Effect of inhaled triple therapies on the small airway in patients with Chronic Obstructive Pulmonary Disease or chronic bronchitis without obstruction exposed to wood smoke: Phase IV randomized controlled clinical trial.

Approved by the Institutional Ethics Committee on November 13th, 2023 under the code C74-23.

DEFINITION OF THE PROBLEM

Domestic pollution secondary to biomass burning is the main risk factor in the field of environmental health, according to the World Health Organization (WHO) it caused up to 4.3 million deaths in 2012 [1]; It is associated with cooking on open stoves with solid fuels such as firewood, charcoal. This activity, common in our Mexican population, can cause chronic obstructive pulmonary disease due to biomass (firewood smoke) (COPD-B), causing persistent respiratory symptoms and a decline in respiratory function [2–4]. However, there is also a proportion of patients who present with symptoms of COPD-B but do not meet the established definition of obstruction and remain asymptomatic [5]. Patients with COPD-B have a predominantly airway phenotype, with small airway dysfunction (SAD) demonstrated by oscillometry. Due to the aforementioned, initiating inhaled treatment in patients with COPD-B classified as GOLD 0 or pre-COPD or as chronic bronchitis without obstruction (BCNO) [6], in an earlier phase, could impact on improving or even reversing the peribronchiolar inflammation. Testing triple therapy (TT) long-acting muscarinic antagonist, long-acting beta-agonist, and inhaled steroid (LAMA/LABA/ICS) is emerging as an alternative to stop the progression of COPD [5], improve the quality of life associated with health, integrating patients into their work and social environment and even reducing the costs related to health care. Currently there are three devices containing umeclidinium, vilanterol, and fluticasone in an Ellipta device using dry powder triple therapy (E-PST); glycopyrronium, formoterol and extra fine particle beclomethasone in pressurized metered dose inhaler (pMDI-EF); glycopyrronium, formoterol, and budesonide also in pMDI (pMDI-F), the three therapies being very recently used in COPD due to cigarette smoking (COPD-C), and we will also compare the Ellipta device with dry powder dual therapy (E-PSD) with umeclidinium/vilanterol) in our social and health context for patients with COPD-C, it is very suitable to have a treatment for COPD-C that allows it to be more precise and personalized according to their phenotype.

RESEARCH QUESTION

In patients with COPD-B and BCNO, is there any difference in small airway resistance, especially R5-R20 and/or AX, when triple therapies (pMDI-EF, E-PST, pMDI-F) are administered for three months? compared to dual therapy (E-PSD)?

BACKGROUND

Background information must be provided to understand the relevance of this study and the purpose and rationale of the study.

A summary of data from non-clinical studies that are potentially of clinical importance and from clinical and epidemiological studies relevant to the present study should be

included, as well as references to the literature relevant to the study and that provide support for the study.
We know that there are multiple risk factors for the development of COPD, the main factor for the burden of COPD is tobacco [7], however, in second place is the burning of biomass. The clinical profile of COPD associated with wood smoke (HL) has been reported that mainly women are affected and develop COPD associated with biomass combustion (COPD-B) [3, 4], they present a decrease in FEV1 slower but homogeneous [8], but they present with a deterioration in quality of life and increased mortality similar to that of patients with COPD-C[9]. Furthermore, they develop little emphysema, but the damage predominates in the VAP, with DVAP manifesting by oscillometry [10]. Understanding the progression of COPD offers new opportunities for prevention, early diagnosis, and intervention. This has brought about concepts such as pre-COPD or GOLD 0, as well as chronic non-obstructive bronchitis (BCNO) [11] refers to individuals of any age who have respiratory symptoms with structural and/or functional abnormalities, in the absence of respiratory limitation airflow, which can have outcomes such as exacerbations or even death. In Mexico, patients exposed to wood smoke have been analyzed and 3.5% present obstruction, but if exposed women are analyzed, 27% and 16% remain symptomatic (referring to cough, phlegm, and dyspnea) [12]. For this group of symptomatic patients without obstruction, pharmacological interventions have been performed [13] and there are currently some trials for patients with COPD-B [14]. Triple therapy has shown a decrease in mortality, which is why it has become one of the standard treatments for patients with COPD who present peripheral eosinophils of 300 cells/mcl, and frequent exacerbations [13], but as far as we know, they are not included. unobstructed symptomatic patients exposed to wood smoke.
Clinical trials of bronchodilator drugs in COPD often investigate the dose-response relationships of different drugs with FEV1, but spirometric measurement of FEV1 is usually the main outcome variable, however, it does not reflect damage to VAP; Furthermore, bronchodilator drugs can improve lung mechanics in patients with COPD despite small changes in FEV1, however, oscillometry seems to be a sensitive option to measure these changes [15]. The most sensitive and constant parameters to measure changes seem to be R5-R20, AX, R5, being associated with quality of life or symptoms [16].
Thus, comparatively, we propose to carry out a randomized, open clinical trial with the different triple therapies U/V/FL, G/F/B and G/F/BD evaluating the response by impulse oscillometry, specifically the reduction of resistances in R5, R20, R5-R20, and the reactance area (AX). In addition to these interventions, we will secondarily investigate the symptoms, and the quality of life evaluated by the Saint George questionnaire, in addition to characterizing the VAP condition through respiratory function and imaging.

JUSTIFICATION

We start from the need to treat a group of patients with characteristics different from patients with COPD-C, from the mechanisms of pathogenesis, symptoms and clinical signs and respiratory function, therefore, even though some patients may not develop obstruction [17 , 18] some of them remain with symptoms and with a quality of life associated with the affected health [19], since we know that in the pathogenic

background of the disease the main respiratory condition is directed at the VAP [10], demonstrated both histologically as functional [20]. Therefore, hypothetically, patients exposed to wood smoke could remain symptomatic and not develop obstruction. This is how we propose early therapeutic intervention; This intervention will aim to reduce the predominant inflammation in symptomatic women exposed to wood smoke with or without obstruction. The evaluation, as mentioned, aims to identify the response by oscillometry in those patients with COPD-B and patients with BCNO with the 3 different triple therapies in a single device compared to dual therapy in a single device.

HYPOTHESIS

Triple device therapies (pMDI-EF, pMDI-F and E-PST) will show a greater proportion of patients with decreased VAP resistance in R5-R20 and/or AX, compared to the E-PSD device in patients with COPD-B and BCNO exposed to firewood smoke after 90 days of treatment.

GENERAL OBJECTIVE

To evaluate if there is a difference in the response of VAP resistance through iOS in R5-R20 and/or AX for triple therapies (pMDI-EF n pMDI-F and E-PST) compared to E-PSD in patients with COPD-B and BCNO in a period of 90 days.

SPECIFIC OBJECTIVES

1. Quantify adherence to treatment according to the inhaler used. [Time frame: 90-day baseline]
2. Quantify the proportion of patients with the different triple therapies who present a change in peripheral airway resistance using iOS (post-bronchodilator change in total resistance, z-score, and percentage change for R5, R20, AX, X5, R5-R20) at 30 minutes, 2 hours, 4 hours and 24 hours, 30 days and 90 days after administering triple therapy or dual treatment."
3. The response to bronchodilator will be quantified in FEV1, FVC, FEF 25-26, and MEF50, at 30 minutes, 2 hours, 4 hours, and 24 hours, 30 days, and 90 days after administering triple therapy or dual treatment.
4. Quantify the change in the exhaled fraction of nitric oxide (ppb) before administering the triple therapies and the dual bronchodilator at 24 hours, 30 days, and 90 days.
5. Compare peripheral airway resistance using body plethysmography with those obtained by IOS [Time frame: baseline and 90 days].
6. Analyze the proportion of individuals with a significant improvement of 2 units in CAT. [Time frame: 90 days].
7. Analyze the proportion of individuals with a significant improvement of 4 units in the Saint George respiratory quality of life questionnaire. [Time frame: 90 days]
8. Assess the change from baseline in 12-hour minimum inspiratory capacity, FEF25-75% and iso-volume FEF25-75% (absolute value and % predicted)
9. Describe the biomarkers associated with Th2 and Th17 inflammatory endotypes: exhaled fraction of nitric oxide ppm, total peripheral serum eosinophils and percentage, serum interleukins 4, 5, 6, 13, 17, 22, 31, 33 and eotaxin.
10. Evaluate the safety profile of inhaled medications E-PS, pMDI-EF or pMDI-F.

MATERIAL AND METHODS

1. Study location.

National Institute of Respiratory Diseases “Dr. Ismael Cosío Villegas” as directing center. It will be a multicenter study where different research centers that care for this type of patients will participate, as well as having the place and supplies necessary to carry out the procedures, as well as the training of the personnel necessary for them. The patients will be those belonging to the COPD Clinic and the COPD Patient Cohort of the COPD and Smoking Research Department, as well as patients from the participating research centers.

2. Description of the study population.

Patients with a diagnosis of COPD-B GOLD I or with chronic non-obstructive bronchitis who belong to the COPD-B Clinic Cohort or participating centers.

3. Inclusion Criteria.

1. The subject must be able to understand and give informed consent.
2. Age 35-85 years
3. Women (not pregnant or using effective contraception).
4. Diagnosis of COPD-B or BCNO

i. Patients diagnosed with COPD-B according to the GOLD 2023 guidelines, secondary to exposure to wood smoke >100 hours-year, with FEV1 > 70%.

ii. Patients with BCNO who have at least one exposure to wood smoke for 10 years and/or > 100 hours-year, and who also present: 1) history of chronic bronchitis and 2) post-bronchodilator spirometry with FEV1/FVC >0.7.

and.

e. Possibility to attend all study visits.

f. Cooperative patients with adequate understanding and skill in using inhalers, or with caregivers capable of administering medications and filling out a daily symptom diary.

g. Stable patients, with no history of exacerbations in the last 4 weeks before inclusion.

4. Exclusion Criteria.

a) Documented allergy or intolerance to any of the study medications.

b) Pregnancy or lactation.

c) History of clinically significant bronchiectasis, tuberculosis, recent respiratory infection (4 weeks), or cardiovascular comorbidity that contraindicates pulmonary function tests or that influences their status and functional class.

d) Patients with suspicion or history of cancer.

e) Uncontrolled diseases: acute hyperthyroidism, acute uncontrolled DM2, acid-peptic disease that causes bleeding, uncontrolled hematological diseases, etc. In general, any decompensated disease that, in the opinion of the principal investigator, may influence the results of the study.

5. Elimination criteria.

a) Side effects that are not tolerated (Adverse effects will be reported immediately (<24 hours) to the Institute's Science and Bioethics Committee)

b) Adherence to treatment < 80% (The devices dispensed will be reviewed at each visit to count consumed doses and remaining doses, the inhalation technique will be corroborated.)

c) Do not attend 1 or more visits.

6. Sample size.
The sample calculation for mean difference was based on Borrill et al [15] with 80% power to detect a difference of 0.1 kPa L -1 s in the primary outcome assuming a reduction in the basal percentage of AX - 28% and/or R5-R20 -8.5% for VAP resistances, expecting an alpha error of 0.05 (two-tailed) with a total of 16 patients per group for each triple therapy and dual therapy for each group (obstructed and non-obstructed by spirometry), with a total of 128 patients.
Primary outcomes:
•Quantify the change in impulse oscillometry (post-bronchodilator change in total resistance measured in percentage change from baseline change R5-R20 and/or AX for patients who used E-PS vs pMDI-EF vs pMDI-F at 3 months.
Secondary outcomes:
• Quantify the change by z-score and percentage change for R5, R20, R15 and Fres.
• Change in total resistances and reactances in kPaL-s, measured by oscillometry in R5-R20, R20,AX, Fres. and total resistances, measured by plethysmography.
• Change in lung function in FEV1, FVC, FEF25-75%, MMEF(L/s) both in ml and in percentage change from predicted.
• Quantify adherence to treatment according to the type of inhaler.
• Change in exhaled fraction of nitric oxide measured by parts per million.
• Change in the level of total peripheral eosinophils and in percentages.
• Change in quality of life in CAT score according to triple therapy.
• Change in quality of life in the Saint George respiratory questionnaire score, according to triple therapy.
• Change in dyspnea score measured by mMRC
Safety evaluation:
Includes the evaluation of adverse events from rare to frequent, which will be reported by patients and recorded in a symptom log.

Definition of variables

1. Impulse Oscillometry Measurement:
to. A Jaeger MasterScreen IOS device will be used, following the technical recommendations of the ERS 2020 standard [5]. The patient will be asked to position himself in an upright sitting position, a nose clip will be placed and he will be asked to place his mouth on the mouthpiece of the device and maintain a tight seal at all times, and his hands will be placed on his cheeks to prevent artifacts caused by the upper airway and oral cavity. You will be asked to take breaths at tidal volume, verify that there are no artifacts (swallowing, glottic closure, cough, obstruction of the mouthpiece by the tongue or leaks), and to breathe for about 30 seconds or until you have adequate measurements without artifacts. 3 acceptable and repeatable maneuvers will be performed (with a coefficient of variation less than 15% in R5) and the final value of each parameter will be the average of the 3 maneuvers.
b. The values or z score will be taken into account to determine if there is an obstruction of the VAP, taking into account an increase in resistances in R5-R20 and in the reactance area (AX) (greater than +1.64z). to that of AX and R5-R20.
c. To determine the primary outcome, the change in post-bronchodilator

oscillometry and in PBD oscillometry at the end of the month will be taken into account, measuring the percentage change.

2. Slow Spirometry Measurement (inspiratory capacity)
a) An EasyOne Pro LAB device from ndd Medical Technologies will be used following the technical recommendations of the ATS 2019 standard [21]. The patient will be asked to position himself in an upright sitting position, a nose clip will be placed and he will be asked to place his mouth on the mouthpiece of the device and maintain a tight seal at all times, he will be asked to perform tidal breaths, Begin the maneuver of relaxed deep inspiration and relaxed deep expiration. At the end, a deep inhalation is requested to complete the closed loop circuit.

3. Measurement of simple forced spirometry and with bronchodilator:
An EasyOne Pro LAB device from ndd Medical Technologies will be used following the technical recommendations of the ATS 2019 standard [21]. The patient will be asked to position himself in an upright sitting position, a nose clip will be placed and he will be asked to place his mouth on the mouthpiece of the device and maintain a tight seal at all times, he will be asked to take a forced inhalation and Subsequently, quickly and forcefully exhale until you reach residual volume, thus, without removing yourself from the mouthpiece, you will be asked to inhale deeply to complete the closed loop circuit of spirometry and the result will be analyzed.

4. Exhaled fraction of nitric oxide:
a) Portable equipment with a NIOX-MINO brand electrochemical sensor (Aerocrine, Solna) will be used, following the procedure recommended by Cantú et al.

5. Simple Plethysmography Measurement:
Jaeger MasterScreen Body equipment will be used following the technical recommendations of ERS/ATS [22]. Explain the procedure to be performed, emphasizing the following instructions to the patient: The patient must remain seated inside the cabin, with the chest and neck in a straight position. and with both feet supported on the floor. You can move the sensor forward or backward to grasp the mouthpiece without flexing or extending your neck. Before starting the measurement, place the clamp on your nose. You will need to hold your cheeks with both hands (demonstrate). Remember that the mouthpiece should be held with your teeth without biting or sticking your tongue in and you should seal your lips around it. You should breathe normally through the mouthpiece for 3 to 10 breaths, then the mouthpiece will be clogged. Don't be scared, it only lasts a few seconds during which you should breathe quickly and shallowly, about one breath per second. When the valve opens, inhale deeply until you fill your lungs and then exhale in a relaxed manner until it tells you that the measurement is over.
b. Once the procedure has been explained, close the cabin door and wait one minute for the pressure and temperature inside the cabin to stabilize.
c. Supervise the proper placement of the mouthpiece and nose clip, as well as adequate cheek support with the hands.
d. Ask him to breathe calmly, obtaining 3 to 10 breaths at tidal volume, waiting for the volume level to stabilize at the end of each expiration (stable FRC).

and. Occlude the valve at the end of an expiration when the patient is at the FRC level, instruct the patient to breathe at a slow rate of .5 to 1.5 Hz or one breath per second (30 to 90 breaths per minute).
F. When the shutter valve opens, ask the patient to take maximum inspiration and then relax expiration until reaching a plateau of at least one second with a volume change of <25 mL.
g. In patients with severe dyspnea who cannot complete the VC maneuver immediately after the ITGV maneuvers, they can perform a few tidal volume breaths and then attempt the VC maneuver.
h. Verify that the FRCpleth (ITGV) measurement generates almost straight ITGV curves that overlap each other, being within the pressure calibration ranges of the transducers (± 10 cmH2O or 1.3 kPa) and correct if necessary.
6. Simple chest tomography, performed on the SOMATOM X equipment, syngo CT VA40, Siemens Healthcare Diagnostics, 128 Dual Energy slices; with the following acquisition parameters:
Adjustment of Kev and mAs according to weight. A tomographic scan in apnea inspiration and maximum expiration.
Iterative reconstructions: Bf 31 and Bf 45, with lung window for quantitative evaluation with Syngovia – Pulmo 3D post-processing software (Siemens). Iterative reconstruction: B 70, for morphological evaluation of the lung parenchyma. Iterative reconstruction: B 21, for evaluation of the mediastinum and associated findings.
The tomographic protocol is established in the equipment command for subsequent reproducibility with the name “pre-COPD”. On average, each tomography involves a radiation dose of 3.9 mSv equivalent to 198.8 plates; compared to a conventional tomography where the radiation dose is 5 mSv for a high-resolution tomography and 7 mSv for a simple tomography, a standardized parameter for the use of effective dose. Image post-processing is carried out in Pulmo3D software, syngo via.client 8.6 (x64) Siemens 2021.
Tomographic findings will be divided into: Morphological and Quantitative: parenchymal and airway.

Procedures:
Each patient will undergo a clinical evaluation and application of questionnaires; Subsequently, baseline spirometry will be performed on both the captive COPD-B population and patients with chronic bronchitis exposed to biomass, in whom obstruction will be confirmed or ruled out. Subsequently, IOS will be performed for EVAP evaluation (R5, R20, AX, R5-R20); in addition to a chest tomography at the beginning of the study, which will be evaluated by a radiologist who will determine if they have findings compatible with COPD with predominance of emphysema or with predominance of air trapping. Assignment to treatment: The assignment to each group will be random using a table of random numbers in the Redcap program; Each patient will take their assignment on the starting day (visit 0) and the technique and dosage will be instructed by the subinvestigators.
Blinding of the study: It is open, the medication cannot be blinded since the labeling on the device indicates what medication the subject who will take it and the doctor evaluating the patient is receiving. Although the coordinator or technician who

applies the questionnaires and respiratory function tests is unaware of the assigned medication.

Visits.
Signing of informed consent (Selection visit day -21 to -1): The diagnosis of COPD-HB or BCNO will be verified. The inclusion criteria will be checked and it will be verified if there are any exclusion criteria (clinical record will be reviewed if necessary). The patient is invited to the study, and will be given detailed information about it, and a copy of the informed consent for evaluation. If you agree to participate in the study, you will be asked to sign the consent in the indicated space, as well as two witnesses. If the patient does not have post-bronchodilator forced spirometry and a six-minute walk in the last 3 weeks, these tests will be performed in the COPD lung function laboratory. A symptom diary will be dispensed and training will be given on how to fill it out. The patient will be instructed to begin the washout time, which will be one week for long-acting bronchodilators (LAMA or LABA, or LAMA/LABA combination), and 3 weeks for inhaled steroids (or ICS/LABA, ICS/LABA combinations). LAMA/LABA). During this period, patients will be able to use their rescue bronchodilator (SAMA, SABA, or combination) by schedule. They will be instructed in the identification of exacerbations and alarm symptoms and, if necessary, communicate with the principal investigator.
Randomization visit and start of treatment. (Visit 0, day 0): A complete patient history will be taken, with main emphasis on the recording of comorbidities and concomitant medication. Inclusion and exclusion criteria will be checked. The washout time of each bronchodilator will be confirmed, and once confirmed, baseline questionnaires will be performed: Measurement of dyspnea (mMRC scale, VAS) and quality of life questionnaires (CAT and SGRQ). Symptom diary will be reviewed. The history of exacerbations in the last 4 weeks will be verified. If you continue to meet the criteria, you will be selected and baseline respiratory function tests will begin: The tests will be performed between 7:00 to 8:00 AM in the following order: Exhaled fraction of nitric oxide (FeNO), impulse oscillometry, slow spirometry, forced spirometry , and simple plethysmography. The selection criteria will be confirmed and if you are a candidate, randomization will be carried out through the Redcap program.
Patients will be assigned one of the four devices contemplated for the study. The first group will be assigned the pMDI-EF device containing Beclomethasone/ Formoterol/ Glycopyrronium 100/6/12.5 mcg with doses of two inhalations every 12 hours; The second group will be assigned the pMDI-F device containing Budesonide/Formoterol/Glycopyrronium 160/4.8/7.2 mcg with doses of two inhalations every 12 hours; the third group will be assigned the E-PST device containing Fluticasone/ Vilanterol/ Umeclidinium 100/25/62.5 mcg with a dose of one inhalation every 24 hours; the fourth group will be assigned the E-PSD device containing Vilanterol/Umeclidinium 25/62.5 mcg with a dose of one inhalation every 24 hours. o Each patient will be given a 100 µg salbutamol device as rescue medication.
Once the study medication is assigned, you will be instructed in technique and dosage, and a corresponding dose will be applied. A blood sample will be taken for a blood count and IgE test and Th2 and Th17 inflammatory profile cytokines. After 30 minutes of application of the study medication, impulse oscillometry, slow

spirometry and forced spirometry will be performed. After 2 hours of application of study medication, impulse oscillometry, slow spirometry and forced spirometry will be performed. After 4 hours of application of study medication, impulse oscillometry, slow spirometry and forced spirometry will be performed. At the end of the respiratory function tests, you will be referred to the imaging service for tomography evaluation if it is not available with volumetry in the last year. Adverse events will be measured at baseline, for the safety outcome. The patient will be instructed in the use of the assigned medication, technique, frequency of use, as well as information and training on possible side effects. Visit 1 will be scheduled on your card the next day without a window period.
Follow-up visit 1 (Visit 1, Day 1): Changes in respiratory symptoms, presence of adverse events, and use of concomitant medication will be questioned and documented. Symptom diary will be reviewed. It will be confirmed that the patient has not applied the morning dose of study medication. Dyspnea questionnaire (mMRC) and quality of life questionnaire (CAT) will be completed. Pulmonary function tests will be performed: FeNO, impulse oscillometry, slow spirometry, forced spirometry and simple plethysmography. Standard doses of SABA (400 mcg of salbutamol) will be applied and after 20 minutes post-bronchodilator tests of impulse oscillometry, slow spirometry and forced spirometry will be performed. You will be instructed in the technique of inhalation of study medication and a corresponding dose will be applied. Study medication will be provided for one month of treatment. A symptom diary will be provided and a follow-up visit 2 will be scheduled 30 days after the randomization visit. Instructions for said visit will be given.

Follow-up visit 2 (Visit 2, 30 days -2/+1 day): Exacerbations during the period, frequency of adverse events, newly diagnosed comorbidities and use of concomitant medication will be questioned and documented. Symptom diary will be reviewed. Devices dispensed at visit 1 will be reviewed to calculate adherence to treatment (≥80%). It will be confirmed that the patient has not applied the morning dose of study medication. Dyspnea questionnaire (mMRC), quality of life questionnaire (Saint George and CAT), and adherence to inhaled medication questionnaire (TAI) will be completed. Baseline pulmonary function tests will be performed: FeNO, impulse oscillometry, slow spirometry, forced spirometry and simple plethysmography. Short-acting bronchodilator (SABA) will be applied, the patient will be left to rest for 20 minutes. Post-bronchodilator tests will be initiated in the following order: impulse oscillometry, slow spirometry, forced spirometry. You will be instructed in the technique of inhalation of study medication and a corresponding dose will be applied. Study medication will be provided for two months of treatment. A symptom diary will be provided and a follow-up visit 3 will be scheduled 12 weeks after the randomization visit. Instructions for said visit will be given.

Follow-up visit 3 (Visit 3, 12 weeks -2/+1 day): Exacerbations during the period, frequency of adverse events, newly diagnosed comorbidities and use of concomitant medication will be questioned and documented. Symptom diary will be reviewed. Devices dispensed at visit 1 will be reviewed to calculate adherence to treatment (≥80%). It will be confirmed that the patient has not applied the morning dose of study medication. Dyspnea questionnaire (mMRC), quality of life questionnaire

(Saint George and CAT), and adherence to inhaled medication questionnaire (TAI) will be completed. Baseline pulmonary function tests will be performed: FeNO, impulse oscillometry, slow spirometry, forced spirometry and simple plethysmography. Standard doses of SABA (400 mcg of salbutamol) will be applied and after 20 minutes post-bronchodilator tests of impulse oscillometry, slow spirometry and forced spirometry will be performed. Participation in the protocol will be terminated and monitoring by the INER Tobacco and COPD clinic will continue.
All data will be collected in questionnaires designed for this study, including a symptom diary. Additionally, some of the data and questionnaires will be collected in redCAP, once the visit and medical note are completed. Subsequently, the information will be entered into a database also designed in redCAP for this project a maximum of 3 days after the visit.

8. Results analysis plan:
Frequencies and comparisons between groups for continuous variables will be analyzed with unpaired t-tests and X2 for proportions. All efficacy analyses will be based on treatment data. To analyze the exacerbation rate, a generalized linear mixed negative binomial model will be used for each group with the treatment variable as a covariate where the number of moderate and severe exacerbations will be considered during the 4-week period.

The model analyzed terms for treatment, type of exposure (biomass or tobacco exposure), initial smoking and current biomass use, and severity of airflow limitation. For the analysis of the treatment effect according to the values of R5, R5-R20, Ax and Fres, Friedman's 2-way analysis of variance will be used and the differences between triple therapies will be analyzed post hoc by Wilcoxon for paired samples.
Program (software) to use for data analysis.
Data analysis will be performed in Stata 16.1 software.

ETHICAL CONSIDERATIONS
The type of risk must be considered in accordance with the provisions of Art. 17 of the Regulations of the General Health Law on Health Research:
• Research with minimal risk.

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