3. STUDY OBJECTIVES

The major objective of this study is to determine whether patients who answer **NO** or **NOT SURE** to the following question –

Does your current maintenance inhaler(s) help your breathing?

- benefit upon switching to nebulized therapy using similar medications.

4. STUDY OVERVIEW

This is a multi-center, randomized, open-label, accessor-blinded, parallel group study over 28 days in patients with stable COPD who are currently using one of more different handheld inhaler devices (pMDIs and/or DPIs). All participants will be required to report unsatisfactory subjective benefit with their maintenance handheld inhalers. There will be three visits. Study workflow is also summarized in the appendix.

Visit 0 (in the clinic) the patient is asked the following written questions:

Does your current maintenance inhaler(s) help your breathing?

If the patient answers **NO** or **NOT SURE**, then they are asked the following :

How satisfied are you that your current maintenance inhaler(s) helps your breathing?

Not at all Satisfied 1 2 3 4 5 6 7 8 9 10 Extremely Satisfied

Patient answers this question by circling one number from the 1-10 Likert scale to provide a semi-quantitive estimate. Eligibility is not based on specific threshold.

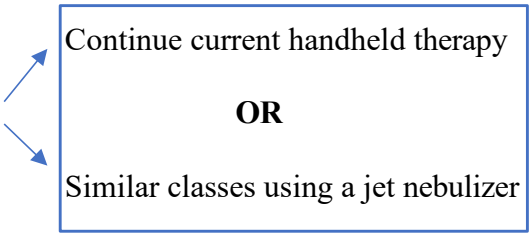
Then they will be asked the following written question:

Are you willing to try a different delivery system?

If the patient answers **YES**, then the investigator/study coordinator describes the study and obtains written signed consent. The patient is scheduled to return 2-14 days later for Visit 1 and instructed to hold/bring in their maintenance handheld inhaler(s) on that date.

Visit 1 (2-14 days after Visit 0), baseline testing includes pulse oximetry, spirometry, peak inspiratory flow against a medium-low resistance (PIFr), observe and critique (using 5-item check list for pMDI and DPI) the patient inhaling from their maintenance handheld inhalers. If the patient demonstrates Acceptable inhaler technique (score of $\geq$ 80% on a 5-item check list), then the following will be completed: Mini-Mental State Exam to assess cognitive function, functional dexterity test (timed test turning over 16 pegs) to assess manual dexterity, baseline dyspnea index (BDI), COPD assessment test (CAT), and spirometry 30 minutes after the patient inhaled their maintenance medications.

Then, the subject is randomized to:



for 28 days

Those patients who demonstrate Unacceptable inhaler technique (score < 80% on a 5-item check list) will be instructed on correct technique, thanked for their participation, and withdrawn from additional testing/randomization.

The block randomization method will be used to randomize subjects into groups that result in equal sample sizes to ensure a balance across groups over time. Similar medication solutions (LABA/LAMA or LABA/LAMA/ICS) along with a breath-enhanced jet nebulizer (PARI LC

Sprint®) will be given to patients assigned to the nebulizer group along with instructions for use/cleaning the system. Patients will be scheduled to return 28 ± 2 days later for Visit 2 and instructed to hold/bring in their maintenance handheld inhaler(s) or nebulizer with medications on that date.

Visit 2 (28 ± 2 days after Visit 1), the interviewer-administered Transition Dyspnea Index (TDI) will be recorded and the patient will complete the CAT. Next, the patient will perform spirometry, inspiratory capacity (IC), and PIFr use their handheld inhaler or nebulizer with medications, and perform spirometry and IC at 2 hours after inhalation. Correct technique will be assessed for use of handheld devices and nebulizer.

5. STUDY POPULATION

5.1 Study Population

Out-patients with established COPD diagnosis who are symptomatic despite using recommended handheld therapy (LABA/LAMA or LABA/LAMA/ICS) for at least one month are eligible to participate in the DELIVERY study if all the following criteria apply:

5.2 Inclusion criteria: Age ≥ 60 years; smoking history ≥ 10 pack-yrs; diagnosis of COPD based on GOLD; post-bronchodilator $FEV_1/FVC < 70\%$; post-bronchodilator $FEV_1 \leq 50\%$ predicted in past 12 months (note: post-bronchodilator testing can be either 15-30 minutes after inhaling albuterol or within 2 hours of taking their maintenance long-acting bronchodilator(s) prior to a previous appointment); current use of a single pMDI or a single DPI using either LABA/LAMA or LABA/LAMA/ICS therapy for at least one month; mMRC dyspnea scale ≥ 2; and a score ≥ 80% (i.e., "Acceptable" inhaler technique) on a 5-

item check list based on direct observation of the patient inhaling from their maintenance handheld inhaler(s) at Visit 1.

5.3 Exclusion criteria: Current diagnosis of dementia or known cognitive impairment; impaired manual dexterity (e.g. severe rheumatoid arthritis, severe tremor, etc.); exacerbation of COPD within the previous 2 months; diagnosis of other respiratory diseases, including asthma; treatment with a LABA/LAMA slow mist inhaler (SMI) (those using a SMI will not be enrolled because the anticipated small number of subjects - only 17% of subjects enrolled in the INHALE used a LABA/LAMA SMI – will limit statistical analysis based on inhaler type); treatment with SABA/SAMA nebulizer medications 3-4x/day as "maintenance" therapy; treatment with prednisone or equivalent oral coticosteroid within two weeks; and a score < 80% (i.e., "Unacceptable" inhaler technique) on a 5-item check list based on direct observation of the patient inhaling from their maintenance handheld inhaler(s) at Visit 1.

5.4 Compensation

Subjects will be paid $75 for completing Visit 1 and $175 for completing Visit 2. If the subject withdraws or has an exacerbation after randomization at Visit 1 and was assigned to receive nebulized therapy, the subject will be paid $25 to return for evaluation (vital signs and return compressor if assigned to that group). Payments will be made electronically with virtual gift cards through Tangocard.com - a secure online platform that delivers digital gift cards to the subject's email address.

6. STUDY PROCEDURES

Visit 1. The following measurements will be obtained in the order listed below:

1. Pulse oximetry at rest

2. Spirometry and inspiratory capacity (IC) using standard equipment at each site
3. Peak inspiratory flow against medium low resistance (R2) using In-CHECK Dial
4. Assessment of inhaler technique by a study coordinator using standardized 5-item check list for pMDI or a DPI with the subject using their maintenance handheld inhaler (either a single pMDI or a single DPI) "as you would at home."

   ► If the patient demonstrates Unacceptable inhaler technique (score of < 80% on a 5-item check list), then the subject will be informed that they are not eligible for participation in the study.

   ► If the patient demonstrates Acceptable inhaler technique (score of ≥ 80% on a 5-item check list), then the following will also be completed:
5. Interviewer-administered baseline dyspnea index (BDI)
6. COPD assessment test (CAT)
7. Cognitive function

   All patients will complete the 2nd Edition of the Mini-Mental State Examination (MMSE) as used in the INHALE study. The MMSE is a 30-point test that takes about 7 – 8 minutes to complete.

Score	Cognitive Impairment
24 – 30	None
18 – 23	Mild
0 – 17	Severe
8. Manual dexterity

   The Functional Dexterity Test is a timed pegboard test that assesses dexterity and sensory skills of the hand as used in the INHALE study. The test involves turning

over the pegs as quickly as possible. Using a stopwatch, the study coordinator records the time, in seconds, that it takes the patient to turn over all the pegs on the board with the dominant hand. Additional details are provided in instructions.

Functional level is determined by time to complete the task.

Time (seconds)	Level
16 – 25	Functional
26 – 33	Moderately functional
34 – 50	Minimally functional
> 50	Nonfunctional

9. Spirometry 30 minutes after the patient inhales their medication
10. Randomization: After testing is completed, patients will be randomized to continue their handheld medications-delivery system (either LABA/LAMA or LABA/LAMA/ICS with either a pMDI or a DPI) or to receive similar classes of nebulized medications.

    ► If assigned to the nebulizer group and if they were using a handheld LABA/LAMA, the patient will be given: a PARI LC Sprint® breath-enhanced jet nebulizer; a table top compressor; a 30-day supply of formoterol fumarate (20 µg) BID and revefenacin (175 µg) q AM. (Subjects will be instructed to use medications sequentially and not to mix solutions).

    ► If assigned to the nebulizer group and if they were using a handheld LABA/LAMA/ICS, the patient will be given: a PARI LC Sprint® breath-enhanced jet nebulizer; a table top compressor; a 30-day supply of formoterol fumarate (20 µg)

BID, revefenacin (175 μg) q AM, and budesonide (0.5 mg) BID. (Subjects will be instructed to use medications sequentially and not to mix solutions).

Correct technique will be reviewed with all patients regardless of group assignment. Finally, the patient will be scheduled to return 28 ± 2 days for Visit 2 and instructed to hold/bring in their maintenance handheld inhaler or nebulizer/compressor with medications on that date. All patients will be instructed to continue to use their as-needed short-acting inhaled medications and to record use on a daily dairy.

<u>After Visit 1 and before Visit 2</u>. The study coordinator will call the patient:

a. ~ 2 to 3 days after Visit 1 to ascertain that the patient is using their medications-delivery system as expected;

b. ~ 2 weeks after Visit 1 to inquire about their clinical status and use of medications-delivery system; and

c. ~ 2 to 3 days prior to Visit 2 to remind the patient of their upcoming appointment and to hold/bring in their maintenance handheld inhaler(s) or nebulizer with medications on that date.

<u>Visit 2</u>. The following measurements will be obtained in the order listed below:

1. Interviewer-administered transition dyspnea index (TDI)
2. CAT
3. Spirometry and IC using standard equipment at each site
4. Peak inspiratory flow against medium low resistance using In-CHECK Dial
5. The subject will use their maintenance handheld inhaler or nebulizer medications "as you would at home." The study coordinator will assess inhaler technique using

standardized 5-item check list for pMDI or DPI or assess nebulizer technique using a standardized check list.

6. Spirometry and IC using standard equipment at 2 hours after inhalation of maintenance medications.
7. After all testing is completed, the study coordinator will instruct each subject to resume use of their handheld maintenance medications with a pMDI or DPI as they were taking prior to the study.

7. RESPONSIBILITIES, STUDY CONDUCT AND MANAGEMENT

7.1 Regulatory and Ethical Considerations

The study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- All applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF and other relevant documents must be submitted to the IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated

During the study, the Investigator will be responsible for the following:

- Providing oversight of the conduct of the study
- Providing required updates to the IRB/EC

7.2 Informed Consent Process

All subjects will be given a copy of the IRB-approved ICF to review before their study participation begins. The Investigator or his/her designee will explain the nature of the study to participants who potentially meet the eligibility criteria and answer all of the potential participant's questions regarding the study.

If the subject decides to participate in the study, they will be asked to sign and date the ICF. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

7.3 Data Infrastructure

Data collected from each participant will be entered into the online case report form. The online system for data collection will be developed by the COPD Foundation's data infrastructure vendor, REDCap Cloud. The case report form will include validations where appropriate to minimize data cleaning and/or missing data. Data confidentiality and security are applied at all levels of data acquisition, transfer and storage at REDCap. REDCap is validated by RISC REDCap Support team to ensure it meets Health Insurance Portability and Accountability Act (HIPAA) compliance. Access to the Data Management System (DMS) requires two levels of identification, one to gain access to the secure server and one to gain access to the data management system. Users of the system are assigned job-specific permissions such as data entry, reporting or query resolution.

All participating site staff will be given access to a password protected data infrastructure, REDCap Cloud portal to enter all data collected from their participants. View restrictions will be applied within the online portal so clinicians can only see data entered for their site and not data that has been entered from other participating sites.

7.4 Randomization Process

The statistician will create a randomization table using statistical software (i.e., SAS, Stata) to upload as a CSV file into the REDCap Cloud system. This table serves as a lookup for assigning participants to one of the two study arms. When the participant is confirmed eligible for randomization, REDCap Cloud consults the uploaded allocation table and any defined stratification factors to determine the group assignment and ensures integrity and validity of the research.

7.5 Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only.

7.6 Data Dissemination

Findings from this research will be submitted for publication in a peer reviewed scientific journal.

7.7 Record Retention

To enable evaluations and/or audits from regulatory authorities, COPDF will retain all study records for a minimum of 3 years following completion of the project dependent upon the study data.

8. STATISTICAL METHODS

8.1 Sample Size

Based on the plan to include four sites for recruitment/testing, we propose that each site complete 30 subjects for a total of 120 with 60 being assigned to receive nebulizer delivery and 60 to continue with their handheld therapy. This number of subjects is based on study costs as there is inadequate data to perform a power calculation to assess the primary outcome - proportion of responders in the TDI ($\geq$ 1 unit improvement) - between nebulizer versus handheld groups.

Calculations

Evaluation at Visit 1 will be adjusted for the expected 29% rate of Unacceptable inhaler technique (an exclusion criterion) as observed in INHALE study.

► Screened at Visit 1: 212 subjects will be screened [212 x 0.71 (with Acceptable technique)] = 150 subjects for subsequent randomization.

► Randomized at Visit 1 to a treatment arm: 150 x 0.8 (expected 20% drop-out between Visit 1 and Visit 2) = 120 completed. A drop-out rate of 20% is expected due to subject withdrawing from the study or experiencing an exacerbation during the 28-days between Visit 1 and 2.

In summary, we plan to screen 212 subjects at Visit 1 and then randomize 150 subjects who exhibit Acceptable inhaler technique.

When will study be stopped?

The study will be stopped once 60 subjects in each treatment arm have completed Visit 2. At this time, all sites will be notified that no new subjects should be screeded/enrolled. Those subjects still active in the study will continue and complete Visit 2. Thus, there may be slightly more than 60 completed subjects per arm.

8.2 Planned Analyses

Descriptive summaries will be produced for all study measurements for each group. Differences between cohorts for primary and other outcomes will be tested using independent t-tests for changes in continuous variables and chi-square tests for categorical variables. Statistical significance will be defined as $p < 0.05$.

8.3 Primary Endpoint:

► Proportion of responders in the TDI ($\geq$ 1 unit improvement) between nebulizer versus handheld groups.

Other Outcomes:

► Proportion of responders in the CAT ($\geq$ 2 units improvement from Visit 1) between

nebulizer versus handheld groups

► Mean ± standard deviation values for TDI and changes in CAT scores

► Differences in changes of FEV_1, FVC, and IC from time 0 to 2 hours post-therapy at Visit 2 between nebulizer versus handheld groups.

► Differences is use of as-needed short-acting bronchodilators between nebulizer versus handheld groups.

► At Visit 2, subjects assigned to receive nebulizer medications will be asked: "Which do you prefer – your previous handheld inhalers or nebulizer therapy?
Why? (select one or more): a. helps my breathing more; b. easier to use; c. takes too much time; d. hard to take nebulizer along if traveling.

9. ADVERSE EVENT REPORTING

Serious adverse events (SAEs) will be captured from the time consent is signed at Visit 0 until completion of Visit 2. SAEs encountered during study participation will be documented by the investigator or delegated site staff. SAEs will be defined under current Good Clinical Practice (cGCP) guidelines as events that result in one or more of the following:

► life-threatening illness or injury

► permanent impairment of a body structure or a body function

► medically necessary in-patient hospitalization

► medical or surgical intervention necessary to prevent permanent impairment to body structure or function, or

► fetal distress, fetal death, or congenital abnormality.

Any participant who experiences a COPD exacerbation following enrollment/randomization at Visit 1 and before completion at Visit 2 will be discontinued/withdrawn from the study. Such individuals will be scheduled to return as soon as clinically possible for evaluation (vital signs and return compressor if assigned to that group).

At the five interactions between the subject and study coordinator (Visit 1 in-person, three telephone calls between Visits 1 and 2, and Visit 2 in-person), the study coordinator will query the subject about any usability issues, product substitution/switching issues, or medication errors. The study coordinator will answer Yes or No for each of these three items on REDCap

TABLES

Table 1: Schedule of Activities

	Visit 0	Visit 1	Visit 2
Identify Potential Participants	X		
Provide Informed Consent	X		
Schedule Visit 1 (2-14 days after V0)	X		
Demographics Data		X	
Exacerbation History		X	
Current Inhaler Type and Medication		X	
Pulse Oximetry		X	
Spirometry, Pre-BD		X	X
COPD Assessment Test (CAT)		X	X
Interviewer-administered Baseline Dyspnea Index (BDI)		X	
mMRC		X	X
PIF, 3 efforts against R2		X	X
Assessment of Inhaler Technique		X	X
Mini-Mental State Exam (MMSE-2nd ed)		X	
Functional Dexterity Test		X	
Spirometry, Post-BD (30 minutes after inhaling maintenance medication)		X	
Spirometry, Post-BD (2 hours after inhaling maintenance medication)			X
Inspiratory Capacity (IC)		X	X
Schedule Visit 2 (28 days after V1)		X	
Interviewer-administered Transition Dyspnea Index (TDI)			X

Table 2: Assessment of Inhaler Technique

pMDI	
1	Prepare the device: uncap; shake; hold inhaler vertical and mouthpiece horizontal
2	Turn away from the inhaler and breathe out completely
3	Place teeth and lips around the mouthpiece and activate the device (pressing down on canist while beginning slow inhalation
4	Breathe in slowly and deeply without stopping
5	Hold the breath for 5 to 10 seconds or as long as possible
DPI	
1	Prepare the device: uncap and load the inhaler if required
2	Turn away from the inhaler and breathe out completely
3	Place teeth and lips around the mouthpiece to form a seal
4	Breathe in with one brisk, deep inhalation
5	Hold the breath for 5 to 10 seconds or as long as possible

These checklists are modified from Sanchis J. Chest 2016; 150(2):394-406 and are the same as used in the INHALE study.

10. APPENDIX

Study Design

