Double-blind Placebo-controlled Randomized Clinical Trial to Assess the Efficacy of Montelukast in Mild to Moderate Respiratory Symptoms of Patients With Long COVID E-SPERANZA COVID PROJECT Study Protocol

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Research Article

Keywords: Montelukast, dyspnoea, clinical trial, COVID-19, SARS-CoV-2, long COVID, Primary care, quality of life, health status

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Trials

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Full Title:	Double-blind placebo-controlled randomized clinical trial to assess the efficacy of montelukast in mild to moderate respiratory symptoms of patients with long COVID E-SPERANZA COVID PROJECT study protocol
Article Type:	Study protocol
Abstract:	Background The coronavirus disease-2019 (COVID-19) pandemic continues to affect the globe. After eighteen months of the SARS-CoV-2 emergence, clinicians have clearly defined a subgroup of patients with lasting, disabling symptoms. While big strides have been made in understanding the acute phase of SARS-CoV-2 infection, the pathophysiology of long COVID is still largely unknown and evidence-based, effective treatments for this condition remain unavailable. Objectives To evaluate the efficacy of 10 mg oral montelukast every 24 hours versus placebo in improving quality of life associated with mild to moderate respiratory symptoms in patients with long COVID as measured with the COPD Assessment Test (CAT) questionnaire. The secondary objectives will evaluate the effect of montelukast versus placebo on improving: exercise capacity; COVID-19 symptoms (asthenia, headache, mental confusion or brain fog, ageusia, and anosmia); oxygen desaturation during exertion; functional status; and mortality. Methods and analysis Phase III, randomized, double-blind clinical trial. We will include 18 to 80 year-old patients with SARS-CoV-2 infection and mild to moderate respiratory symptoms lasting more than 4 weeks. Participants will be randomly allocated in a 1:1 ratio to the intervention (experimental treatment with 10 mg/day montelukast) or the control group (placebo group), during a 28-day treatment. Follow up will finish 56 days after start of treatment. The primary outcome will be health-related quality of life associated with respiratory symptoms according to the COPD Assessment Test 4 weeks after starting treatment. Secondary outcomes a) Exercise capacity and oxygen saturation (1Min Sit-to-Stand test); b) Post-COVID-19 Functional Status scale; c) Other symptoms: asthenia, headache, mental confusion (brain fog), ageusia and anosmia (Likert scale); d) Use of healthcare resources; e) Mortality; f) Sick leave duration in days g) Side effects of montelukast. Ethics and dissemination This study has been approved by the Clinical Research Ethics Committee of the IDIAPJGol (reference number 21/091-C). The trial results will be published in open access, peer-reviewed journals and explained in webinars to increase awareness and understanding about long COVID among primary health professionals. Trial registration: ClinicalTrials.gov Identifier: NCT04695704 first posted on January, 5, 2021. EudraCT number 2021-000605-24). Prospectively registered. Keywords: Montelukast, dyspnoea, clinical trial, COVID-19, SARS-CoV-2, long COVID, Primary care, quality of life, health status

Double-blind placebo-controlled randomized clinical trial to assess the efficacy of montelukast in mild to moderate respiratory symptoms of patients with long COVID:

E-SPERANZA COVID PROJECT study protocol

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Abstract

Background. The coronavirus disease-2019 (COVID-19) pandemic continues to affect the globe. After eighteen months of the SARS-CoV-2 emergence, clinicians have clearly defined a subgroup of patients with lasting, disabling symptoms. While big strides have been made in understanding the acute phase of SARS-CoV-2 infection, the pathophysiology of long COVID is still largely unknown and evidence-based, effective treatments for this condition remain unavailable.

Objectives. To evaluate the efficacy of 10 mg oral montelukast every 24 hours versus placebo in improving quality of life associated with mild to moderate respiratory symptoms in patients with long COVID as measured with the COPD Assessment Test (CAT) questionnaire.

The secondary objectives will evaluate the effect of montelukast versus placebo on improving: exercise capacity; COVID-19 symptoms (asthenia, headache, mental confusion or brain fog, ageusia, and anosmia); oxygen desaturation during exertion; functional status; and mortality.

Methods and analysis. Phase III, randomized, double-blind clinical trial.

We will include 18 to 80 year-old patients with SARS-CoV-2 infection and mild to moderate respiratory symptoms lasting more than 4 weeks.

Participants will be randomly allocated in a 1:1 ratio to the intervention (experimental treatment with 10 mg/day montelukast) or the control group (placebo group), during a 28-day treatment. Follow up will finish 56 days after start of treatment.

The primary outcome will be health-related quality of life associated with respiratory symptoms according to the COPD Assessment Test 4 weeks after starting treatment.

Secondary outcomes: a) Exercise capacity and oxygen saturation (1Min Sit-to-Stand test); b) Post-COVID-19 Functional Status scale; c) Other symptoms: asthenia, headache, mental confusion (brain fog), ageusia and anosmia (Likert scale); d) Use of healthcare resources; e) Mortality; f) Sick leave duration in days g) Side effects of montelukast.

Ethics and dissemination. This study has been approved by the Clinical Research Ethics Committee of the IDIAPJGol (reference number 21/091-C). The trial results will be published in open access, peer-reviewed journals and explained in webinars to increase awareness and understanding about long COVID among primary health professionals.

Trial registration: ClinicalTrials.gov Identifier: NCT04695704 first posted on January, 5, 2021, https://clinicaltrials.gov/ct2/show/NCT04695704. EudraCT number 2021-000605-24). Prospectively registered.

Keywords: Montelukast, dyspnoea, clinical trial, COVID-19, SARS-CoV-2, long COVID, Primary care, quality of life, health status

Strengths and limitations of this study

Montelukast is an authorised medicine with extensive experience of use, good tolerance, and a known safety profile at the dose used in this trial.

Currently (August 2021), several studies are evaluating the efficacy of montelukast in the acute phase of COVID-19, and two clinical trials evaluate montelukast efficacy in reducing SARS-CoV-2 hospital admissions.

In a previous empirical treatment with montelukast in a case series of patients with long COVID, clinical improvement of symptoms was observed.

Since long COVID is an emergent condition, there are no validated scales for symptoms and quality of life.

To overcome memory bias in participants, telephone calls are added between office visits.

Background and rationale

From June 22, 2020, to June 30, 2021, 3,547,032 cases of coronavirus disease (COVID-19) have been reported in Spain, with 7.3% patients admitted to hospital, 0.7% admitted to intensive care units, and a mortality of 1.4% [1].

In patients with mild to moderate symptoms and severe to critical coronavirus disease, full recovery might take up 2 and 3-6 weeks from the onset of symptoms, respectively [2].

A few months into the pandemic, it was observed that in some patients symptoms persisted for more than 4 weeks. The prolongation of the disease is now known as long COVID [3-7]. Some studies estimate that long COVID affects 10% of patients with COVID-19 [8]. The probability of developing long COVID does not seem to be related to the severity of the acute phase or to some of the risk factors associated with poor prognosis (male sex, older age and comorbidities) [6].

Current data suggest that patients with long COVID are primarily women (78.9%), between 30-59 years old (86.9%), and only 8.43% have been previously admitted to hospital for SARS-CoV-2 infection. In 65% patients with long COVID, symptoms persist at least for 6 months from the onset of the disease [9].

Long COVID is a multi-organ disease characterized by a wide range of symptoms, including cough, headache, arthralgia, fever, abdominal pain, asthenia, brain fog and skin manifestations. Dyspnoea is one of the most frequent symptoms, as well as difficulty in performing activities of daily living, including self-care and social activities [9-11].

Although much progress has been achieved in understanding the acute phase of SARS-CoV-2 infection, the physiopathology of long COVID is less known [5,7]. It has not been yet elucidated whether chronic symptoms are directly caused by the viral infection in multiple organs, indirectly through hyperactivation of the immune system, or due to development of autoimmunity [7].

Physiopathology of SARS-CoV-2 infection

SARS-CoV-2 penetrates the human cell using angiotensin converting enzyme 2 (ACE2) as a receptor. ACE2 is mainly expressed in the lung, but also in the heart, kidney, intestine, vascular endothelium and other [12]. The inflammatory process

produced at pulmonary and extra pulmonary level and the overall immune response have been identified as important mechanisms in the physiopathology of COVID-19 [13].

The inflammatory process is a common response to viral infections; however, SARS-CoV-2 can over activate the immune system leading to a cytokine storm, very likely associated with disease progression and multiple organ failure [13].

The high prevalence of antinuclear antibodies and other autoimmune markers observed in patients with COVID-19 points at the potential usefulness of specific treatments[14.] Leukotrienes, pro-inflammatory metabolites that participate in the regulation of the immune response, are possibly involved in the respiratory symptoms derived from the systemic inflammation in long COVID [165-17].

Leukotriene antagonists (LTRAs) are a group of drugs used to treat symptoms of asthma and allergic rhinitis. Their bronchodilator action and inhibition of airway inflammation improve respiratory function and airway hyperresponsiveness. By decreasing the action of leukotrienes C4, D4 and E4 when binding to CysLT1 receptors in the lungs and bronchi, LTRAs diminish bronchoconstriction and inflammation. [18-20]

Some recent studies have proposed the use of montelukast in the acute phase of COVID-19 due to a possible antiviral and anti-inflammatory effect [21-23]. Montelukast could prevent the entry of SARS-CoV-2 into the cell because of its affinity with the receptor ACE2, thus shortening the course and severity of the disease [22]. Moreover, it has been hypothesized that montelukast could reduce the replication cycle of the virus [23-24].

Clinical experience in patients admitted for COVID-19 suggests that montelukast could be associated with a reduction in clinical deterioration [25]. There are currently two registered clinical trials that evaluate the efficacy of montelukast in acute SARS-CoV-2 infection in outpatients [26,27]. The first trial will compare the efficacy of montelukast versus placebo in reducing emergency visits and hospital admissions[26]. The second trial will evaluate the effect of montelukast and favicovir in reducing hospital admissions [27]

A pilot study was carried out using montelukast off-label in patients with COVID-19. [28] Dyspnoea, chest pain, malaise, dry cough and nasal symptoms improved and patients could return to work sooner.

This trial is based on prior clinical results and the hypothesis that antileukotrienes can reduce the cytokine cascade of inflammation triggered by SARS-CoV-2 infection. The E-SPERANZA COVID clinical trial aims to demonstrate the efficacy of montelukast in reducing respiratory symptoms and improving the quality of life of patients with long COVID (> 4 weeks).

Objectives

The main objective of this study is to evaluate the efficacy of 4 weeks of treatment with 10 mg/day of oral montelukast versus placebo in improving the health-related quality of life associated with mild to moderate respiratory symptoms in patients with long COVID as measured by the CAT questionnaire [29].

The secondary objectives are to evaluate the effect of montelukast versus placebo on improving the following: exercise capacity; COVID-19 symptoms (such as asthenia, headache, brain fog, ageusia, and anosmia); oxygen desaturation during exertion; functional status; mortality; use of healthcare resources; days of sick leave; and medication side effects. Additionally, we will evaluate antinuclear antibodies as markers of the response to montelukast.

Methods and analysis

Trial design

Phase III, randomized, double-blind, placebo-controlled clinical trial of superiority, with a two-arm parallel group design, in which patients will be randomized to study treatment or placebo (1:1 allocation ratio).

Study setting

The study will be carried out in thirteen primary healthcare centres in four health areas of Catalonia and Aragon, Spain. The list of study sites can be found at the Spanish Clinical Studies Registry website (https://reec.aemps.es)

Study period

The study will be carried out from August 1st, 2021, to March 1st, 2023.

Participants

Subjects aged 18 to 80 years diagnosed with SARS-CoV-2 infection and persistent mild-to-moderate respiratory symptoms lasting between 4 and 12 weeks since the onset of the disease. Subjects will be included in the study if they meet all the eligibility criteria shown in Table 1.

Table 1. Participants' eligibility criteria. Inclusion and exclusion criteria for the study participants.

INCLUSION CRITERIA *Participants are required to meet all inclusion criteria*
a) Individuals ≥18 and ≤ 80 years old with SARS-CoV-2 infection (positive SARS-CoV-2 detection test (RT-PCR, antigenic test or equivalent <10 days from the onset of symptoms) treated in Primary Care.
b) Persistent respiratory symptoms lasting for more than 4 weeks and less than 12.
c) Mild to moderate dyspnoea: score from 1 to 3 at the beginning of the study according to the modified Medical Research Council scale (mMRC).
d) Patient must sign informed consent form.
EXCLUSION CRITERIA ***Participants meeting one or more of the following criteria will be excluded***
a) Severity criteria: fever> 38ºC, O2 saturation <93%.
b) Patients with pneumonia in the acute / subacute phase due to SARS-Cov-2.
c) Patients who have required hospital admission for SARS-Cov-2.
d) Chronic respiratory disease: Chronic Obstructive Pulmonary Disease (COPD), asthma, bronchiectasis, pulmonary fibrosis, obstructive sleep apnea syndrome (OSAS), chronic respiratory failure from any cause, home oxygen therapy.
e) Use of montelukast or zafirlukast ≤ 30 days prior inclusion.
f) Use of gemfibrozil.
g) Hypersensitivity to montelukast, lactose intolerance or to any of the excipients of study treatment or placebo.
h) Active malignancy, current or recent chemotherapy treatment (<6 months).
i) Medical history of Human Immunodeficiency Virus (HIV) infection or any severe immunosuppression.
j) Patients who have been in a clinical trial 30 days prior to the study.
k) Pregnancy or planning a pregnancy .
l) Breastfeeding mother.
m) The principal investigator considers that the subject will not be able to perform the test procedures

The centers and investigators of the study were chosen from the network of collaborating centers with experience in studies that have agreed to participate.

Outcomes

The primary outcome is health-related quality of life associated with respiratory symptoms according to the CAT scale [29] 4 weeks after starting treatment. CAT is a validated scale to quantify and monitor the impact of COPD on well-being and daily life. It consists of 8 questions (rated from 0 to 5 points), and a total score of 0-40 (0-9 mild, 10-20 moderate, 21–30 severe and 31–40 very severe). A difference of 2 or more points in health status is considered clinically significant [30].

Secondary outcomes:

a) Exercise capacity will be measured as the number of repetitions performed in the 1Min Sit-to-Stand test (1MSTS) [31], which consists of sitting down and getting up from a chair with no hand support as many times as possible for 1 minute while connected to a saturation monitor. Measurements include number of repetitions and oxygen saturation before and after performing the exercise.

b) The Post-COVID-19 Functional Status scale (PCFS) [32] focuses on relevant aspects of daily life during post-infection follow-up. The scale is intended to help health professionals become aware of functional limitations and to determine degree of disability.

c) Severity of common symptoms of patients with long COVID will be evaluated using Likert scales [33] [0 (less severe) to 10 (most severe)]: asthenia, headache, mental confusion (brain fog), ageusia and anosmia.

d) Use of health services, counting number of visits: virtual, primary care centre, emergency room and hospital admissions.

e) Mortality.

f) Sick-leave days at day 28 (end-of-treatment).

g) Side effects of the drug occurring at any time of the study period will be assessed and recorded in the data collection platform eCRF?

h) **Treatment compliance** (percentage of pills taken at the end of treatment) will be estimated at the end-of-treatment by counting the remaining pills in the bottle or, if not possible, by directly asking the patient.

Sample size

In the data published by Wang *et al.* [34] to evaluate an intervention in stable COPD patients, a weighted common standard deviation of the CAT score of 5.69 was observed. Basing the sample calculation on these data, in a study of superiority of montelukast compared to placebo with an intention-to-treat analysis, accepting an alpha risk of 0.05 and a beta risk under 0.2 in a two-tailed contrast, 142 individuals in

the treatment group and 142 in the control group are needed to detect a difference of 2 units. We assume a 10% loss to follow-up rate.

Recruitment

Potential participants will be identified by the collaborator investigators at primary health centers and contacted in office visits or by telephone. If participants with persistent respiratory symptoms score from 1 to 3 (mild to moderate) dyspnoea according to the modified Medical Research Council scale (mMRC)[35] and they agree to participate, an appointment will be set-up with a physician investigator to assess eligibility and to sign the informed consent. The recruitment period is estimated to finish by May 2022 or when sufficient sample size is reached.

Randomization, allocation, implementation and blinding process

Participants will be randomly allocated to the intervention (treatment) or control (placebo) group. The randomization will be carried out by a IDIAPJGol statistician not involved in the recruitment using the program R statistical software to obtain computer-generated random numbers without stratification, in a 1:1 allocation ratio by blocks of 4. The distribution will be made by blocks to ensure the proportionality of treatments between centres.

The randomization list will be provided to the pharmacy, which will label the trial treatments accordingly. Each treatment will be identified with a unique code. The centres will have medication in sequential order. The medication code dispensed to the patient will be registered on the medication dispensing form and on the data collection logbook. Since this is a double blind study, neither healthcare professionals, patients nor the research team will be aware of the allocated group. Montelukast pills and their placebo equivalent will be visually identical.

Unblinding of a participant's treatment will be allowed when information of the treatment received is needed for the effective and secure management of the patient,unblinding of a participant's treatment will be allowed when information of the treatment received is needed for the effective and secure management of the patient,

Intervention

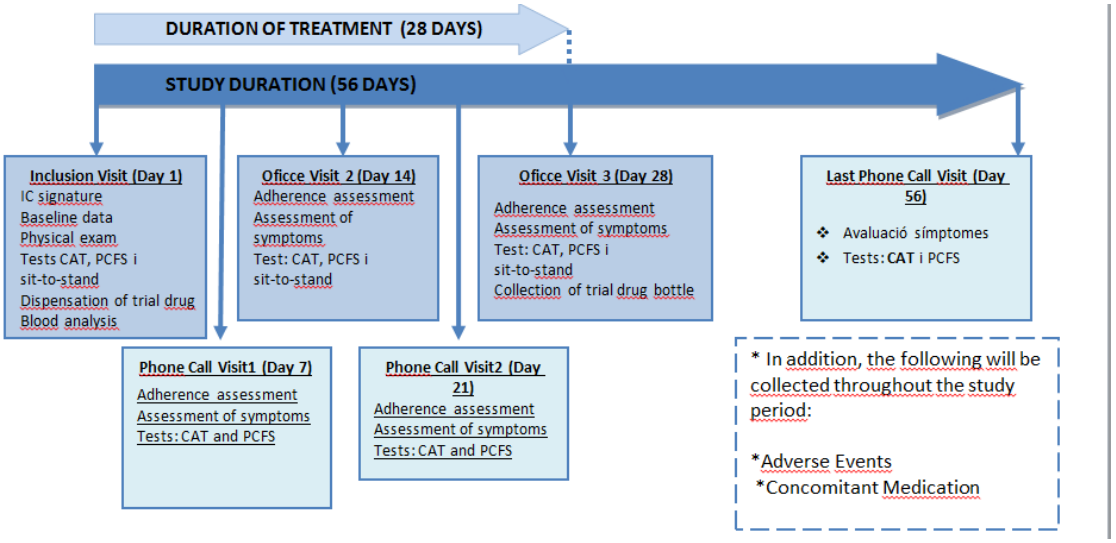
The intervention consists of a 28 day treatment, with oral administration of 1 capsule per day (research drug or placebo). Participants belonging to the:

- Intervention group will be treated with montelukast 10 mg
- Control group will receive the placebo (microcrystalline cellulose)

The Pharmacy Department of Bellvitge University Hospital will encapsulate montelukast and the placebo.

Follow-up consists of a series of office (days 1, 14 and 28) and telephone visits (days 7, 21 and 56), as described in Figure 1 and Table 2. A window period of ± 2 days for each visit will be accepted.

Figure 1. Summary and steps for the E-COVID study



IC=informed consent; CAT=COPD Assessment Test; PCFS=Post-COVID-19 Functional Status Scale; 1MSTS=1-min-sit-to-stand test

Inclusion visit (day 1)

Investigators will collect the following baseline information: sociodemographic data; clinical data; use of concomitant medication; health-related quality of life associated

with respiratory symptoms; functional status post-COVID-19; scoring of asthenia, headache, mental confusion, ageusia and anosmia.

Participants will perform the 1MSTS test to evaluate degree of dyspnoea on exertion and oxygen desaturation.

A baseline blood test will be performed the next day, including: complete blood count, electrolytes, kidney function, liver function, C-reactive protein, creatine kinase, ferritin, D-dimer, type B natriuretic peptide, antinuclear antibodies, lupus anticoagulant and quantitative anti-SARS-CoV-2 antibodies.

A bottle with the medication (montelukast or placebo) and treatment instructions will be handed to participants and an appointment for the next visit (on day 7) will be scheduled.

The patient will be asked to return the bottle with the study medication at the end of the study.

Office visit (days 14 and 28)

Evaluation of symptoms, treatment adherence, 1MSTS test and oxygen desaturation, and hospitalization since the previous visit will be assessed, as well as the use of concomitant medication, evaluation of adverse events and compliance with study medication.

Phone call (days 7, 21 and 56)

Health-related quality of life associated with respiratory symptoms, post-COVID-19 functional impairment and symptom progression will be evaluated by means of a telephone call using the same questionnaires. Information regarding number of visits to the health centre, primary and / or hospital emergency care, and hospitalization since the previous visit will be assessed, as well as the use of concomitant medication, evaluation of adverse events and compliance with study medication.

Visit 5 (day 28)

Last office visit and end-of-treatment. Patients will be asked to return the bottle with the study medication, and treatment compliance will be evaluated. We will administer the same questionnaires and collect the same data of previous visits.

Relevant concomitant care and interventions are permitted during the trial, with the exception of antileukotrienes use.To take gemfibrozil

Table 2. Time schedule of recruitment, enrolment, intervention, assessments of the study and visits for participants.

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	t_0	0	t_1	t_2*	t_3	t_4*	t_5	t_f*
ENROLMENT:								
Eligibility screen	X	X						
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Intervention [Montelukast]								
Control [Placebo]								
ASSESSMENTS:								
CAT scale	X		X	X	X	X	X	X
PCF Scale			X	X	X	X	X	X
1 MSTS test			X		X		X	
Severity of symptoms			X	X	X	X	X	X
Health services use				X	X	X	X	X
Mortality				X	X	X	X	X
Sick-leave days							X	
Side effects & concomitant medication				X	X	X	X	X
Treatment compliance				X	X	X	X	

** Phone call visits*

Data collection and **data management and quality assurance procedures**

Study data will be collected and managed using REDCap, hosted at the Institut Universitari de Recerca en Atenció Primària Jordi Gol i Gurina (IDIAPJGol). REDCap

(Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures to common statistical packages; and 4) procedures for data integration and interoperability with external sources [36,37].

Only the principal investigator or those who have permission can access the data.

A risk approach monitoring plan will be developed and followed via periodic on-site/online visits. Investigators will be instructed in good clinical practice and specific standard operational procedures for the trial.

Statistical Analysis

Baseline characteristics of the sample will be described for each group using mean and standard deviation for quantitative variables and absolute and relative frequencies for qualitative variables. Bivariate comparison of characteristics between patients taking montelukast and patients taking placebo will be carried out to verify group comparability. The Wilcoxon test will be used for comparison of quantitative variables, and the chi-square test for comparison of qualitative variables (or the Fisher test in case of extreme distributions in the crossed tables). In all comparisons, statistical significance will be set at 5%.

Outcome measures will be described and compared between the montelukast and placebo groups using the same statistics. No multivariate analysis will be performed.

For the primary endpoint analysis (montelukast efficacy) and secondary endpoints, we will primarily use an intention-to-treat analysis. We will also conduct a per-protocol analysis. R-4.0.2 for Windows will be used.

It will no develope additional subgroup analyses.

Discussion

The main goal of this study is to demonstrate the efficacy of montelukast, an already approved and commercialised drug, in reducing dyspnoea and other persistent symptoms in patients with long COVID.

Since it is a new condition, there are no validated scales that evaluate long COVID symptoms and quality of life. The mMRC scale is a self-rating tool validated for COPD and interstitial lung diseases to measure the degree of disability caused by dyspnoea on daily activities. The main variable of the study is quality of life as measured by the CAT scale. CAT is a short, simple, standardized assessment test completed by patients to measure health-related quality of life in patients with COPD, providing reliable and standardized measurement of health [29,30] This scale was chosen because validated quality of life scales for long COVID are not yet available. Both scales were selected to cover a wide range of disease severity, with the intention that the greatest discriminating power would be in the mild to moderate range. We will also use 1MSTS test, a clinical scale to assess dyspnoea during exercise.1MSTS test has been validated for use in COPD and pulmonary fibrosis and has already been recommended in long COVID [31]. The recently developed Post-COVID-19 Functional Status Scale has also been included in the evaluation [32].

Different publications have lately proposed the use of montelukast in the acute phase of COVID-19 because of possible antiviral and anti-inflammatory effects [22-25]. It has been postulated that due to the affinity of montelukast for the ACE receptor, it could interfere with the entry of SARS-CoV-2 into the cell. Consequently, montelukast could shorten the course and severity of acute COVID-19 [23]. Additionally, it has been hypothesised that montelukast could reduce the replication cycle of the virus [24].

Clinical experience has suggested that montelukast may reduce clinical deterioration among hospitalized COVID-19 patients [25].

Two already registered clinical trials will evaluate the efficacy of montelukast during acute SARS-CoV-2 infection in non-hospitalized patients [26,27]. One trial aims to evaluate the efficacy of montelukast in reducing the number of emergency room visits and hospital admissions [26]. The second trial will evaluate the efficacy of montelukast and favicovir in decreasing the number of hospital admissions [27].

No treatments have been evaluated for long COVID. The severity of the COVID-19 pandemic with its huge human and economic cost, together with the anticipated long COVID wave, demand urgent, effective therapies to reduce complications associated with the SARS-CoV-2 infection. Based on previous clinical experience[28], we expect to generate evidence on the effect of montelukast in improving quality of life related to respiratory symptoms in patients with long COVID.

Ethics and dissemination

This study was approved by the Clinical Research Ethics Committee of the IDIAPJGol (reference number 21/091-C) and authorized by the Spanish Agency of Medicines and Medical Products (AEMPS, EudraCT number 2021-000605-24). It has been considered a low intervention trial, following European legislation in Clinical Trials. It has been registered at ClinicalTrials.gov (NCT04695704). This study protocol has been written in accordance with Standards Protocol Items: Recommendations for Interventional Trials (SPIRIT). Relevant amendments will be submitted to the appropriate authorities (ethics committee and/or AEMPS) for approval. Investigators and patients will be properly informed about the protocol changes. Patients will re-consent if needed. Changes will be communicated to the study registries.

The clinical trial will be conducted in accordance with the protocol and the Tripartite Harmonized Guide (ICH) for Good Clinical Practice (GCP). The authors guarantee compliance with the General Regulation of Data Protection (RGPD) EU 2016/679, approved by the European Parliament on April 27, 2016, and the tenets of the Declaration of Helsinki and the Belmont Report.

Participants will be properly informed of the clinical trial, have enough time to decide and signed the informed consent form prior the start of the trial and their participation will be reflected in their medical records. Participant specimens can only be used for the purpose described in the protocol and inform consent and they will be destroyed by the end of the study.

Participants' data will be collected using the REDCAP platform hosted by the IDIAP JGOL servers. The data will be stored in the local web server, only accessible to computers with a trusted VPN connection and secure credentials. Only the application service can send the data to the back office, with a firewall that only allows requests from the application IPs. The web server enables you to configure the HTTP X-Frame-Options caption with the value "same-origin" to prevent clickjacking attacks. The final trial dataset will be only accessible for the data management investigators of the research team.

The results of the study will be published in open access, peer-reviewed journals. To ensure quick translation of the research findings into clinical practice, we will conduct webinars on management of long COVID in Primary Care, to increase awareness and understanding about long COVID among primary health professionals.

The authorship eligibility will be based on the author's contribution.

Abbreviations

AA: Adverse Event

SAE: Serious Adverse Event

AR: Adverse reaction

SUAR: Severe and Unexpected Adverse Reaction

AEMPS: Spanish Agency for Medicines and Health Products

GCP: Good Clinical Practice

mERC: Ethical Committee for Research with Medicines

DCN: Data Collection Notebook

eDCN: Electronic Data Collection Notebook

ICH: International Conference on Harmonization

ICS: Catalan Institute of Health

IDIAPJGol: University Institute for Primary Health Care Research Jordi Gol i Gurina

CAT: COPD Assessment Test Scale

mMRC: Modified Medical Research Council Scale

COPD: Chronic Obstructive Pulmonary Disease

1MSTS: 1 Minute sit to stand test

PCFS: post-COVID Functional Status scale

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Footnotes

Contributors: FMC: conception, design, clinical coordination, data collection, interpretation of data. **SBM:** design, interpretation of data. **JAO:** design, analysis, interpretation of data. AGS: design, clinial trial management. OCP: design, analysis and interpretation of data. SCM: design, analysis and interpretation of data. GAM: clinical coordination, data collection, interpretation of data. MBJ: design, interpretation of data. RME: design, clinical trial monitoring and management, data collection and audit. RMP: design, clinical trial supervision, pharmacovigilance, interpretation of data. BSG: design, general coordination and interpretation of data.

FMC, SBM, SCM, RMP, BSG have written the manuscript. All authors have reviewed and approved the final version of the manuscript.

Trial sponsor. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)

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Roles and responsabilities:

Coordinating center. Costa de Ponent Research Unit. Design and conduct of the study, site recruitment, analysis and results.
Site Principal investigators: Responsible for trial conduct in the site and patient recruitment.

Steering committee. Conformed by members of the coordinating center and the sponsor. Responsible for supervision of the overall conduct of the study.

Data management team. Sponsor. Responsible for supervision of data collection and database closure.

Availability of data and materials: The datasets generated during and/or analysed during the current study are not publicly available due data confidentiality but are available from the corresponding author on reasonable request.

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Laboratorios Alter S.A. supplied the drug (montelukast) to manufacture the treatment pills.

The whole study (design; collection, management, analysis, and interpretation of data; writing of the report and the decision to submit the report for publication) is entirely independent of the funding bodies, which have no ultimate authority over any of these activities.

Competing interests: None declared.

Access to data: The data that support the findings of this study is available on request from the corresponding author (Francisco Mera Cordero, fmera@ambitcp.catsalut.net) The data are not publicly available due to ethical restrictions and confidentiality of research participants.

Trial status: Recruitment of patients started in August 2021.

Appendices

Patient information sheet and informed consent

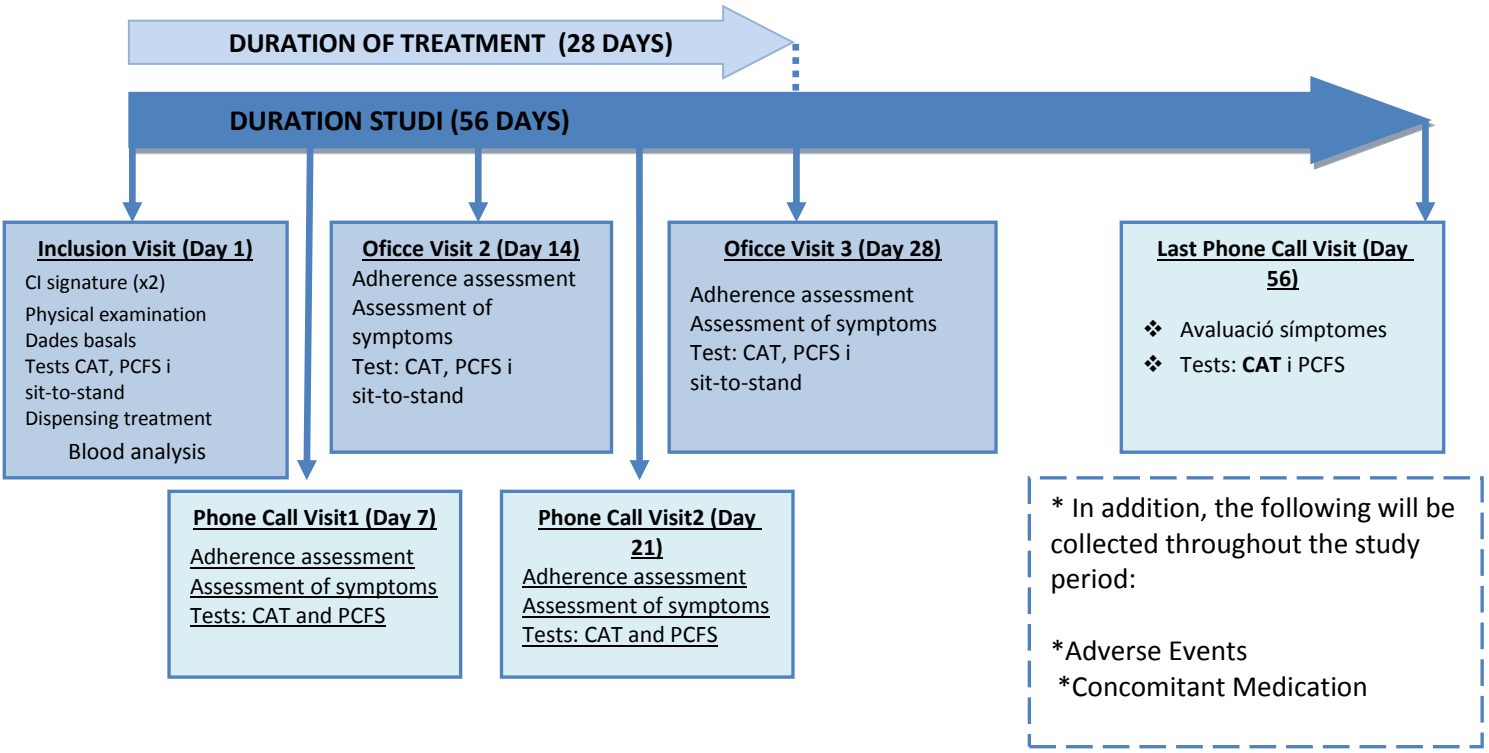
Table

INCLUSION CRITERIA ***Participants are required to meet all inclusion criteria***
a) Individuals ≥18 and ≤ 80 years old with SARS-CoV-2 infection (positive SARS-CoV-2 detection test (RT-PCR, antigenic test or equivalent <10 days from the onset of symptoms) treated in Primary Care.
b) Persistent respiratory symptoms lasting for more than 4 weeks and less than 12.
c) Mild to moderate dyspnoea: score from 1 to 3 at the beginning of the study according to the modified Medical Research Council scale (mMRC).
d) Patient must sign informed consent form.
EXCLUSION CRITERIA ***Participants meeting one or more of the following criteria will be excluded***
a) Severity criteria: fever> 38ºC, O2 saturation <93%.
b) Patients with pneumonia in the acute / subacute phase due to SARS-Cov-2.
c) Patients who have required hospital admission for SARS-Cov-2.
d) Chronic respiratory disease: Chronic Obstructive Pulmonary Disease (COPD), asthma, bronchiectasis, pulmonary fibrosis, obstructive sleep apnea syndrome (OSAS), chronic respiratory failure from any cause, home oxygen therapy.
e) Use of montelukast or zafirlukast ≤ 30 days prior inclusion.
f) Use of gemfibrozil.
g) Hypersensitivity to montelukast, lactose intolerance or to any of the excipients of study treatment or placebo.
h) Active malignancy, current or recent chemotherapy treatment (<6 months).
i) Medical history of Human Immunodeficiency Virus (HIV) infection or any severe immunosuppression.
j) Patients who have been in a clinical trial 30 days prior to the study.
k) Pregnancy or planning a pregnancy .
l) Breastfeeding mother.
m) The principal investigator considers that the subject will not be able to perform the test procedures

Figure

Click here to access/download;Figure;Summary and steps E-COVID.pdf

Summary and steps for the E-COVID study



Ehiocal approval english

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry - Page 3
	2b	All items from the World Health Organization Trial Registration Data Set. All the items have been considered.
Protocol version	3	Date and version identifier - Page 1
Funding	4	Sources and types of financial, material, and other support - Page 21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - Page1 & 21
	5b	Name and contact information for the trial sponsor - Page 21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities - Page 21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) - Page 21 .
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - Page 4-6
	6b	Explanation for choice of comparators N/A. As there is no treatment available, study medication is compared to placebo.
Objectives	7	Specific objectives or hypotheses Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 6
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 6

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - Page 7-8?
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - Page 10- 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) - Page 12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) - Page 9 - Page 12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial - Page 13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - Page 8 - 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Page 11 - 13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Page 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 9-10

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Page 10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Page 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - Page 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial - Page 10

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol - Page 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols - Page 11-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol - Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol - Page 12 - 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) - Page 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) - Page 13

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed N/A - A researcher of the team's project will be in charge of monitoring the assay, No DMC is involved in the project.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A - No interim analyses is considered
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A- No auditing trial conduct are considered

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 14 - 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Page 16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 10 & 13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A There are not biological specimens
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Page 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site - Page 21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators - Page 22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation N/A - This is a low-intervention trial using an already commercialised drug, and no compensation is contemplated. pag 16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - Page 14-15
	31b	Authorship eligibility guidelines and any intended use of professional writers - Page 16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A - The protocol will be published under the open access policy, but there is no plan to grant public access to participants' dataset or statistical code.
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Page 22-23
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Page 11 & 14

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- ethicalarticleBMC.docx