Study Title:

Establishing Outcomes of Once-Daily ICS/LABA/LAMA Plus PRN Respiratory Therapy Treatments in Hospitalized Patients with COPD Exacerbations (SUNDIAL-COPD)

ORIGINAL PROTOCOL Version 1.4

Dated	8 March 2023
Protocol History	
Original Protocol	12 May 2021; Version 1.0 20 October 2021; Version 1.1 21 June 2022; Version 1.2
Amendment 1	9 December 2022; Version 1.3
Amendment 2	08 March 2023 Version 1.4
Site Location:	Baylor University Medical Center 3500 Gaston Avenue Dallas, TX 75246 Center for Advanced Heart and Lung Disease / Annette C. & Harold C. Simmons Transplant Institute 3410 Worth St., Suite 250, Dallas, Texas 75246 Phone: 214-820-6856 Fax: 214-820-1474
Principal Investigator:	Mark W. Millard, MD
Sub (Co)-Investigators:	Susan Mathai, MD

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PROTOCOL SIGNATURE PAGE

Study Title: Establishing Outcomes of Once-Daily ICS/LABA/LAMA Plus PRN Respiratory Therapy Treatments in Hospitalized Patients with COPD Exacerbations (SUNDIAL-COPD)

Protocol Number: N/A

IRB Number: 021**-182**

I have read this protocol and agree to adhere to the requirements outlined within. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed regarding the requirements of this protocol. I will also ensure that this study is conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory agencies and their requirements.

_____

Clinical Investigator (Printed Name)

_____ _____

Clinical Investigator (Signature) Date

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PROTOCOL AMENDMENT HISTORY TABLE

Protocol # Version Date	**Section** *(Section & page #)*	**Language Added/Revised/Deleted**	**Rationale**
V1.1	Header	IRB number added	
	Section 9.3	A telephone call will be made by an authorized study research staff member to assess if the subject was readmitted within 30 days of discharge.	Detail added
V1.2	Section 5.2.3, 5.2.5	Adding St. George questionnaire-short version to enrollment. And adding short version term to 5.2.5 Questionnaire name.	
Amendment 1 9 December 2022	Section 4 b i Page 20	Inclusion criteria Diagnosis of COPD inspiratory flow rate	Diagnosis of COPD (per investigator's discretion by prior spirometry results or by spirometry assessment at screening visit) Acronym has been added (PIFR)
Amendment 1 9 December 2022	Section 5.2.2, section 5.2.3 Page 23-22	Change in the procedures during the screening visit section and enrollment section	The procedures during the screening visit will include: 1. Assignment of screening number 2. Spirometry (FEV1, FVC, FEV1/FVC) 3. Demographics 4. Medical History 5. Decision by investigator to enroll subject or to

			declare screen failure.
Amendment 1 9 December 2022	Section 5.2.4 Page 24	Change in the time of treatment administration	Treatments will be administered by a respiratory therapist daily in the morning between 06:00 AM and 12:00 PM.
Amendment 1 9 December 2022	Section 5.2.5 Page 25	A schedule a follow-up with the subject in the research clinic	To obtain the missed assessments.
Amendment 1 9 December 2022	Section 16.1 Pages 37-38	Gilead Science is deleted	The sponsor is GlaxoSmithKline plc. (GSK)
Amendment 1 9 December 2022	Section 16.2 Page 39	FDA Form 1572 is deleted from the Essential Documents list	Invalid
Amendment 2 8 March 2023	Section 1, Page 14 Section 4, Page 20 Section 8.7, Page 32	9-month enrollment duration removed	Updated enrollment timeline.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
Ab	Antibody
Ag	Antigen
CRF	Case report form
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act of 1996
IHC	Immunohistochemistry
IL-1R	Interleukin-1 Receptor
IR	Increased risk
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
PHI	Protected health information
PI	Principal Investigator
PRN	Pro re nata-as need arises
SAE	Serious adverse event
SOP	Standard operating procedure

1. SYNOPSIS

Summary/Rational:	This phase IV, post market approval single-center, open-label study will be used evaluate to a more standardized open-label protocol which would allow for a more accurate assessment of intervention outcomes when a combination LABA/LAMA/ICS inhaler is used as the primary scheduled daily inhaled therapy.
Study Objectives:	**Primary objective:** 1. To establish the requirements for PRN respiratory therapy treatments in patients hospitalized with the diagnosis of COPD exacerbation receiving once-daily ICS/LABA/LAMA (fluticasone furoate/umeclidinium/vilanterol) therapy. **Secondary objectives:** 1. To measure the distribution of inspiratory flow rates with an InCheck Dial device set on measuring PIF using the medium low resistance setting in patients admitted with COPD exacerbations at Baylor University Medical Center, Dallas TX at the time of enrollment and day of discharge 2. To determine the hospital length of stay for patients admitted with the diagnosis of COPD exacerbation 3. To monitor and report any side effects from using once-daily ICS/LABA/LAMA or PRN therapy. 4. To evaluate the transition of care in delivering respiratory therapy medications from hospital to home 5. To compare the number of PRN treatments, length of hospital stay, and rate of readmissions with findings in a previously

	analyzed historical cohort of 60 patients in our healthcare system. **Exploratory Objectives** To determine the cost of respiratory care for patients hospitalized with the diagnosis of COPD exacerbation.
Study Design:	Phase IV, post market approval, single-center, open-label study
Number of Subjects:	Up to 120 subjects will be enrolled out of which approximately 80 will be TRELEGY ELLIPTA Treated Subjects; this allows for an anticipated acceptance rate of 2/3
Inclusion Criteria:	A patient will be eligible for inclusion in this study if **he or she** meets **all** the following criteria: 1. Willing and capable of providing written informed consent. 2. Subjects aged 18 years or older at time of enrollment 3. Diagnosis of COPD with or without asthma for ≥12 months 4. Hospitalized ≤24 hours prior to enrollment and currently hospitalized for COPD exacerbation with or without asthma. 5. Able to properly use the Ellipta medication delivery device. 6. Able to generate ≥ 30 L/min inspiratory flow at screening, measured with an InCheck DIAL adjusted to medium low resistance, to document a subject's ability to

	effectively inhale medication delivered via an Ellipta device.
Exclusion Criteria:	1. Clinically significant lung disease other than COPD with or without asthma 2. Positive SARS-CoV-2 test at the time of ED or hospital admission, or any time between admission and enrollment. 3. History of severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients 4. Unable to perform inspiratory flow or spirometry procedures. 5. Critically ill patients, or patients with rapidly deteriorating or life-threatening episodes of COPD or asthma including: • Patients in critical care unit or transferred from critical care unit. o Patients who are transferred to critical care after enrollment will be withdrawn from the study and continue to receive care according to institutional standard practice. • Patients who initiate Bilevel Positive Airway Pressure (BiPAP) after hospitalization. o Patients who use BiPAP at baseline (prior to COPD exacerbation) may be included if BiPAP settings remain consistent with pre-exacerbation settings. Patients will be withdrawn if BiPAP settings are changed after enrollment.

	6. Pregnant or lactating women or women of child-bearing potential (WOCBP). Women must meet the non-productive potential definition below to be eligible. ➢ Non-reproductive potential is defined as: • Pre-menopausal females with one of the following: o Documented tubal ligation. o Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal ligation. o Hysterectomy. o Documented Bilateral Oophorectomy. • Postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile (e.g., age appropriate, >45 years, in the absence of hormone replacement therapy). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory. Females under 60 years of age, who are on HRT and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, subjects can resume use of HRT during

	the study without use of a highly effective method to avoid pregnancy.
Sponsor:	GlaxoSmithKline plc. (GSK)-Only provide the drug. Baylor Scott and White Research Institute (BSWRI)
Principal Investigators:	Mark W Millard MD
Primary Study Site/Data Center:	Annette C. & Harold C. Simmons Transplant Institute 3410 Worth St., Suite 250, Dallas, Texas 75246 Phone: 214-820-6856 Fax: 214-820-1474
Medication:	TRELEGY ELLIPTA (fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)
Medication Delivery Device:	ELLIPTA

Efficacy Assessments:	➢ Number of in-hospital PRN respiratory therapy treatments with PRN nebulized albuterol 2.5mg. ➢ Time in between PRN respiratory therapy. ➢ Change in respiratory inspiratory flow rate measured by InCheck DIAL at medium resistance from baseline to discharge. ➢ Length of stay. ➢ At-home drug compliance. ➢ 30-day re-admissions (all-cause and COPD exacerbation), 30-day survival, cost of in-hospital respiratory therapy, response to a patient satisfaction questionnaire (QOL questionnaire).
Safety Assessments:	• Vital signs and vital status. • Concomitant medication use. • Reporting of adverse events. • Pregnancy test (women of childbearing potential).

2. OBJECTIVES & ENDPOINTS

a. Primary Objective

1. To establish the requirements for PRN respiratory therapy treatments in patients hospitalized with the diagnosis of COPD exacerbation receiving once-daily ICS/LABA/LAMA (fluticasone furoate/umeclidinium/vilanterol) therapy.

b. Secondary Objectives

1. To measure the distribution of inspiratory flow rates with an InCheck Dial device set on measuring PIF using the medium low resistance setting in patients admitted with COPD exacerbations at Baylor University Medical Center, Dallas TX at the time of enrollment and day of discharge.
2. To determine the hospital length of stay for patients admitted with the diagnosis of COPD exacerbation.
3. To monitor and report any side effects from using once-daily ICS/LABA/LAMA or PRN therapy.
4. To evaluate the transition of care in delivering respiratory therapy medications from hospital to home.
5. To compare the number of PRN treatments, length of hospital stay, and rate of readmissions with findings in a previously analyzed historical cohort of 60 patients in our healthcare system.

c. Exploratory Objectives

To determine the cost of respiratory care for patients hospitalized with the diagnosis of COPD exacerbation.

d. Study Endpoints

To attain these objectives, the following study endpoints will be evaluated. Primary and secondary endpoints include the number of in-hospital PRN respiratory therapy treatments, time in between PRN respiratory therapy, change in peak inspiratory flow rate from baseline to discharge, length of stay, at-home drug compliance, 30-day re-admissions (all-cause and respiratory), 30-day survival, cost of respiratory therapy, QOL score, and safety measures (AEs and SAEs; Section 5). See section 8.7 on analytical methods to evaluate these endpoints.

3. BACKGROUND

a. Disease

The disease under study is Chronic Obstructive Pulmonary Disease (COPD), a group of progressive chronic inflammatory diseases that cause obstruction of airflow in the lungs. COPD affects 16 million people in the United States, and its death rate is approximately 40 per 100,000.[1] Symptoms include breathing difficulty, cough, mucus/sputum production, and wheezing. The main cause of COPD in the United States is tobacco smoking. COPD may co-occur with asthma.

b. Therapy/Agent

TRELEGY ELLIPTA is supplied as a disposable light grey and beige plastic inhaler containing 2 foil strips, each with 30 blisters. One strip contains fluticasone furoate (100 mcg per blister), and the other strip contains a blend of umeclidinium and vilanterol (62.5 mcg and 25 mcg per blister, respectively). A blister from each strip is used to create one dose. The inhaler is packaged within a moisture-protective foil tray with a desiccant and a peelable lid.

It will be stored at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C). It will be stored in a dry place away from direct heat or sunlight.

Subjects will be given TRELEGY ELLIPTA once daily at the same time every day (± 2 hours). TRELEGY ELLIPTA will be initiated the morning of enrollment if feasible, or the morning following hospital enrollment otherwise. It will be administered as 1 inhalation by the orally inhaled route only.

Although FDA approved, TRELEGY ELLIPTA is seldom prescribed to hospitalized COPD patients by treating physicians. Study participants will be consented prior to being prescribed TRELEGY ELLIPTA as part of this study.

c. Rationale for study

When exacerbations of COPD that require hospitalization occur, short-acting bronchodilators (both beta agonists and anticholinergics) are routinely prescribed as part of a comprehensive regimen that includes supplemental oxygen, parenteral corticosteroids, antibiotics (usually), and if severe, non-invasive positive pressure ventilation.

According to GOLD 2018 recommendations,[2] long-acting bronchodilators are to be introduced as soon as possible prior to discharge from the hospital if not continued during hospitalization. However, the recommendation to use short-acting bronchodilators as a primary therapeutic inhalant is based on grade C level of evidence, suggesting a paucity of data to support that position. Primarily related to pharmacy-driven cost considerations, the exclusive use of short-acting bronchodilators has become the standard of care in treating hospitalized patients with COPD exacerbations, with the introduction of long-acting inhalants only upon discharge, by a number of institutions including Ben Taub Hospital in Houston (Nicola Hanania MD: personal communication), and throughout the Baylor Scott and White Healthcare System in Texas. This therapeutic substitution of short-acting for long-acting bronchodilators has been estimated to result in a cost savings of ~$400k at Baylor University Medical Center alone (personal

communication: director of pharmacy services). Even so, few if any studies have evaluated the length of stay, in-hospital adverse events (nocturnal awakenings related to respiratory symptoms that occur beyond the window of pharmacologic efficacy of short-acting medications), respiratory therapy utilization or the potential impact upon re-hospitalizations with this paradigm shift of care. Sanford Hospital System in North Dakota recently published a study comparing a once daily long-acting combination with compared with a twice-daily combination and saw minimal cost savings and no real change in outcomes.[3] This same system had previously studied substitution of twice daily beta agonist and once daily anticholinergic bronchodilators for combination short-acting bronchodilators and found improved outcomes and cost savings but reported their results in a non-peer reviewed journal in (AARC Times, November 2011).

Results of an analysis of 60 patient charts randomly selected after hospitalization at Baylor University Medical Center for an exacerbation of underlying airways disease (>90% with COPD) showed tremendous variation in practice patterns; with 30% of patients receiving short-acting beta-antagonists and muscarinic agonists (SABA/SAMA) only, 70% receiving long-acting beta-antagonists (LABA) with PRN SABA/SAMA, and only 42% receiving a long-acting muscarinic agonist (LAMA), despite practice guidelines encouraging the use of SABA/SAMA only (typically 4 times daily and as needed).

It is this large variability that renders the evaluation and interpretation of institution-specific outcomes difficult. The main impetus for the proposed study is therefore to establish a more standardized open-label protocol which would allow for a more accurate assessment of intervention outcomes. As one of several secondary goals of this study, we aim to compare key outcomes (including, number of PRN treatments, length of hospital stay, and rate of readmission) with those from the historical cohort described above, when a combination LABA/LAMA/ICS inhaler is used as the primary scheduled daily inhaled therapy.

4. PATIENT POPULATION

a. Enrollment Goal

This study aims to enroll 80 subjects. With an anticipated acceptance rate of 2/3, this means we will approach 120 eligible candidates over that period. We estimate we will be able to achieve 30-day follow-up in 80% of enrolled patients.

b. Eligibility Criteria

i. Inclusion Criteria

a. Willing and capable of providing written informed consent.
b. Subjects aged 18 years or older at time of enrollment.
c. Diagnosis of COPD (per investigator's discretion by prior spirometry results or by spirometry assessment at screening visit) with or without asthma for ≥12 months.
d. Hospitalized ≤24 hours prior to enrollment and currently hospitalized for COPD exacerbation with or without asthma.
e. Able to properly use the Ellipta medication delivery device.
f. Able to generate ≥ 30 L/min inspiratory flow rate (PIFR) at screening, measured with an InCheck DIAL adjusted to medium low resistance, to document a subject's ability to effectively inhale medication delivered via an Ellipta device.

ii. Exclusion Criteria

a. Clinically significant lung disease other than COPD with or without asthma.
b. Positive SARS-CoV-2 test at the time of ED or hospital admission, or any time between admission and enrollment.
c. History of severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients.
d. Unable to perform inspiratory flow or spirometry procedures.
e. Critically ill patients, or patients with rapidly deteriorating or life-threatening episodes of COPD or asthma including:
    - Patients in critical care unit, or transferred from critical care unit.

- Patients who are transferred to critical care after enrollment will be withdrawn from the study and continue to receive care according to institutional standard practice.
- Patients who initiate Bilevel Positive Airway Pressure (BiPAP) after hospitalization.
    - Patients who use BiPAP at baseline (prior to COPD exacerbation) may be included if BiPAP settings remain consistent with pre-exacerbation settings. Patients will be withdrawn if BiPAP settings are changed after enrollment.

f. Pregnant or lactating women or women of child-bearing potential (WOCBP). Women must meet the non-productive potential definition below to be eligible.

➢ Non-reproductive potential is defined as:

- Pre-menopausal females with one of the following:
    - Documented tubal ligation.
    - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal ligation.
    - Hysterectomy.
    - Documented Bilateral Oophorectomy.
- Postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile (e.g., age appropriate, >45 years, in the absence of hormone replacement therapy). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory. Females under 60 years of age, who are on HRT and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrolment. For most forms of HRT, at

least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, subjects can resume use of HRT during the study without use of a highly effective method to avoid pregnancy.

5. STUDY VISITS AND ACTIVITIES

5.1 DESIGN

This is a single-center, phase IV, post market approval prospective, open-label study evaluating outcomes of TRELEGY ELLIPTA (fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder) on PRN nebulized short-acting beta agonist (SABA) treatment in hospitalized subjects with COPD with or without asthma.

Approximately 80 adult subjects with COPD with or without asthma will take part in this study at Baylor University Medical Center. Subjects will be given TRELEGY ELLIPTA, using the Ellipta device, placed on a consistent short-term systemic corticosteroid therapy, and followed until 30 days post hospital discharge. This study will not include patients with rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.

5.2 STUDY VISITS

5.2.1 PRE-SCREENING

The inpatient hospital team will identify and refer the potential subject to the study team. The study team will verify that all inclusion criteria and none of the exclusion criteria are met.

5.2.2 SCREENING (+ 24 hours)

Subjects will be identified from the inpatient hospital team. Prior to participation in the study, each subject will be given an opportunity to ask questions and to understand the details of study participation, including risks and benefits. The consent process will be documented in the subject's source documents.

Assessments and procedures at screening

- Informed consent
- Assignment of screening number
- Inspiratory Flow Rate (PIFR) evaluation, with InCheck DIAL device set to measure medium low resistance. The best of 3 maximum inspiratory flow measurements, taken from RV will be recorded.
- Spirometry (FEV1, FVC, FEV1/FVC)
- Inclusion/Exclusion Criteria
- Demographics
- Medical History
- Decision by investigator to enroll subject or to declare screen failure.

5.2.3 ENROLLMENT (within 24 hours of admission)

The following procedures/assessments will be done the morning or following morning of admission into study:

- Concomitant Medications
- Adverse Events (AE) Assessment
- Patient Satisfaction Questionnaire (St George's Respiratory questionnaire-short version)

In addition, data from the specified assessments will be collected when available, and entered the case report forms (CRFs):

- Vital signs

- Physical Exam

5.2.4 TREATMENT (Enrollment to Discharge)

TRELEGY ELLIPTA (fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder) will be initiated on the morning of enrollment if feasible, or the morning after enrollment otherwise. Treatment will continue daily until discharge. Treatments will be administered by a respiratory therapist daily in the morning between 06:00 AM and 12:00 PM. Patients will receive nebulized short-acting beta-2 agonist (SABA) treatments of albuterol sulfate (2.5mg) as needed during hospitalization. Patients will receive prednisone 40 mg PO daily for the first 7 days from enrollment, subtracting 1 day for each consecutive day the patient received systemic corticosteroid treatment prior to enrollment.

Treatment procedures/assessments include:

- Concomitant Medications
- AE Assessment
- TRELEGY administration

Data from the following specified assessments will be collected daily, when available, and entered the case report forms (CRFs):

- Vital Signs
- Short-acting beta agonist (SABA) therapy: number and time of treatments

5.2.5 DISCHARGE

Upon discharge, patients will receive a full TRELEGY ELLIPTA inhaler containing 30 doses with instructions to take 1 puff daily in the morning for 30 days. The in-hospital use TRELEGY ELLIPTA used by the patient will be discarded.

The following procedures/assessments will be done prior to hospital discharge:

- Spirometry (FEV1, FVC, FEV1/FVC)
- Peak inspiratory flow rate, measured by the InCheck Dial set at medium resistance.
- Concomitant Medications
- Adverse Events (AE) Assessment
- Patient Satisfaction Questionnaire (St George's Respiratory questionnaire, short version)

In addition, data from the specified assessments will be collected when available, and entered the case report forms (CRFS):

- Vital signs
- Withdrawal from protocol

If for any reason, some of the research assessments at discharge are not performed, the study team may (at investigator's discretion) schedule a follow-up with the subject in the research clinic to obtain the missed assessments.

5.2.6 30 DAY POST DISCHARGE/WITHDRAWAL FOLLOW-UP

Subjects will receive a follow-up phone call from a study coordinator and Medical Charts will be reviewed to assess if the subject was readmitted within 30 days of discharge. Follow-up phone call and Medical Chart review will instead occur 30 days after withdrawal for patients who are withdrawn prior to discharge.

6. SAFETY & EVENT REPORTING

6.1 ADVERSE EVENTS

An AE is any untoward sign, symptom or medical condition occurring at any time after the subject receives his/her first dose of study drug, even if the event is not considered to be related to the study drug. Information about all AEs whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected, and recorded on the AE CRF and followed as appropriate.

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, and are considered clinically significant, or require therapy. They will be recorded on the AE CRF under signs, symptoms, or diagnosis associated with them.

As far as possible, each AE will be described by:

- Its duration (start and end dates)
- The severity grade (mild, moderate, severe)
- Its relationship to the study drug (suspected/not suspected)
- The action (s) taken and as relevant
- The outcome

Criteria for determining the severity of an AE and its relationship to the study drug are shown below in Table 5-1. These criteria are guidelines. It is the responsibility of the Investigator to decide of severity and whether or not a relationship to study drug is suspected.

Table 1 Adverse Event Severity and Relationship to Study Drug

AE Severity	
Mild	Awareness of sign or symptom but easily tolerated

Moderate	Discomfort sufficient to cause interference with normal activities
Severe	Incapacitating, with inability to perform normal activities
AE Relationship	
Suspected	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, which might or might not be also explained by concurrent disease or other drugs or chemicals
Not Suspected	A clinical event, including laboratory test abnormality, judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.), or with a temporal relationship to drug administration which makes a causal relationship improbable, and/or for which other drugs, chemicals or underlying disease provide a much more plausible explanation

Adverse events (including serious adverse events) will be monitored and reported from enrollment to discharge.

6.2 SERIOUS ADVERSE EVENTS

All Serious Adverse Events (SAEs) will be reported to the sponsor within 24 hours of awareness of the event. An AE will be considered serious if it meets any of the following criteria:

- Events resulting in death.
- Life-threatening events
- Events requiring hospitalization or prolongation of existing hospitalization.
- Events resulting in persistent or significant disability/incapacity.

- Events not meeting any of the above criteria deemed to be serious by the Investigator.

6.3 **DEVICE INCIDENTS REPORTING**

Study drug administered via the ELLIPTA device is a drug/device combination product. All device incidents should be notified to the sponsor. A Medical Device Incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health and a Serious Adverse Device Effect (SADE) that has resulted in any of the consequences characteristic of a serious adverse event and any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstance had been less fortunate. Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel. It is sufficient that: an incident associated with a device happened; and the incident was such that, if it occurred again, it might lead to death or serious deterioration in health.

Device incidents should be reported as outlined below, and not as a safety event.

It is possible for a reportable safety event to occur at the same time as a device incident. Safety events are reported as described in Section 5.1 and should be reported in parallel as an AE/SAE as appropriate.

If a device incident is detected, the following process should be followed:

- Report the incident to the sponsor using the Combination Product with Device Deficiency/Incident Report Form within 24 hours of awareness of the incident

- Arrange for a new device to be provided if not already done so by a pharmacy/ prescription.

6.4 COVID-19 CONSIDERATIONS

It is standard practice for patients admitted with respiratory symptoms to receive SARS-CoV-2 testing at the time of admission. The study will not require additional testing but will record results of any additional SARS-CoV-2 testing that occurs during hospitalization.

Patients with positive SARS-CoV-2 test at the time of admission or in the time between admission and enrollment will be excluded from the study. Patients with positive SARS-CoV-2 test after the time of enrollment will be withdrawn from the study and will continue to receive care according to institutional standard practice.

6.5 PREGNANCY REPORTING

If pregnancy occurs in a female participant, the pregnancy should be reported as outlined below.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the safety follow-up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section.
- While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention but may remain in the study (if consent is not withdrawn).

7. CONCOMITANT MEDICATION

7.1 Data Collection

Concomitant medications will be assessed from Enrollment to Discharge. The stop and start date, dose, brand name, generic name, and indication for each concomitant medication will be documented in source documents and on CRFs.

7.2 Disallowed Medications

Subjects will be prohibited from taking the following medications during the study:

- Inhaled short-acting muscarinic antagonist (SAMAs), such as ipratropium bromide.
- Inhaled therapies other than TRELEGY ELLIPTA containing any of the following: ICS, LAMA, or LABA.

8. PROTOCOL DEVIATIONS

Any event, whether planned or not, where the procedures as outlined in the documents approved by the IRB are not followed. Record all protocol deviations in the CRFs.

Report all unplanned deviations that involve a potential for increased risk to the subjects to the IRB within 10 days of occurrence or becoming aware of the occurrence. Report all unplanned deviations that do not involve increased risk to the subjects to the IRB at the next continuing review.

9. STATISTICAL ANALYSIS & DATA MANAGEMENT

Continuous variables will be reported as means ± standard deviations or medians [quartile 1, quartile 3], if skewed. Categorical variables will be reported as frequencies and percentages.

8.1.Measurement of Safety

Safety will be assessed by monitoring vital signs, body weight, concomitant medication use, adverse events (AE), and serious adverse events (SAE).

8.2.Measurement of Efficacy

Efficacy will be assessed by the number of in-hospital PRN respiratory therapy treatments with PRN nebulized albuterol 2.5mg, time in between PRN respiratory therapy, change in respiratory inspiratory flow rate measured by InCheck DIAL at medium resistance from baseline to discharge, length of stay, at-home drug compliance, 30-day re-admissions (all-cause and COPD exacerbation), 30-day survival, cost of in-hospital respiratory therapy, and response to a patient satisfaction questionnaire (QOL questionnaire).

Drug compliance at home will be assessed through follow-up phone call at 30-day post-discharge. Compliance will be calculated as the difference between 100 and the percentage of doses left on the TRELEGY ELLIPTA inhaler out of 30.

8.3.Response Criteria

N/A

8.4.Data Reporting

It is intended that the results of the study will be published in at least one abstract for a scientific meeting and one manuscript.

8.5.Regulatory Requirements

All subject records will only be identified by a unique screening number. Subjects' names are not to be transmitted to the Sponsor. The Investigator or designated site personnel will keep a master subject list containing the patient identification number, full name, date of birth, and hospital (or other) identification number of each subject.

8.6.Multicenter Guidelines

This is a single-center study.

8.7.Statistical Considerations

a. Study Design Endpoints

Primary and secondary endpoints include the number of in-hospital PRN respiratory therapy treatments, time in between PRN respiratory therapy, change in peak inspiratory flow rate measured with an InCheck DIAL through medium low resistance from baseline to discharge, length of stay, at-home drug compliance, 30-day re-admissions (all-cause and respiratory), 30-day survival, cost of respiratory therapy, and QOL score.

b. Sample Size & Accrual Rate

Enrollment of 80 patients.

c. Analysis of Primary Endpoint

The number of PRN respiratory treatments during hospitalization will be reported as the median [quartile 1, quartile 3] and as the average number of PRN respiratory treatments per-inpatient day ± standard deviation. A comparison between patients who were and were not readmitted within 30-days will be made using a Wilcoxon signed rank test for the number of PRN respiratory treatments. Additionally, the incident rate ratio of the average per-inpatient

day PRN treatments will be estimated using a robust Poisson regression model comparing patients who were readmitted within 30-days to those who were not.

d. Analysis of Secondary Endpoints

Time (in days) in between PRN treatments, change in respiratory inspiratory flow rate from baseline to discharge, length of stay, at-home drug compliance, 30-day readmissions (all-cause and COPD/Asthma exacerbation), and 30-day survival will be compared between patients who were and were not readmitted using t-tests or chi-square tests (or Wilcoxon Rank Sum tests and Fisher's Exact tests), as appropriate.

The efficacy of the treatment protocol in the study cohort compared to the historical cohort will be assessed by comparing (1) the average number of PRN treatments per patient day while hospitalized estimated using a robust Poisson regression model (2) length of stay in the hospital, and (3) the rate of rehospitalization, using the Wilcoxon Rank sum test.

e. Reporting and Exclusions

Missing data will not be imputed or carried forward in any of the analyses.

The sample size for continuous variables will be the number of subjects with non-missing data; in the summary of categorical variables, subjects with missing data will be excluded in the calculation of percentages.

9 ETHICS AND GOOD CLINICAL PRACTICE

9.1 Institutional Review Board/Independent Ethics Committee

The Investigator will submit this protocol and ICF for IRB approval prior to starting the study. The Investigator will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the Investigator. Before implementation, the Investigators will submit to and receive documented approval from the IRB of any modifications made to the protocol or any accompanying material to be provided to the subject

after initial IRB approval, except for those necessary to reduce immediate risk to study subjects.

9.2 Informed Consent

The investigator or delegated person must explain to each subject the nature of the study, its purpose, the procedures involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study before his/her informed consent has been obtained. The ICF must be submitted by the Investigator for IRB approval.

There will also be an option to do electronic consenting and electronic signatures by using study approved methods such as hospital telehealth system, patient iPad, telephone calls/telephone video conferencing. Documents will be sent electronically to the email address you provide for you to review the documents and sign off on.

A telephone call will be made by an authorized study research staff member to assess if the subject was readmitted within 30 days of discharge.

9.3 Declaration of Helsinki

The Investigator must conduct the study in accordance with the principles of the current version of the Declaration of Helsinki. Copies of the Declaration of Helsinki and

amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/en/30publications/10policies/b3/index.html

10. **COMPENSATION**

Participants will not receive any compensation for participating in this study.

11. **COSTS**

Participants will not incur any additional costs due to study participation. Patient or their insurance company will be required to pay for all expenses related to regular care including hospital care.

12. **SAFETY MONITORING**

Safety will be assessed by monitoring the following:

- Vital signs,
- height,
- body weight,
- concomitant medication use,
- AEs, SAEs,
- Pregnancy testing for women of childbearing potential, as determined by the study PI

13. **DATA SAFETY MONITORING COMMITTEE (DSMC)**

It has been determined that this study does not need a DSMB as the study drug has full FDA approval.

14. **RISK AND BENEFITS TO PARTICIPANTS**

14.1 POTENTIAL BENEFITS

There may or maynot be be any direct benefit to the patients who participate in this study.

14.2 POTENTIAL RISKS

14.2.1 Drug Adverse events

- COPD: Most common adverse reactions (incidence ≥1%) are upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, headache, back pain, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, dysgeusia, constipation, urinary tract infection, diarrhea, gastroenteritis, oropharyngeal pain, cough, and dysphonia. (6.1)
- Asthma: Most common adverse reactions (incidence ≥2%) are pharyngitis/nasopharyngitis, upper respiratory tract infection/viral upper respiratory tract infection, bronchitis, respiratory tract infection/viral respiratory tract infection, sinusitis/acute sinusitis, urinary tract infection, rhinitis, influenza, headache, and back pain. (6.2)

14.2.2 Physical Risks

The Ellipta oral inahler may cause a bad taste, soreness or irritation of the mouth and throat.

14.2.3 Psychosocial & Privacy Risks

Any time information is collected there is a potential for loss of confidentiality. Every effort will be made to keep participant's information confidential, however this cannot be guaranteed.

Participation in research study may make participants feel uncomfortable.

Participants will be informed that they may refuse to participate or stop their participation at any time without effect on future medical treatment or relationship with the treating physician.

14.2.4 Reproductive Risks and Contraception Guidelines

Women must meet the non-productive potential definition below to be eligible.

Non-reproductive potential is defined as:

- *Pre-menopausal females with one of the following:*
  - Documented tubal ligation.
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal ligation.
  - Hysterectomy
  - Documented Bilateral Oophorectomy
- *Postmenopausal defined as:*

  12 months of spontaneous amenorrhea with an appropriate clinical profile (e.g., age appropriate, >45 years, in the absence of hormone replacement therapy). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory. Females under 60 years of age, who are on HRT and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, subjects can resume use of HRT during the study without use of a highly effective method to avoid pregnancy.

15. RISK/BENFIT ASSESSMENT

There may be no direct benefit to the subjects. However, the information obtained may help to advance the understanding of COPD disease and improve treatment protocols, may thus be of future benefit to patients with these disorders or to at-risk members-of-society. The subjects incur

no cost from participating in this study. They are also not paid for their participation. As, except for the study drug, all other medical care will be part of routine care, they are still responsible for the costs of the hospitalization, clinic visit, and any clinical labs ordered by their doctors.

16. **Protocol amendment procedures and data retention**

16.1 PROTOCOL AMENDMENTS AND OTHER CHANGES IN STUDY CONDUCT

Protocol Amendments

Any substantive changes will be made as formal amendments to the protocol and will be submitted for appropriate review by an institutional review board (IRB), and to regulatory authorities.

Any change or addition to this protocol requires a written protocol amendment that must be approved by GlaxoSmithKline plc. (GSK)and the Investigator before implementation. Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB. Examples of amendments requiring such approval are:

1. A significant change in the study design (e.g., addition or deletion of a control group)
2. An increase in the number of invasive procedures to which subjects are exposed
3. Addition or deletion of a test procedure for safety monitoring

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator to ensure the safety of all subjects included in the study. If an immediate change to the protocol is deemed necessary by the Investigator and is implemented by him/her for safety reasons, GlaxoSmithKline plc. (GSK)should be notified, and the IRB should be informed within 10 working days.

Protocol changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such administrative changes.

16.2 RECORDING OF DATA, DOCUMENTATION, AND RETENTION OF DOCUMENTS

Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. All study records must be available for inspection by the Sponsor, its authorized representatives, the FDA, and other regulatory authorities.

Data on subjects collected on CRFs during the study will be documented in an anonymous fashion and the subject will only be identified by the study number and by initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both Gilead Sciences, Inc. and the Investigator are bound to keep this information confidential.

The Investigator must maintain source documents for each subject in the study, consisting of all demographic and medical information, and must keep a copy of the signed ICF. The subject's clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include but are not limited to the subject's hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, pathology, and special assessment reports and signed ICFs. All information on the CRFs must be traceable to these source documents in the subject's file. Data without a written or electronic record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data.

Essential documents defined in the ICH Guidance on Good Clinical Practice (ICH E6) and listed below, must be retained by the Investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required. The Investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include:

1. IRB approvals for the study protocol and all amendments
2. All source documents and laboratory records
3. CRF copies
4. Subjects' ICFs (with study number and title of study)
5. Country-specific regulatory documents

16.3 **Auditing Procedures**

Investigator understands that source documents for this study must be made available to appropriately qualified personnel from the Sponsor or its designees, to the IRB, and/or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. The Sponsor conducts audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the Investigator must immediately inform the Sponsor that this request has been made.

17. Publication of Results

An integrated clinical and statistical report will be prepared at the completion of the treatment period. However, it is intended that the results of the study will be included on http://clinicaltrials.gov and published and/or presented at scientific meetings.

18. DISCLOSURE AND CONFIDENTIALITY

By signing this protocol, the Investigator agrees to keep all information provided by GlaxoSmithKline plc. in strict confidence and to request similar confidentiality from his/her staff and the IRB. The information provided by GlaxoSmithKline plc. to the Investigator may not be disclosed to others without direct written authorization from GSK, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

All information will be kept private. The Investigator will assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. The Investigator should keep a subject enrollment log relating codes to the names of subjects. The Investigator should maintain documents not for submission to the Sponsor, (e.g., subjects' signed consent forms), in strict confidence.

If scientific reports, publications, or educational materials are written using information from the database, patients within the database will not be identified by name, and data will be present only in aggregate form. They will be given a subject identification number.

Access to this database will be restricted by a database manager and will be password protected. The only individuals who will be able to see patient identifiers, like name, date of birth, date of surgery will be the Principal Investigator, research coordinators, recruiters, and the database managers. Other investigators will have different passwords that will provide restricted access to the database. Those with restricted access will be able to query the database for scientific information/variables but will not be able to view information on patient identifiers such as name, address, and social security number. If investigators with restricted access want to conduct studies which require them to obtain patient identifiers so that patients can be contacted for follow-up information/follow-up visits, these investigators will have to submit a separate protocol to IRB to get permission to obtain patient identifiers and contact patients.

The information in the database will help study pulmonary disease and lung transplant. These studies will require authorization by the Principal Investigator. Any approved study run by an investigator must be approved by an Institutional Review Board.

All personnel that are involved with this protocol or that will have access to the Biobank have passed the IRB certifying examination. The personnel will only include faculty and staff employed at the recruitment site (BUMC).

19. **DATA SHARING**

Data generated from this study may be shared with the study sponsor. No information that can directly identify participants will be shared outside the study site/study team.

Information that may be released to institutional study researchers may include, but is not limited to medical information, age, sex, ethnic background, family history, imaging data, blood samples, and blood sample products. Identifiers, like names, addresses, and social security numbers, will not be released, except if patients need to be contacted again for specific purposes in new IRB-approved studies. All efforts will be made to keep true identities confidential.

20. **STUDY DISCONTINUATION**

The study site reserves the right to discontinue the study at any time. The sponsor reserves the right to terminate the study in its entirety or at the study center at any time and as specified in the clinical study agreement.

21. **REFERENCES**

1. Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease (COPD). Department of Health and Human Services; 2018 [Available from: https://www.cdc.gov/copd/index.html.
2. Global Initiative for Chronic Obstructive Lung Disease. Global trategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 Report). Global Initiative for Chronic Obstructive Lung Disease, Inc.; 2019 [Available from: https://goldcopd.org/gold-reports/.

3. Chapin TW, Mann MA, Brown GL, Leitheiser TL, Anderson B, Leedahl DD. Effectiveness of Umeclidinium-Vilanterol for Protocolized Management of Chronic Obstructive Pulmonary Disease Exacerbation in Hospitalized Patients: A Sequential Period Analysis. Chronic Obstr Pulm Dis 2018;5(1):38-45.

22. **APPENDICES**

TRELEGY-ELLIPTA-PI-PIL-IFU (9/2020) (attachment)