Statistical Analysis Plan

Study ID: 217658

Official Title of Study: A 12-week, Prospective, Open Label, Single Cohort Study to Evaluate the Real-world Effectiveness of Fluticasone Furoate/ Umeclidinium Bromide/Vilanterol in a Single Inhaler (Trelegy Ellipta) in Symptomatic Chronic Obstructive Pulmonary Disease (COPD) Patients

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TITLE PAGE

Protocol Title: A 12-week, prospective, open label, single cohort study to evaluate the real-world effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a single inhaler (Trelegy Ellipta) in symptomatic chronic obstructive pulmonary disease (COPD) patients.

Study Number: 217658

Compound Number: GSK2834425

Abbreviated Title: Phase IV study of GSK2834425 in symptomatic COPD patients

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP 1.0	10 Nov 2023	Original (02Feb2022)	Not Applicable	Original version
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Add 'to evaluate the proportion of patients achieving health status response with Trelegy.' as the third secondary objective. Add an additional secondary outcome to see CAT score change at week 4.	To align with Protocol Amendment.
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Remove Interim analysis in the section of '1.2 study design'. Change the name of the Interim Analysis section to additional analysis for license renewal.	To add flexibility to provide data for license renewal.
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Inverse-probability weighted mixed model for repeated measures (MMRM) was updated and written into the primary analysis.	The MMRM may provide additional insights to the primary endpoint.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Update the baseline and post-baseline covariates for the primary analysis.	Further specification of covariates used in IPW and MMRM.
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Delete the description of the process of filtering covariates. Update the description of using MMRM model to analyze the change from baseline in CAT score. Add the description that the week 4 and week 12 may have different IPW weights.	For clarification
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Update the description of sensitivity analysis and indicate the covariates included in the model.	The description of the mothed of primary analysis changes.
SAP amendment 1.0	10 Nov 2023	Amend (27Jan2023)	Delete the exploratory endpoint 'Change from baseline of FEV1/FVC ratio at week 12'.	Correction.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 217658. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• The primary objective of this study is to evaluate the effectiveness of Trelegy on health status in patients with symptomatic COPD at week 12.	• Change from baseline of CAT score at week 12
Secondary	
• to evaluate the effectiveness of Trelegy on dyspnea in patients with symptomatic COPD at week 12. • to evaluate the effectiveness of Trelegy on lung function in patients with symptomatic COPD at week 12. • to evaluate the proportion of patients achieving health status response with Trelegy. • to evaluate the effectiveness of Trelegy on health status in patients with symptomatic COPD at week 4.	• Change from baseline of Modified Medical Research Council (mMRC) at week 12 • Change from baseline of pre-dose FEV1 at week 12 • Proportion of CAT responder (defined as ≥ 2 unit decrease from baseline) at week 12 • Change from baseline of CAT score at week 4
Exploratory	
• to evaluate the effectiveness of Trelegy on lung function in patients with symptomatic COPD	• Change from baseline of Forced Vital Capacity (FVC), Forced Expiratory Flow at the 25 and 75% (FEF_{25-75}), Inspiratory Capacity (IC) at week 12

Objectives	Endpoints
Safety	
• The safety objective is to collect the safety information of participants using Trelegy.	• Trelegy related AEs • SAEs • AEs that lead to the discontinuation of Trelegy

Primary estimand refers to Section 4.2.1.

1.2. Study Design

Overview of Study Design and Key Features	
Design Features	This is a 12-week, prospective, open label, single cohort study. The enrolled participants will be those who are symptomatic under COPD maintenance treatments, and newly prescribed with Trelegy under the discretion by clinical physicians. The study applies a single cohort design to evaluate the effectiveness following 12-week treatment with Trelegy by comparison to baseline data, which can reflect the benefits (i.e., CAT score and FEV1, etc.) of patients who remain symptomatic with their prior maintenance treatment. The decision to prescribe Trelegy shall be independent to the study with medical records providing documentation of a Trelegy prescription. The prospective data collection starts from Visit 1 when Trelegy is taken by patients for the first dose. The participants will complete the CAT score at Visit 1, Visit 2 and Visit 3 or early discontinuation/withdrawal visit (E.D.), and the mMRC at Visit 1 and Visit 3 or E.D. The participants' pulmonary function test will be assessed at Visit 1 and Visit 3 or E.D.. The investigators will record Trelegy-related adverse events (AEs), serious adverse events (SAEs) and AEs that lead to withdrawal from Trelegy.
Study Treatment	All patients will receive Trelegy (FF/UMEC/VI ELLIPTA 100/62.5/25 μg) according to the local SmPC. Participants are expected to inhale one dose in the morning from the Trelegy Ellipta at approximately the same time each day for 12 weeks after enrolment.

2. STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate the effectiveness following 12-week treatment with Trelegy by comparison to baseline data. There are no formal hypothesis tests associated with this objective and no formal significance tests.

2.1. Multiplicity Adjustment

Not applicable.

3. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were prescreened or screened, i.e. those having signed the informed consent.	Disposition
Enrolled	All participants who entered the study, i.e. those having passed the screening procedure.	Disposition
Full Analysis Set (FAS)	All participants who enrolled into the study and take at least one dose of Trelegy	• Disposition • Demographic and baseline characteristic • All effectiveness analyses • All safety analyses

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Confidence intervals will use 95% confidence levels unless otherwise specified.

4.1.2. Baseline Definition

For all endpoints, the baseline value will be the latest pre-dose of Trelegy assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline, and values at scheduled visit have higher priority than the ones at the unscheduled visits if the two records are on the same day.

Unless otherwise stated, if baseline data is missing, no derivation and/or imputation will be performed and baseline will be set as missing.

All baseline values will be referred to as ‘Baseline’ in the summary outputs.

4.2. Primary Endpoint Analyses

4.2.1. Definition of estimand

The primary clinical question of interest is: what is the change from baseline in CAT score at week 12, regardless of receiving a new COPD maintenance therapy or treatment discontinuation.

The estimand is described by the following attributes:

- Population: Symptomatic Chinese COPD participants who are receiving COPD maintenance treatment
- Treatment condition: Trelegy (FF/UMEC/VI ELLIPTA 100/62.5/25 µg) one dose daily, inhaled
- Variable: change from baseline of CAT score at week 12.
- Intercurrent events:
    - Receiving other COPD maintenance therapy is addressed by the treatment policy strategy.
    - Treatment discontinuation due to any reason is addressed by the treatment policy strategy.
- Summary measure: average change from baseline in CAT score at week 12.

Rationale: Interest lies in the treatment effect at week 12 in the real-world setting, maybe confounded by other COPD maintenance therapies or the event of treatment discontinuation due to any reason. Therefore, treatment policy strategy is employed to handle the intercurrent events of receiving a new COPD maintenance therapy and treatment discontinuation due to any reason as it reflects the clinical practice.

The COPD Assessment Test (CAT) is a validated 8-item questionnaire developed for use in routine clinical practice to measure the health status of patients with COPD [Jones, 2009; Jones, 2012]. Participants rate their experience on a 6-point scale (Protocol Appendix 1-1), ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicated greater disease impact.

In the derivation of CAT total score, the score of an item at a visit is set as the average of the other non-missing items when only this item is missing at that visit.

4.2.2. Main analytical approach

Primary analysis will be conducted using an inverse-probability weighted mixed model for repeated measures (MMRM) for the change from baseline in CAT score under the missing at random (MAR) assumption to handle missingness which may occur during the data collection.

The inverse probability weighting (IPW) method can reduce the selection bias caused by the missingness, by weighting the participants whose change from baseline of CAT score is observed at week 12 using the inverse probability of completeness in the endpoint. The key assumption for the IPW method is MAR which means that the missingness mechanism of the primary endpoint could be modelled using the observed factors, i.e. the baseline covariates and the post-baseline covariates by the time of missingness, and no unmeasured confounders are involved in the missingness mechanism.

To estimate the probability of the completeness of the primary endpoint, a logistic model is constructed to model its missingness mechanism with the missingness status as the dependent variable (status=observed, status=missing as the reference group). The following baseline and post-baseline covariates will be considered for the missingness of change from baseline in CAT score at week 12:

- Age,
- Gender,
- Years of COPD,
- Smoking history: smoking status and number of pack years,
- Pre-dose FEV1 at baseline,
- COPD maintenance treatment at baseline,
- CAT score at baseline,
- The change from baseline in CAT score at week 4,
- Intercurrent event status: no intercurrent events, received other COPD maintenance therapy, Trelegy discontinued due to other reason.
  The subjects receiving other COPD maintenance therapy are those who have discontinued their Trelegy therapy and switched to other COPD maintenance therapy.
- Duration of Trelegy

The right tail of estimated weights may be truncated by its appropriate percentile if deemed necessary.

The change from baseline in CAT score will be analysed using the MMRM model with the covariates of smoking status, CAT score at baseline, visit, the interaction of CAT score at baseline*visit, in which each observation is weighted with the inverse probabilities derived from the above logistic regression models.

If a covariate is with missing values, the missing values in the covariate may be imputed if deemed necessary using appropriate imputation models with information by the time of its missingness. If any imputed covariate is used, the multiple imputation process will be employed to ensure the variability in the missingness of covariates are considered. At least 1000 datasets will be generated which include both observed and imputed values for the covariates. The inverse-probability weighted MMRM estimates, the corresponding standard errors and 95% confidence intervals from each dataset will be combined using the Rubin's rule.

Descriptive statistics will be summarized using the observed data.

4.2.3. Sensitivity analyses

Sensitivity analysis will be conducted using a MMRM with the covariates of smoking status, CAT score at baseline, visit, the interaction of CAT score at baseline*visit to derive the point estimate and the standard error of change from the baseline in the CAT score, but in which the

missing data in the primary endpoint will be imputed using monotone linear regression multiple imputation under missing at random assumption, for participants with no intercurrent events, receiving other COPD maintenance therapy, with treatment discontinuation, separately if data permits, otherwise may be imputed for the pooled groups, using the observed factors, i.e. the baseline covariates and the post-baseline covariates by the time of missingness.

The missing values in the covariate may be imputed with information by time of its missingness if deemed necessary.

At least 1000 datasets will be generated which include both observed and imputed values for the covariates. The MMRM estimates for the primary endpoint as well as the corresponding standard errors from each complete dataset will be combined using the Rubin's rule.

4.3. Secondary Endpoints Analyses

4.3.1. Secondary endpoints

The analysis approach for the below secondary endpoints is analogous to the primary analysis and the sensitivity analyses for the primary endpoint:

- Change from baseline of Modified Medical Research Council (mMRC) at week 12
- Change from baseline of pre-dose FEV_1 at week 12
- Proportion of CAT responder (defined as ≥ 2 unit decrease from baseline) at week 12
- Change from baseline of CAT score at week 4

In the analysis for the proportion of CAT responder (defined as ≥ 2 unit decrease from baseline) at week 12, the considerations follow:

- Summary measure is the proportion of participants having ≥ 2 unit decrease from baseline at week 12.
- The response status of a participant at a visit is set to missing if his/her CAT score at baseline or at the visit is missing.
- The IPW weights used for primary endpoint were applied here to estimate the proportion of CAT responder at Week 12.

The missingness of the change from baseline in CAT score at week 4 will be modelled analogously as the primary analysis but with the covariates collected before week 4. The missing values in the covariates may be imputed with information by time of its missingness. The IPW weights are applied at the observation level, thus the observations for a same subject with available change from baseline in CAT score values at the week 4 and week 12 may have different weights.

4.4. Exploratory Endpoints Analyses

The analysis approaches for the below exploratory endpoints are analogous to the primary analysis and the sensitivity analyses for the primary endpoint:

- Change from baseline of Forced Vital Capacity (FVC) at week 12
- Change from baseline of Forced Expiratory Flow at the 25% and 75% (FEF_{25-75}) at week 12
- Change from baseline of Inspiratory Capacity (IC) at week 12

4.5. Safety Analyses

The safety analyses will be based on the Full Analysis Set, unless otherwise specified.

4.5.1. Adverse Events

AE terms will be coded using Medicinal Dictionary for Regulatory Activities (MedDRA) dictionary.

The number and percentage of participants experiencing at least one AE of below category will be summarized:

- Overview of AEs
- On-treatment AEs will be summarized by system organ class (SOC) and preferred term (PT) for:
    - Trelegy related non-serious AE
    - SAEs
    - Trelegy related SAEs
    - AE leading to discontinuation of Trelegy
    - Trelegy related AE leading to discontinuation of Trelegy
- Post-treatment AEs will be summarized for:
    - SAEs by SOC and PT

4.5.2. Vital Signs and Others

Body Temperature, Pulse Rate, and Blood Pressure (systolic and diastolic) will be summarized at the scheduled time points specified in Visit 1 and Visit 3.

Pregnancy status will be listed if any.

4.6. Other Analyses

4.6.1. Subgroup analyses

Subgroup analyses of the primary endpoint will be further investigated across the CAT score at baseline:

- Moderate impact [CAT 10-20],
- Severe impact [CAT 21-30],
- Very severe impact [31-40].

4.6.2. Other variables and/or parameters

Not applicable.

4.7. Sequence of Planned Analyses

To support the license renewal, an additional analysis may be performed with the early available study data (i.e. the data in participants who are enrolled by 29 May 2023 and at the time when they all have completed the study or withdrawn from study). This analysis is exclusively for the license renewal purpose and will not have any impact on the study design and other study criteria.

The whole study data will be analysed when all the participants have completed the study or withdrawn from study.

4.8. Changes to Protocol Defined Analyses

Protocol defined that sensitivity analysis will be conducted using the arithmetic mean and missing data will be imputed using multiple imputation under missing at random assumption. The change is that sensitivity analysis will employ a mixed model for repeated measures (MMRM) to estimate the treatment effect. By employing the MMRM model, although the estimate of mean will not change, its standard error may be reduced due to the information from covariates, and the MMRM model provides additional insight to the impact of covariates.

5. SAMPLE SIZE DETERMINATION

INTREPID study [study 206854 China CSR GSK Document Number 2019N418769_00] showed that in the real world setting 19% participants had early withdrawn from the Trelegy treatment prior to week 24. Considering the difference in the China clinical practice and study designs, it is assumed that 79% enrolled participants would complete 12 weeks of Trelegy treatment with no intercurrent events, 20% would have the intercurrent event of receiving a new COPD maintenance therapy, 1% would have the intercurrent event of treatment discontinuation.

Based on results from a few studies, i.e., IMPACT [Lipson, 2018; study CTT116855 China CSR GSK Document Number 2018N356723_00], INTREPID [study 206854 China CSR GSK Document Number 2019N418769_00] and one randomized controlled trial (RCT) [Bansal,

2021], it is assumed that a decrease of 2 in the primary endpoint at week 12 will be observed in this study with a common standard deviation of 7.

A sample size of 460 is planned. With the assumptions in Table 1 of the protocol, the sample size would be able to provide a half-width ranging from 0.64 to 0.73 for the 95% confidence interval (CI) of the inverse probability weighted mean of the change from baseline in CAT score at week 12 in the primary analysis under different missingness scenarios.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Full Analysis Set.

6.1.1. Participant Disposition

A summary of the number of participants in each of the participant level analysis set will be provided.

The participant disposition will be summarized for:

- Number of withdrawals leading to the screening failure, number of subjects in the screening, number of subjects having failed the screening, based on the Screened Analysis Set.
- Trelegy conclusion and the primary reason of the Trelegy discontinuation
- Study conclusion and the primary reason of the Study discontinuation

6.1.2. Demographic and Baseline Characteristics

The following demographic characteristics will be summarized:

- Age: continuous and also in the category of 18-<40, 40-<65, 65-<85 and >=85 ages. Age is derived using the date of the informed consent date. Day and Month of birth are imputed as 30 June.
- Sex: male, female
- Height: continuous
- Weight: continuous
- Body Mass Index (BMI): continuous, calculated as weight (kg)/[height (m)]2.

The following baseline characteristics will be summarized:

- COPD History:
    - Year of COPD, derived using the date of the informed consent date, continuous and also in the category of <6 months, >=6 months to <1 year, >=1 to <5 years, >=5 to <10 years, >=10 to <15 years, >=15 to <20 years, >=20 to <25 years and >=25 years.
    - Number of severe COPD Exacerbation during the Past Year,
    - Number of moderate COPD Exacerbation during the Past Year,
    - Number of moderate/severe COPD Exacerbation during the Past Year, continuous and also in the category of 0, 1 and >=2.

- Existing COPD Maintenance Treatment: ICS/LABA, LAMA/LABA, Free combination of ICS, LAMA, LABA
- Medical history
    - The number and percentage of participants with each medical history condition
- Smoking history
    - Smoking status
    - Year of smoking
    - Average Number of Units Consumed Per Day
    - Number of Pack Years
- Physical examination: Normal, Abnormal - Not Clinically Significant, Abnormal - Clinically Significant
- Electrocardiogram (ECG): Normal, Abnormal - Not Clinically Significant, Abnormal - Clinically Significant

6.1.3. Protocol Deviation

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Treatments

Prior and concomitant medication tables will be summarized by Anatomical Therapeutic Chemical (ATC) level 1 and ingredient for:

- Pre-treatment COPD Medications
- On-treatment COPD Medications
- Post-treatment COPD Medications
- Prior and Concomitant Non-COPD Medications

Multi-ingredient medications will be presented according to their combination ATC classification rather than the classification of the ingredients.

Prior and Concomitant Non-Drug Treatments will be summarized.

6.1.5. Trelegy Exposure and Compliance

The duration of Trelegy, the actual dose will be summarized.

A summary of overall compliance for Trelegy based on the exposure data will be produced. Overall compliance will be summarized using descriptive statistics as well as the categories <80%, 80%-105%, and >105%.

Trelegy Compliance (%) = [Total cumulative actual dose / Total cumulative scheduled dose] *100.

Number of subjects with treatment switch will be summarized.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-treatment is defined as time prior to the first dose of Trelegy.

On-treatment is defined as time from first dose to last date of Trelegy.

Post-treatment is defined as any time post on-intervention window, i.e. > last dose date of Trelegy.

For AE, if the study period cannot be determined due to partial or missing data, the study period would be classified as “on-treatment”, unless the end date of the AE rules out this probability. Trelegy-related AEs are classified as “on-treatment”.

For COPD medications, a COPD medication may be classified into one or multiple categories of “pre-treatment”, “on-treatment” and “post-treatment” medication. If the study period cannot be determined due to partial or missing data, the medication would be classified into one or multiple categories of “pre-treatment”, “on-treatment” and “post-treatment” if it might satisfy the study period definition(s).

6.3. Appendix 3 Assessment Windows

6.3.1. General

In general, data will be reported according to the nominal time of clinic visits and assessments as specified in the protocol.

6.3.2. E.D. Data

To make full use of effectiveness outcomes data, the effectiveness measurements collected at E.D. including CAT score, mMRC and Pulmonary function test (Pre-dosed FEV_1, FVC, FEF_{25-75} and IC) will be used according to the following rules:

- If E.D. date of the participant is before Day 55 (<=55), the participant's value of week 12 related endpoints will be treated as missing and its analysis approach can be found in Section 4. Otherwise, the participant's value of week 12 related endpoints will be mapped to E.D. results.
- If E.D. date of the participant is before Day 12 (<=12), the participant's value of week 4 related endpoints will be treated as missing and its analysis approach can be found in Section 4. Otherwise, the participant's value of week 4 related endpoints will be mapped to E.D. results, if E.D. date of the participant is before Day 21 (<=20).

6.4. Appendix 4 Handling of Missing or Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First day of the month will be used, respectively, unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Section 6.2.1: Study Period. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications or medical history recorded in the CRF will be imputed using the following convention: o If the partial date is start date, a '01' will be used for the day and 'Jan' will be used for the month. o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

6.5. References

Bansal S, Anderson M, Anzueto A, Brown N, Compton C, Corbridge TC, et al. Single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy versus tiotropium monotherapy in patients with COPD. NPJ Prim Care Respir Med. 2021 May 25;31(1):29.

China Clinical Study Report for study CTT116855 - A phase III, randomized, double-blind study comparing the efficacy, safety and tolerability of the Trelegy with the fixed dose dual combinations of FF/VI and UMEC/VI in subjects with COPD [GlaxoSmithKline Document Number 2018N356723_00]

China Clinical Study Report for study 206854 - The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGY TM ELLIPTA TM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting [GlaxoSmithKline Document Number 2019N418769_00]

Clinical Study Protocol for study CTT116855 - A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease [GlaxoSmithKline Document Number 2013N176913_05]

Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009. 34(3):648-54.

Jones PW, Harding G, Wiklund I, Berry P, Tabberer M, Yu R, et al. Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. Chest. 2012 Jul;142(1):134-140.

Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378: 1671-80.

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