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LONG-COVID CONDITION THERAPEUTICS: A MULTI-MODAL INVESTIGATION OF TREATMENT EVIDENCE, OFF-LABEL PRESCRIBING PATTERNS, AND CLINICAL OUTCOMES

PhD thesis

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List of abbreviation

6MWT	6-Minute Walk Test
ACE inhibitor	Angiotensin-Converting Enzyme inhibitor
AI	Artificial Intelligence
ARB	Angiotensin II Receptor Blocker
AT1R	Angiotensin II Type 1 Receptor
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRS	Cytokine Release Syndrome
CT	Computer Tomography
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-Dimension 5-Level (Quality of Life Scale)
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GCoVS	Global COVID Vaccine Safety Project
HR	Hazard Ratio
IACC	Infection-Associated Chronic Condition
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
ILD	Interstitial Lung Disease
IV	Intravenous
LABA	Long-Acting Beta-2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
LDN	Low Dose Naltrexone
mRNA	Messenger Ribonucleic Acid
NAD+	Nicotinamide adenine dinucleotide (oxidized form)
NASEM	National Academies of Sciences, Engineering, and Medicine
NCT	National Clinical Trial (identifier)
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NNGYK	National Center for Public Health and Pharmacy, *Nemzeti Népegészségügyi és Gyógyszerészeti Központ*
NNT	Number Needed to Treat
OR	Odds Ratio
PASC	Post-Acute Sequelae of SARS-CoV-2 Infection
PCC	Post-COVID Condition
PCR	Polymerase Chain Reaction
PCS	Post-COVID Syndrome
PFT	Pulmonary Function Test

PIDM	Programme for International Drug Monitoring
PoCoVIT	Post-Corona-Virus Immune Treatment
QC	Quality Control
RAS	Renin-Angiotensin System
RCT	Randomized Controlled Trial
RECOVER	Researching COVID to Enhance Recovery
RR	Risk Ratio
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SABA	Short-Acting Beta-2 Agonist
SAMA	Short-Acting Muscarinic Antagonist
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SOC	Standard of Care
SOC+RDV	Standard of Care plus Remdesivir
STRONGER	Statin Treatment for COVID-19 to Optimise Neurological Recovery
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VigiBase	WHO Global Individual Case Safety Reports database
WHO	World Health Organization

1. Introduction

The COVID-19 pandemic has transformed healthcare, presenting challenges not only due to the acute effects of infection but also owing to significant, persistent symptoms associated with long-term complications. (1, 2) The umbrella term "long COVID" or "post-COVID-19 condition" refers to persistent, fluctuating, or recurring symptoms that develop after the initial acute SARS-CoV-2 infection. (2, 3) These symptoms—ranging from fatigue, shortness of breath, and cognitive impairment to neuropsychiatric and multi-organ complaints—not only impair individuals' quality of life but also place a substantial burden on healthcare systems and society worldwide. (1, 2)

Most people who have had SARS-CoV-2 infection recover completely, but according to some estimates, approximately 10–20% develop a range of symptoms after recovering from the initial illness. (1, 4) Long COVID can develop in any patient, but according to several studies, the development of long COVID syndrome may be related to the severity of the acute illness. (1, 5) Risk factors include hospitalization (with mechanical ventilation), admission to the intensive care unit, age (over 50), gender (female), and comorbidities. (1, 6) The exact mechanism of long COVID is still unclear, and its treatment remains unresolved. (1, 2) Promising results have been published on vaccines that have been shown to effectively reduce the risk of long COVID; however, other data suggest that vaccination provides only partial protection in the post-acute phase of the disease. (1, 2) Certain antiviral drugs (nirmatrelvir+ritonavir, molnupiravir) have been administered orally, which may reduce the severe progression of mild to moderate COVID-19 infection and thus also reduce the likelihood of developing long COVID. Numerous clinical trials have been launched with dietary supplements or drugs with different mechanisms of action in search of a solution to the symptoms of long COVID. (1)

The COVID-19 pandemic itself is a relatively new phenomenon, and the post-COVID condition [PCC] is an even newer area of research, so the related concepts, definitions, and scientific directions are still constantly changing.

In our study published in 2023 (Sebők S, Gyires K. Long COVID and possible preventive options), we provided a comprehensive synthesis of the scientific literature available at that time regarding the pathophysiology, clinical features, and potential preventive

interventions for long COVID. (1) The field was characterized by significant heterogeneity in terminology (“Long COVID,” “Post-COVID syndrome,” “Chronic COVID,” “Long-haul COVID,” etc.), and the diagnostic criteria also varied, with definitions ranging from persistent symptoms after 4 weeks (National Institute for Health and Care Excellence [NICE], Centers for Disease Control and Prevention [CDC]) to ≥12 weeks (World Health Organization [WHO], NICE). (1, 7-10) The reported prevalence likewise varied widely—from 7% to 30%—depending on the definitions, the affected populations, and the methods used. (1, 5, 6) Our analysis highlighted known risk factors (female gender, older age, severe or intensive care–treated initial illness, comorbidities) and also noted that persistent symptoms may develop even after mild or asymptomatic infection. (1, 4, 5, 11) At the time, there was no proven, universally accepted pharmacologic treatment for long COVID, although vaccination, antiviral therapy, and other interventions showed promise in reducing the severity of acute illness and possibly in preventing long-term complications. (1) Numerous randomized clinical trials were conducted with antiviral agents, immunomodulators, and off-label drugs, but most showed limited and inconsistent efficacy. (1)

Since 2023, knowledge about post-COVID conditions has expanded significantly. The latest international consensus documents—including the 2024 report from the US National Academy of Sciences, Engineering, and Medicine [NASEM], updated WHO and CDC guidelines, and NICE rapid recommendations—have harmonized terminology and definitions. (2, 3, 12, 13) The term "Post-COVID-19 Condition" (synonymous with "Long COVID" or "Infection-Associated Chronic Condition," IACC) should be used for symptoms lasting at least 3 months, recurring or newly appearing after confirmed or probable SARS-CoV-2 infection, regardless of the severity of acute illness or laboratory confirmation. (2, 12, 13) The term PASC ("Post-Acute Sequelae of SARS-CoV-2 infection") is the terminology used by the US National Institutes of Health (NIH) and the associated RECOVER cohort program but has now become widely accepted in the international literature. (12, 14) Long COVID (long COVID, post-COVID-19 condition, or PASC – post-acute sequelae of SARS-CoV-2 infection, based on the abbreviation used in the literature) refers to a set of criteria that are partly overlapping and partly different, based on various consensus definitions. (2, 3, 13, 14) The RECOVER project, coordinated by the US NIH, uses the term PASC to refer to persistent or new symptoms occurring 4

or more weeks after acute infection. (14) European and WHO recommendations define the same syndrome based on symptoms lasting at least 12 weeks (post-COVID-19 condition). (2) Updated prevalence estimates generally range from 4% to 13% in rigorous population-based studies, but self-reported and registry data reach 30% or more, depending on symptom duration and assessment intervals. (4) The spectrum of clinical manifestations and risk factors remains broad, and the mechanistic basis of long COVID is still actively being investigated. (2-4, 6)

Among the various organ-specific manifestations of post-COVID-19 condition, pulmonary complications—especially interstitial lung diseases (ILD)—merit particular attention due to their long-term impact on respiratory health. Interstitial lung diseases (ILD) are progressive conditions that can lead to fibrosis and decreased lung function, significantly impairing patients' quality of life. While some epithelial and alveolar damage occurring during COVID-19 infection heals without sequelae, in certain cases persistent interstitial changes and fibrotic alterations develop, which may also accelerate the progression of existing ILD. Common pulmonary symptoms of post-COVID syndrome include dyspnea, cough, chest pain, fatigue, and sleep disorders. Radiological examinations reveal persistent abnormalities such as ground-glass opacities and reticulation, particularly after severe cases and mechanical ventilation. (15)

To date, no single drug can be said to be clearly effective in treating or preventing post-COVID conditions. (1-3, 13) Vaccines and early antiviral treatment are accepted as reducing the severity of acute infection and the likelihood of developing persistent symptoms, but data on long-term protection are inconclusive. (1-3, 13) Most of the therapies studied (off-label drugs, supportive therapies) have not shown breakthrough results in randomized trials, confirming the need for further research and the development of robust, harmonized methodologies. (1-3)

The term long COVID is used throughout this dissertation. Since the terminology and definitions of post-COVID conditions vary across the literature, the original wording has been preserved in the cited sources to reflect their intended meaning accurately.

2. Objectives

The primary aim of this dissertation is to provide a systematic and comprehensive synthesis of current scientific evidence on post-COVID conditions, extending the framework established in our previous publication and critically comparing recent advances with the findings of the 2023 study. This includes an in-depth evaluation of emerging therapeutic strategies, incorporating data from ongoing and completed clinical trials, their reported outcomes, and international guidelines and consensus statements published since 2023. The objective of this comparative analysis is to identify significant developments in the field and to contextualize them within the continuum of ongoing and future research.

A further aim is to investigate the application of off-label therapeutic interventions in the management of post-COVID symptoms. This is achieved by systematically comparing treatment practices documented in Hungary with those reported in the international literature, in order to assess the degree of integration of such approaches into domestic healthcare and their alignment with international trends.

The third component of this dissertation undertakes a quantitative analysis of medication usage data from a cohort of 470 post-COVID patients, with the goal of generating descriptive statistics to characterize patterns of medication utilization and to investigate potential associations between post-COVID interstitial lung disease (ILD) and pharmacological treatment behaviours within this population.

3. Methods

3.1. Long COVID and possible preventive options

Updated overview and database analysis: A targeted re-assessment of the data and results presented by Sebők et al. (2023) was conducted, incorporating recent evidence from the scientific literature and clinical trial databases published between 2023 and 2025.

Data source: A systematic PubMed search was performed using the terms "long COVID," "post-acute sequelae," and "COVID drug intervention," restricted to the years 2024–2025. In addition, the clinicaltrials.gov registry was queried with the search term "long COVID," replicating the methodology of the original article.

Data screening: From the PubMed search results, priority was given to meta-analyses published within the past year. Eligible studies and registered trials were reviewed for relevance and consistency with the central research questions and hypotheses formulated in the original publication. The search of clinicaltrials.gov initially yielded 665 entries. Two additional filters were subsequently applied: for the “Intervention” field, the option “Drug” was selected, and the date range was confined to November 30, 2022, through September 8, 2025. This procedure resulted in 109 records, each of which was reviewed individually. Entries involving dietary supplements and non-pharmacological interventions were excluded, yielding a final set of 70 clinical trials evaluating drug-based interventions.

Data processing and tabulation: Findings and tabular data from the original article were updated and refined on the basis of the newly identified publications and the extracted clinical trial records.

3.2. Off-label drug use for long COVID

Database analysis: Processing of off-label COVID-related applications (*Nemzeti Népegészségügyi és Gyógyszerészeti Központ* [NNGYK] data)

Data source: As a starting point, I used a nationwide table of off-label requests downloaded from the official website of the NNGYK. The database covers the period from 2008 to May 2025, including all off-label requests broken down by year.

Data filtering — selection of relevant cases: Database filtering was performed by selecting records with indications containing the terms 'COVID,' 'post-COVID,' or 'SARS'. Only records containing one of these terms in the indication field were retained.

Data review and categorization: I reviewed the filtered records to ensure that all documented off-label requests/uses were related to COVID-19, SARS-CoV-2, or post-COVID (long COVID) indications. The dataset includes the following fields: year, active ingredient, dosage form, strength, authorization number, case number, requested indication, planned dosage/duration of therapy, patient gender/age, decision, date of decision, professional justification, and conditions of authorization.

Structuring and tabulation of data: After processing the results, I organized the records into a standardized table, where each row corresponds to a single off-label authorization (or rejection) request.

Global review of off-label pharmacological interventions in long COVID

Keyword literature search: In the context of Hungarian regulations governing off-label prescribing, when a drug–indication pair lacks previous authorization or precedent, applications for approval are required to include supporting evidence such as peer-reviewed clinical trial publications, documented clinical experience, or relevant professional guidelines and consensus statements. (16)

To identify literature related to off-label drug therapies, I performed an unrestricted search in the PubMed database using the following search terms: "post covid syndrome off-label treatment" OR "post-acute covid sequelae off-label drugs" OR "long covid off-label medication therapy." This search produced 72 results, including one duplicate; the search was conducted on August 25, 2025.

Search term optimization was supported by an AI-based assistant (Perplexity AI): following preliminary searches, I incorporated the relevant keywords and phrase variations suggested by the artificial intelligence tool into my own systematic literature search strategy. The prompt was: "Suggest an optimal PubMed search string for identifying articles on off-label treatment options in post-COVID conditions."

Screening of literature sources: Abstracts of all publications were individually reviewed, and the full text was read when a paper appeared relevant. Only original publications reporting off-label medication use for post-COVID (or synonymous conditions) treatment were included in the analysis. I excluded literature reviews, review articles, meta-analyses, and studies for which results were not yet available. Six publications fulfilled all inclusion criteria.

To further verify the comprehensiveness of the PubMed literature search, I used Perplexity AI, an artificial intelligence-based research assistant. Specifically, I asked Perplexity to rerun the search queries I had used and to compare its results with my own. The AI tool flagged any relevant articles present in its search results but absent from my initial compilation, thus enabling the identification of potentially overlooked publications. No additional relevant articles meeting the inclusion criteria were found through this cross-validation process.

Categorization: The results were organized into a summary table, presenting data by: active ingredient, main indication, inclusion criteria, dosing regimen, patient number and methodology, and study conclusions.

3.3. Post-COVID interstitial lung disease: medication usage analysis

The analysis is based on data from 470 patients. Sampling, data collection, and patient recruitment were performed as described in the article by Fésü et al., 2023. (15) In accordance with the terminology used in Fésü et al., 2023, this chapter uses the term "post-COVID".

Study Population: The retrospective study was based on outpatient data from post-COVID patients managed at the post-COVID outpatient clinic of the Pulmonology Department of Semmelweis University between February 2021 and January 2023. (15)

- Inclusion criteria were based on symptom duration (4-12 weeks after hospital discharge) and the presence of persistent post-COVID symptoms.
- Details of hospital treatment during COVID-19 (e.g., oxygen therapy, ventilation, antiviral or COVID-specific treatment, CT findings) were also systematically recorded.

- In case of suspected ILD: Multidisciplinary discussion decided on the exact diagnosis as well as further investigation and therapy.

Patient group classification and statistical groups

The entire population was divided into two main groups based on diagnosis:

- ILD-suspected/confirmed ILD: Patients with signs of interstitial lung disease or meeting post-COVID ILD criteria.
- Non-ILD: Post-COVID patients in whom ILD was not confirmed.

In addition to anthropometric and clinical data (age, gender, comorbidities, main symptoms), pulmonary function parameters and therapeutic characteristics were also compared.

Data processing and individual analysis steps

Source data: Complete, anonymous, tabular data (Excel) from 470 individuals, containing detailed demographic data, diagnosis, medication status, medications taken by brand name, and comorbidities.
Data linking is performed based on unique identifiers (ID), so demographic, medication, and disease description data can be unambiguously assigned to each patient.
Data cleaning and categorization: First, active ingredient names were assigned to drug names, followed by classification into active ingredient groups based on this. 1-2 preparations could not be identified based on the given name.
Diagnosis-based breakdown: Medication usage analyses were performed in ILD, post-COVID ILD, and non-ILD groups, supplemented with demographic data and comorbidity data when such information was available.
Statistical methods: Mainly descriptive statistics (percentages, mean/median by age group) and chi-square test for highlighted drug groups (p-value calculation for identified differences).
Visualization: Results were summarized in tabular and descriptive form.

4. Results

4.1. Long COVID and possible preventive options

4.1.1. Pathomechanism of long Covid

Long COVID syndrome is a complex disease process that is not yet fully understood and is the result of several interrelated pathophysiological mechanisms. One theory suggests that SARS-CoV-2 and its fragments remain in the body for a longer period of time, continuously stimulating the immune system, which can lead to persistent inflammation and organ abnormalities. In addition, the infection can trigger the production of antibodies that can damage not only the virus but also the body's own proteins (autoimmune mechanism), resulting in prolonged cell and tissue damage. (1, 17, 18)

Microvascular dysfunction resulting from SARS-CoV-2 infection can cause the formation of microscopic blood clots (microthrombi), which significantly reduce oxygen supply to tissues, contributing to the development of multisystem damage. According to the CDC summary, organ damage resulting from acute infection, persistent inflammation, microvascular abnormalities, ongoing viral activity (role of viral reservoirs), autoimmune processes, and insufficient or irregular antibody response play an important role in the etiology of long COVID. (1, 18)

Abbas et al, (2025) point out that the virus binds to the ACE2 (angiotensin-converting enzyme 2) receptor and inhibits the breakdown of angiotensin II, causing AT1R (angiotensin II type 1 receptor) overactivation. This can lead to vasoconstriction, hypertension, inflammation, oxidative stress, fibrosis in multiple organs (heart, lungs, kidneys, liver), as well as neurological disorders, metabolic and skin changes. The widespread tissue expression of ACE2 amplifies the systemic effects of RAS (renin-angiotensin system) dysfunction. (17)

Possible mechanisms of long COVID: persistent viral antigen or RNA, which generates a sustained immune response; prolonged cell and tissue damage after the acute phase; persistently elevated levels of inflammatory cytokines; and the presence of activated T cells. The central nervous system is particularly affected, where the virus can cause inflammation and microthrombotic abnormalities, which can lead to structural changes, loss of smell and taste, and sleep disturbances. Long-term cardiovascular consequences

may also be due to immune responses, prothrombotic factors, and autoantibodies. Overall, long COVID is caused by RAS system dysfunction, immunological and autoimmune abnormalities, microthrombotic processes, and persistent viral antigen presence, leading to multiorgan, multidirectional damage. (1, 17, 18)

More than 200 different symptoms have been reported, with the most frequently observed including fatigue, musculoskeletal pain, shortness of breath, headache, cognitive difficulties (such as impaired concentration), and changes in taste perception. (2)

4.1.2. Definitions of long Covid

The diverse symptoms following COVID infection have been present in clinical practice for 5 years. However, recent research (Lauren E. Wisk et al., 2025) points out that there is still no uniform, standard definition of long COVID, so it is diagnosed based on different duration and symptom criteria, which makes it difficult to compare research and provide uniform care to patients. (19)

In our 2023 article (Sebők et al., 2023), we stated the following regarding the definition of post-COVID conditions:

"Fernández-de-las-Peñas et al. (2021a, b) distinguished four stages in the course of Long COVID: a./4–5 weeks after the initial phase of the disease characterized by infection-related symptoms, b./from week 5 to 12 after the onset acute post-COVID symptoms, c./from week 12–24 after the initial period Long post-COVID symptom, and d./over 24 weeks after the acute infection the persistent post-COVID symptoms (Fernández-de-Las-Peñas et al. 2021a).

Other definitions by the same group distinguished two phases: acute post-COVID (from week 5 to week 12) and chronic post-COVID (lasting more than 12 weeks after symptom's onset) (Fernández-de-las-Peñas 2022). Similarly, two phases, the ongoing symptomatic COVID-19 (from 4 to 12 weeks) and the post-COVID-19 syndrome (12 weeks or more) were suggested by Datta et al. (2020). Furthermore, according to Yong (2021) when the symptoms persist for more than 3 months after the onset of the disease, it can be taken as Long COVID.

The National Institute for Health and Care Excellence guideline (United Kingdom) distinguishes Long- and post-COVID conditions: Long COVID means the ongoing symptomatic COVID-19, where symptoms last for 4 to 12 weeks and post-COVID-19 syndrome, where the symptoms persist beyond 12 weeks in the absence of an alternative diagnosis (NICE 2020).

Similarly, the World Health Organization (WHO) defines Long COVID as symptoms that persist for 3 months after the onset of COVID infection, and the symptoms cannot be explained by an alternative diagnosis (Soriano et al. 2022)." (1)

The NICE, WHO, NASEM, and CDC consensus statements and recommendations currently represent the most frequently cited and accepted definitions of long COVID in professional practice, but there is still no completely uniform definition in the literature, and there is significant variability in definitions. (19)

NICE: According to the latest update (January 2024), long COVID refers to symptoms that persist for more than four weeks after COVID-19 infection; between 4 and 12 weeks, it is called "ongoing symptomatic COVID-19," and after 12 weeks, it is called "post-COVID-19 syndrome," in the absence of an alternative diagnosis. (13)

The guideline for healthcare professionals recommends the following three definitions:

- Acute COVID-19: Symptoms of COVID-19 infection, lasting up to 4 weeks.
- Ongoing symptomatic COVID-19: Symptoms of COVID-19 infection, lasting from 4 to 12 weeks after infection.
- Post-COVID-19 syndrome: Symptoms that develop during or after COVID-19 infection, persist for more than 12 weeks, and cannot be explained by another diagnosis. It usually presents as a cluster of symptoms, the severity of which can often vary over time and affect any part of the body. A diagnosis of post-COVID-19 syndrome may be made before 12 weeks, but alternative causes should be considered. (13)

Long COVID: Beyond the three basic definitions, the term "long COVID" is generally used to describe symptoms that persist or develop after acute COVID-19. This includes both ongoing symptomatic COVID-19 (4-12 weeks) and post-COVID-19 syndrome (12 weeks or more). (13)

There is currently no long-term evidence on how long symptoms persist after SARS-CoV-2 infection. The term "post-COVID-19 syndrome" only marks the end of the acute phase. Because symptom duration is uncertain, terms like "chronic" or "persistent" are avoided. "Syndrome" reflects the simultaneous, fluctuating, and overlapping multi-organ symptoms seen in patients. (13)

WHO: According to the WHO's 2025 definition, post-COVID-19 condition consists of symptoms that appear 3 months after the initial infection and persist for at least 2 months, which cannot be explained by any other diagnosis. (2)

Severe, long-term symptoms that develop after COVID-19 infection are collectively referred to as post-COVID-19 condition (PCC) or long COVID. Post-COVID-19 symptoms appear within 3 months of the initial COVID-19 infection and persist for at least 2 months. It is important to note that the WHO uses the phrase "usually 3 months from onset ... lasting at least 2 months," meaning that the 3-month time frame is a guideline in most cases, but not an absolute diagnostic criterion; clinical flexibility is required in the assessment. (2)

NASEM: According to the 2024 NASEM definition, long COVID is when symptoms persist for at least 3 months after acute SARS-CoV-2 infection. This timeframe is independent of whether the symptoms are continuous, recurrent, fluctuating, or occasionally go into remission. It is important that the treating physician monitor and follow up on symptoms before the 3-month period has elapsed. The use of diagnostic code U09.9 (post-COVID-19 condition, unspecified) is permitted even before the official diagnosis of long COVID. (3)

The definition does not include mandatory or exclusionary symptoms: it does not require a precise list of symptoms, laboratory markers, or the exclusion of alternative diagnoses. (3)

CDC: Long-term COVID-19 is considered a chronic condition that occurs after SARS-CoV-2 infection and persists for at least 3 months. These symptoms can be varied, persistent, and the condition can improve or worsen. (12)

The definition of post-COVID condition has undergone continuous change since the beginning of the pandemic, but after reviewing the positions of leading international

organizations (NICE, WHO, NASEM, CDC) and the latest research, it is clear that there is still no uniform and universally accepted definition. The use of different duration and symptom criteria makes it difficult to assess the prevalence of the disease, compare research results, and provide consistent care to patients. It would be important to develop a sensitive yet sufficiently specific, consensus-based definition that can be reliably applied in both clinical practice and research. The diversity of definitions continues to pose significant clinical, social, and scientific challenges.

The four organizations fundamentally agree that long COVID is a persistent, diverse set of symptoms that can persist after the acute illness has resolved. The main differences lie in the temporal definitions, the emphasis on risk factors, and the assessment of diagnostic flexibility.

Main differences

Time criteria:

- NICE refers to symptoms lasting longer than 4 weeks as "long-lasting," 4-12 weeks as "ongoing symptomatic COVID-19," and longer than 12 weeks as "post-COVID-19 syndrome." (13)
- WHO, NASEM, CDC: typically use a 3-month (12-week) threshold for diagnosis, but the WHO also requires that symptoms persist for at least 2 months, while the CDC and NASEM definitions are less specific. (2, 3, 12, 13)

Wisk et al., in a study published in JAMA Network Open in August 2025, conclude that there is still no uniform definition of long COVID. The field is characterized by definitional variability, with no uniform definition of long COVID. The most prominent organizations (NASEM, CDC, WHO) use different criteria, and there is also wide variation in ongoing studies and published studies in terms of which symptoms, time intervals, and severity levels are taken into account. (19)

A standardized definition is needed: According to the authors, there is an urgent need for a sensitive (identifying true patients) but sufficiently specific (avoiding misdiagnosis) standard definition of long COVID for both research and clinical purposes. (19)

Evolution of definitions: The criteria are likely to remain looser for clinical care/validation or social security claims, while they may be stricter and narrower for research or the selection of therapeutic interventions. (19)

The definition of post-COVID condition has undergone continuous change since the beginning of the pandemic, but after reviewing the positions of leading international organizations (NICE, WHO, NASEM, CDC) and the latest research, it is clear that there is still no uniform and universally accepted definition. The application of different duration and symptom criteria makes it difficult to assess the prevalence of the disease, compare research results, and provide uniform care to patients. It would be important to develop a sensitive yet sufficiently specific, consensus-based definition that can be reliably applied in both clinical practice and research. The diversity of definitions continues to pose serious clinical, social, and scientific challenges.

4.1.3. Prevalence of long COVID syndrome after the acute SARS-CoV-2 infection

The analysis described in the chapter *Definitions of Long Covid* pointed out that there is no uniform, internationally accepted definition of long COVID. Different organizations and studies apply varying criteria, which fundamentally affect prevalence estimates. This definitional and methodological heterogeneity is a critical factor in interpreting long COVID prevalence data. (19)

In our review published in 2023 (Sebők et al., 2023), a wide range of prevalence figures was identified in the literature. (1) For example, Ballering et al. (2022) reported that approximately 10–20% of patients experience prolonged symptoms following SARS-CoV-2 infection. (4) Some studies found even higher rates, up to 30% (Yoo et al., 2022), while others, such as Xie et al. (2021), observed much lower prevalence—around 7%. (5, 6) These differences are explained primarily by the variation in definitions and study methodologies used in the respective research.

According to the most recent data, prevalence rates are highly sensitive to the applied diagnostic criteria. The large INSPIRE cohort study, summarized by Wisk et al. (JAMA Network Open, 2025), demonstrated that prevalence estimates could range from 31% to 42% at three months post-infection, and from 14% to 22% at six months, depending on which published definition was applied. Studies employing stricter, population-based

criteria typically report lower rates (~7–13%), while those utilizing self-report or broader symptom sets yield higher estimates, up to 30% or more. This clearly illustrates how study design and operational definitions impact prevalence findings. (19)

According to RECOVER Consortium Research Update (2025), an American study based on data from 6 million patients, the prevalence of long COVID is 10–26% in adults and 4% in children, and although the rate is lower in the Omicron era, the risk remains persistent. (20)

Currently, the NASEM definition is considered a gold standard for research and clinical care in the United States, although there remain significant international differences in recommendations. (19) The NASEM definition notably does not set a maximum time window (incubation period) for symptom onset, recognizing that diagnoses may depend on factors such as delayed recognition or limited access to healthcare; this approach is likely to increase the number of cases classified as long COVID compared to earlier or more restrictive criteria. (3)

4.1.4. Susceptibility to long COVID

Based on data available in 2023, long COVID can develop in any patient group, regardless of the severity of the acute infection, regardless of age, even in those who did not require hospital care or who had asymptomatic COVID-19 infection. (1)

However, more severe COVID disease (hospitalization or intensive care, mechanical ventilation), age over 50, gender (female), as well as asthma, previous respiratory disease, obesity, and high BMI increase the risk of long COVID. Diabetes, high blood pressure, tumors, and immunosuppression can worsen the acute phase, but no clear link has been found with the development of long COVID. After leaving the intensive care unit, the likelihood of neuropsychiatric problems is 56% higher, and persistent symptoms (fatigue, sleep disturbances, shortness of breath, coughing, anxiety, cognitive impairment) remain common in a significant proportion of patients. (1)

Current, up-to-date literature reiterates and further refines the main risk factors already known in 2023, but differences in vaccination status, lifestyle, and age are also emphasized.

Consistent with previous findings, severe COVID-19 infection, hospital/intensive care treatment, ventilation, older age, female gender, obesity, high BMI, and comorbidities (e.g., respiratory diseases, hypertension, cardiovascular diseases) remain among the most significant risk factors. (20-22)

Long COVID can develop in infected individuals of any severity, even those who are asymptomatic: this is confirmed by previous and recent analyses, but more recent articles show even more clearly that long-term symptoms can occur even in mild or asymptomatic cases. (21, 22)

New emphases

Vaccination: A new feature of the 2025 studies is that they focus on the protective effect of vaccination (at least two doses), which significantly reduces the development of long COVID. This factor was still rarely mentioned in the literature in 2023. (20, 21)

Comorbidity: Recent meta-analyses highlight the crucial role of hypertension, obesity, cardiovascular disease, multiple comorbidities, and ICU care, while diabetes, tumours, and immunosuppression are more closely linked to the acute phase than to the occurrence of long COVID. (21, 22)

Ethnic and lifestyle factors: The latest articles also emphasize health behaviours, smoking, physical activity, sleep quality, and poor dietary patterns, which were less prominent in the 2023 summaries. (22)

High-risk populations: According to RECOVER 2025 data, older people (especially those over 65), people who have had repeated COVID infections, and women are at particular risk. (20)

Finally, the COVID variant causing the infection should also be mentioned among the predisposing factors. Zhang et al.'s 2025 article points out that the incidence of long COVID is significantly lower with the Omicron variant than with Delta or earlier variants. (23)

4.1.5. Potential preventive options of long COVID

Vaccination

Based on the literature available in 2023, the protective effect of vaccination against long COVID was controversial. Some studies showed a significant reduction in risk, while others showed only modest, partial protection. (1)

According to the evidence at the time, the preventive effect of vaccination against long COVID was not clear: on the one hand, there were studies that showed significant protection (two or three Pfizer-BioNTech vaccinations reduced the incidence of long-term symptoms by up to 75-85%, and in another study by 50%), while other results showed only partial, modest protection (e.g., 15% in a large US cohort). (1)

Several large population studies were based solely on self-reporting, and due to population differences, the results remained inconsistent and indicated that further research was needed. (1)

The inconsistencies observed in previous findings remain unaddressed by the most recent research.

According to more recent studies involving larger populations, the preventive effect of COVID-19 vaccination against long COVID is moderately confirmed but increases with dose: while the 2023 article by Sebők et al. emphasized significant inconsistencies in the results, emphasized population and methodological differences, recent meta-analyses show a significant protective effect after two or more doses, which depends on the type of vaccine, with mRNA vaccines providing greater protection than AstraZeneca. The effectiveness of vaccines in preventing long COVID is more moderate in the case of the Omicron variant. A brief overview of the studies can be found in Table 1. (1, 24-27)

Table 1. Summary of major studies on vaccine protection against long COVID (2023–Aug 2025)

Reference	Year	Number of studies	Population size	Main result	Interpretation
Byambasuren et al. (BMJ Med)	2023	16 observational study	614 392 participants	1 dose OR: 0.22–1.03 2 doses OR: 0.25–1.02 3 doses OR: 0.16 Post-infection vaccine OR: 0.38–0.91	Moderate protective effect, high heterogeneity, meta-analysis not possible. Quality of evidence: low.
Chow et al. (J Infect)	2024	25 observational study	14 128 260 participants	1 dose pre-COVID OR: 1.01 (ns) 2 doses pre-COVID OR: 0.76 (24% reduction) 1 dose post-COVID OR: 0.85 (15% reduction) 2 doses post-COVID OR: 0.63 (ns)	Two doses pre-COVID and one dose post-COVID significantly reduce the risk of long COVID. Greater effect on certain symptoms (fatigue, headache).
Català et al. (Lancet Respir Med)	2024	4 large national cohorts	>10 000 000 vaccinated, >10 000 000 unvaccinated	mRNS HR: 0.54–0.71, AstraZeneca HR: 0.84–0.85	Significant protection after one or two doses, stronger for mRNA vaccines; very large-scale, multi-country population
Peine et al. (Clin Microbiol Infect)	2025	65 NRSI	>5.7 million participants	≥1 dose VE: 41.0% (CI: 27.8–51.7%) 1 dose VE: 19.1% (CI: −119.4–70.2%) 2 doses VE: 43.2% (CI: 4.5–66.2%) 3 doses VE: 70.0% (CI: 30.0–87.0%)	Dose dependent protective effect. Uncertain results after one dose, significant protection after two or three doses. Lower efficacy (~21%) during the Omicron variant.

Pharmacovigilance and vaccine safety

The issue of potential side effects remains a focus of attention in relation to vaccines, particularly COVID-19 vaccines.

The safety of vaccines is monitored worldwide by several complex drug safety surveillance systems. The WHO Global Drug Monitoring Program (PIDM) and VigiBase, operated by the Uppsala Monitoring Centre, is the world's largest database with more than 40 million reports, providing international collaboration to analyse the short- and long-

term side effects of COVID-19 vaccines and early detection of rare events. The European Medicines Agency (EMA) and European Member States operate the EudraVigilance system and use national databases, while the Food and Drug Administration (FDA) and CDC conduct active and passive surveillance through the US VAERS system. Large-scale, multi-country projects such as the Global COVID Vaccine Safety Project (GCoVS) also pay particular attention to rare neurological, haematological, or cardiological complications. (28-32)

Short-term side effects

According to the latest reports from the EMA, CDC, and UK NHS, the most common side effects following COVID-19 vaccination include fatigue, headache, muscle pain, fever, chills, and pain or swelling at the injection site. These symptoms occur in the majority of vaccine recipients, are typically mild or moderate, and resolve spontaneously within 1-3 days. Severe allergic reactions (anaphylaxis) are extremely rare, occurring in less than 5 cases per million vaccinations, according to the EMA, FDA, and CDC. As it has been reported by UK's current 2025 information leaflet, "serious side effects are very rare." (33-36)

Long-term and serious side effects

Among the major long-term or rare side effects, myocarditis and pericarditis represent a clearly documented and quantified risk, mainly in teenage and young men after mRNA vaccination. According to the 2025 FDA safety summary (JAMA), the estimated incidence of myocarditis and/or pericarditis with newer mRNA vaccines is 27/1 000 000 doses (1 in 37 000) in males aged 12–24 years, but most cases are mild, with permanent heart damage occurring only in exceptional cases. (37) According to the EMA and CDC, Guillain-Barré syndrome, thrombosis with thrombocytopenia syndrome, and certain neurological complications are also extremely rare, with a frequency of 1–3 per 1 000 000 doses. According to the 2024 report of the GCoVS, no long-term, new, or more serious risks have been identified for any of the vaccines studied, and ongoing European monitoring does not indicate an increased risk. (33, 36, 38)

Antiviral compounds

In their 2023 review, Sebők et al. suggested that certain oral and parenteral antiviral agents may indirectly help prevent long COVID by reducing the likelihood of hospitalisation in patients with mild to moderate infection and by lowering the risk of subsequent long-term complications. The drugs examined included nirmatrelvir/ritonavir (Paxlovid), molnupiravir, remdesivir (parenteral), and bebtelovimab (monoclonal antibody), all of which play a role in the acute phase, mainly in outpatients or hospitalized patients in risk groups. The literature at the time did not yet clearly confirm a direct, long-term post-COVID preventive effect—it mainly focused on vaccination and the course of acute treatment. (1)

Nirmatrelvir-ritonavir (Paxlovid)

Based on the results of three large, peer-reviewed studies, Paxlovid (nirmatrelvir-ritonavir) treatment moderately or significantly reduces the risk of developing long COVID (post-COVID syndrome) during acute COVID-19, especially in high-risk and non-hospitalized groups, and may improve the main post-acute symptom groups. However, the extent of the risk reduction may be influenced by population, definition, or methodological differences. (39-41)

Molnupiravir

According to the EMA, molnupiravir (Lagevrio) has not been clinically proven to offer significant benefits in the treatment of COVID-19 in adults at risk of severe disease, and therefore rejected its central European marketing authorization in June 2023. (42)

Remdesivir

Based on the results of a large-scale systematic literature review and meta-analysis published in 2025, the use of remdesivir significantly increases the survival rate among patients hospitalized due to acute SARS-CoV-2 infection, regardless of severity. Furthermore, it also significantly reduces the risk of rehospitalization (OR 0.72). This result is consistent with current international treatment recommendations. However, there is still no consensus on the prevention of long COVID; most guidelines and meta-analyses

suggest that prospective, dedicated studies are needed to clearly confirm the preventive effect against long COVID. (43)

In a study conducted at Semmelweis University (Fésü et al. (2025)), data from 293 COVID-19 patients previously hospitalized who participated in post-COVID follow-up after infection were analysed. Using propensity score matching, two groups were created: standard treatment (SOC, 94 patients) and remdesivir + standard treatment (SOC + RDV, 94 patients), thus ensuring the thoroughness of the comparison. (44)

The primary endpoints were symptom-free status and at least a 50% reduction in symptoms at the post-COVID follow-up examination, while the secondary endpoints were respiratory function tests, a 6-minute walk test, and quality of life questionnaires. The results showed that symptom relief occurred significantly earlier in the group receiving remdesivir, although no significant difference in functional indicators was found between the two groups. (44)

Bebtelovimab

In the Sebők et al, (2023) article mentioned parenterally administered bebtelovimab as a possible prevention option. This is a monoclonal antibody isolated from a patient who recovered from COVID-19, which targets the spike protein of the virus. It was recommended for the treatment of high-risk outpatients with mild to moderate COVID-19 when Paxlovid and remdesivir were not available. (1)

A 2023 systematic literature review and meta-analysis, which included thirty-nine studies, examined the effect of bebtelovimab in hospitalized and outpatient COVID-19 patients. The results showed that bebtelovimab effectively neutralizes SARS-CoV-2, including emerging variants, and can be used safely in high-risk populations. The drug showed particular benefit in early treatment, but only modest or non-significant benefits were observed in clinical endpoints (hospitalization, mortality) compared to other monoclonal antibodies and antiviral agents. No conclusions were made regarding the prevention of long COVID. (45)

Other antiviral agents

Other antiviral preparations have also been used in everyday practice, such as favipiravir to reduce acute symptoms in Hungary, and since the article by Sebők et al. (2023) was

written, the possibility of using new drugs to prevent long COVID has also emerged, the data for which are summarized in the Table 2.

Table 2. Additional antiviral drugs that can be used to prevent long COVID

Active ingredient	Mechanism	Data on long COVID prevention
Favipiravir	RNA polymerase inhibitor	Several trials show faster symptom resolution and improved viral clearance in mild/moderate COVID-19, but larger RCTs and meta-analyses do not support a significant effect on long COVID prevention: insufficient evidence for a preventive role. (46, 47)
Ensitrelvir	Protease inhibitor	FDA is currently reviewing as an oral, post-exposure prophylactic; early studies are promising but no direct human data yet for long COVID prevention. Ongoing trials aim to clarify effect. (48)
Sipavibart	Long-acting monoclonal antibody (spike protein)	Used for pre-exposure prophylaxis in immunocompromised or high-risk patients; shown to lower acute infection rates, but no direct evidence for long COVID prevention to date. (49) The aim of the ongoing clinical trial is to monitor the safety of the treatment and changes in long COVID symptoms (e.g., cognitive impairment, autonomic dysfunction, exercise capacity). (50)
Pemivibart	Long-acting monoclonal antibody (spike protein)	Similar to sipavibart; effective in acute prevention for vulnerable populations, but data on long COVID prevention are lacking, further research ongoing. (49)

Glucocorticoids

The use of glucocorticoids (e.g., dexamethasone) in COVID-19 has shown mixed results. In severe COVID-19, when patients received respiratory support (oxygen or mechanical ventilation) and therapy was started after the first week—when immunopathological processes dominate and viral replication becomes less significant—glucocorticoids offer significant benefits, reducing mortality and disease progression. However, in patients who

did not require respiratory support, no benefit (and even potential harm) was demonstrated with the use of these agents. (1)

The effect of glucocorticoids on the risk of developing long COVID is unclear. Some data suggest that more severe initial infection increases the risk of long COVID, so glucocorticoid treatment given during the acute phase may even reduce this risk. (1)

Two recent studies also point out that the use of glucocorticoids for the prevention and treatment of post-COVID remains controversial; in some cases, they have a beneficial effect, while in others, their protective effect has not been proven, or they may even increase the risk. (51, 52)

Glucocorticoid therapy effectiveness in long COVID symptoms

According to a 2024 study reviewing data from 131 patients receiving glucocorticoid treatment who continue to experience long COVID symptoms—mainly persistent shortness of breath, radiological abnormalities, and decreased gas exchange—glucocorticoid treatment can improve lung function, radiological findings, and the subjective condition of patients. (51)

The treatment is particularly effective in patients with persistent lung damage or parenchymal abnormalities and typically requires 8–13 weeks of therapy. (51)

Risks and contradictions of glucocorticoid therapy

Meanwhile, based on the results of another large-scale study in 2024, glucocorticoid therapy used during COVID-19 infection was associated with a higher long COVID risk, meaning that more patients who received glucocorticoids during infection developed long-term symptoms (OR: 1.28) than those who were not treated. (52)

In summary, there is currently no proven preventive role for glucocorticoids against long COVID, and in certain situations they may even pose an increased risk. Further research is needed to clarify the exact indications and efficacy. (51, 52)

Other medications

The 2023 review by Sebők et al. did not include metformin, which more recent studies suggest may contribute to COVID-19 prevention. Evidence from several primary research articles indicates that the potential protective effect of metformin against long

COVID has been observed mainly in overweight or obese adults, particularly when the drug is administered early in the course of infection. A systematic review by BMJ Medicine and the results of the COVID-OUT phase III trial suggest that metformin administration may reduce the risk of long COVID in a statistically significant manner (RR 0.6; 95% CI 0.4–0.9). However, the certainty of this evidence is limited due to several methodological constraints, including that approximately half of the study participants were unvaccinated, the overall sample size was modest (n = 1126), and there was substantial loss of follow-up data, with 14.9% of long-term outcome data missing. (53)

A large population cohort study in primary care in the UK followed 624 000 people infected with COVID-19: in overweight/obese patients treated with metformin, the one-year incidence of long COVID was 12.6% lower in absolute terms and 64% lower in relative terms than in the control group (HR 0.36; 95% CI 0.32–0.41). (54)

The biological mechanism of action has been shown to include anti-inflammatory and antiviral activity, but the Chowdhury et al. (2025) emphasizes that metformin did not significantly affect acute COVID-19 endpoints (mortality, hospitalization) and that the generalizability of the prevention data may be limited, especially in vaccinated populations. (53)

Overall, based on current evidence, metformin may be one of the most promising non-antiviral, non-vaccine prophylactic agents for the prevention of long COVID in predominantly early-treated COVID-19 infected individuals, but further large RCTs that include vaccinated populations are still required to establish definitive recommendations. (53, 54)

4.1.6. Ongoing and completed clinical trials for the management of long Covid syndrome

The 21 ongoing long COVID drug clinical trials published in the article by Sebők et al, (2023), collected from the clinicaltrials.gov database as of November 19, 2022, were aimed at targeting the various pathomechanisms of long COVID (virus persistence, immune dysregulation, neurological disorders, fibrosis, chronic inflammation). Compared to the data queried in November 2022, there have been significant changes by September 2025 (09/05/2025), which are summarized in Table 3. (1)

Status of investigations ongoing in November 2022 in September 2025

The vast majority of clinical trials for long-term pharmacological/biological treatment of COVID-19 that were ongoing in November 2022 had been completed or were no longer active in September 2025. The available results (summarized in Table 3) indicate that there is still no significant therapeutic breakthrough in these trials. Studies of lithium, cannabidiol, Paxlovid, naltrexone, fluvoxamine, montelukast, metoprolol, temelimab, pimozide, vortioxetine, and atorvastatin have either shown negative results or had a statistically insignificant effect on the persistent symptoms of long COVID and therefore have not become clinical recommendations. In some studies, the side effect profile is favourable, but no meaningful improvement has been demonstrated; some studies (e.g., Paxlovid platform trial, Ampligen, NAD+ combination) showed partially positive secondary results, but these cannot be considered a breakthrough and require further investigation.

If only a ClinicalTrials.gov NCT number is given for a trial in Table 3, the trial data is available at clinicaltrials.gov under that number. I have indicated separate references (articles, summaries, publications) where further results or analyses are available. For each study, the terminology used reflects the original trial title or publication, so the disease and condition names in the table correspond to those applied in the source references.

Table 3. Clinical trials on drug interventions for long COVID listed in Table 2 of Sebők–Gyires (2023): updated with current status and results (as of September 2025)

NCT Number	Title	Aim	Interventions	Study design	Population	Current status (Sept. 2025) and results
NCT05618587	Effect of Lithium Therapy on Long COVID Symptoms	To assess efficacy of lithium for long COVID symptoms	Lithium, placebo	Randomized, placebo-controlled	Planned: 52; Enrolled: 52; Age: ≥18; Sex: all; Adults with history of COVID-19, persistent symptoms	Completed. Negative result; low dose ineffective (55)
NCT04997395	Feasibility of Cannabidiol for the Treatment of Long COVID	To study cannabidiol safety and feasibility for long COVID	MediCabilis Cannabis Sativa 50	Feasibility, open-label pilot	Planned: 30; Enrolled: 30; Age: ≥18; Sex: all; Adults with long COVID (NICE criteria)	Completed. No results posted on ClinicalTrials.gov; feasibility and safety confirmed in published report, but no significant efficacy. (56)
NCT05595369	RECOVER-VITAL platform trial, SARS CoV-2 Viral Persistence Study (PASC) - Study of Long COVID-19	To assess Paxlovid antiviral use for long COVID (RECOVER-VITAL)	Paxlovid, placebo	Platform trial, multicentre	Planned: >10 000; Enrolled: 965 Age: ≥18; Sex: all; Adults with long COVID	Completed. Preliminary results submitted; Quality Control Review ongoing (QC not concluded as of 2025-09).
NCT05576662	Paxlovid for Treatment of Long Covid	To evaluate Paxlovid for ongoing long COVID	Nirmatrelvir, ritonavir placebo, ritonavir	Randomized, placebo-controlled	Planned: 100; Enrolled: 168; Age: ≥18; Sex: all; Vaccinated adults with long COVID	Completed. No positive results, safe but not significantly beneficial in improving selected PASC symptoms in a mostly vaccinated cohort with long-lasting symptoms. (57)

NCT Number	Title	Aim	Interventions	Study design	Population	Current status (Sept. 2025) and results
NCT05220280	SOLIDARITY Finland Plus Long COVID	To test Imatinib, Infliximab in long COVID	Imatinib, infliximab	Randomized, ongoing	Planned: ≈600–800; Enrolled: 400 (estimated)ongoing; Age: ≥18; Sex: all; Adults post-acute COVID-19	Ongoing (long-term follow-up in progress); interim results available, efficacy of imatinib or infliximab for long COVID not confirmed. (58)
NCT05513560	Canadian Adaptive Platform Trial for Long COVID-19	To evaluate Ibudilast, Pentoxifylline	Ibudilast, pentoxifylline, placebo	Adaptive platform trial	Planned: 64; Enrolled: 460; Age: ≥18; Sex: all; Adults diagnosed with long COVID	Suspended; no active recruitment or data collection.
NCT04978259	SOLIDARITY Finland Long COVID (Remdesivir Long-term Follow-up Study of COVID Patients)	Remdesivir effectiveness for long COVID	Remdesivir	Cohort follow-up	Planned: 208; Enrolled: 202; Age: ≥18; Sex: all; Hospitalized COVID-19 survivors	Unknown status on ClinicalTrials.gov; results published, remdesivir did not demonstrate long-term efficacy for post-COVID recovery or symptom reduction. (59)
NCT05592418	Study to Evaluate the Efficacy and Safety of Ampligen in Patients with Post-COVID Conditions	Efficacy/Safety of Ampligen (Rintatolimod) for post-COVID	Rintatolimod, placebo/Saline	Randomized, placebo-controlled	Planned: ≈80; Enrolled: 80; Age: ≥18; Sex: all; Adults with post-COVID moderate/severe symptoms	Completed. Primary endpoint not met, but secondary analyses suggest Ampligen may improve fatigue and functional capacity in moderate-to-severe Long COVID; well tolerated.
NCT04604704	Pilot Study Into LDN and NAD+ for Treatment of Patients With Post-COVID-19 Syndrome	LDN + NAD+ for post-COVID syndrome	Naltrexone, dietary supplement NAD+	Open-label pilot	Planned: 50–75; Enrolled: 36; Age: ≥18; Sex: all; Moderate/severe post-COVID fatigue	Completed. Open-label pilot: LDN + NAD+ improved fatigue and quality of life in half of patients with moderate/severe post-COVID fatigue; well tolerated. (60)

NCT Number	Title	Aim	Interventions	Study design	Population	Current status (Sept. 2025) and results
NCT05216614	Fluvoxamine to Augment Olfactory Recovery For Long COVID-19 Parosmia	Fluvoxamine for olfactory dysfunction	Fluvoxamine, placebo	Randomized, planned, withdrawn	Planned: n.a.; Enrolled: 0 (withdrawn); Age: ≥18; Sex: all; Parosmia in Long COVID	Withdrawn; study cancelled prior to enrollment due to inability to obtain investigational drug (fluvoxamine).
NCT04695704	Efficacy of Montelukast in Mild-moderate Respiratory Symptoms in Patients with Long COVID-19: (E-SPERANZA)	Montelukast in long COVID respiratory symptoms	Montelukast, Placebo	Randomized, placebo-controlled	Planned: ≈80–120; Enrolled: 86; Age: ≥18; Sex: all; Mild-moderate long COVID respiratory symptoms	Terminated; study was ended prematurely, so only limited data are available. The montelukast did not show significant benefit for mild respiratory symptoms in long COVID, but conclusions are limited due to early termination. (61)
NCT04948203	Assessing the Efficacy of Sirolimus in Patients With COVID-19 Pneumonia for Prevention of Post-COVID Fibrosis	Sirolimus for post-COVID fibrosis prevention	Sirolimus	Randomized, ongoing	Planned: ≈200–300; Enrolled: 60; Age: ≥18; Sex: all; COVID-19 pneumonia	Active, not recruiting
NCT05507372	Treatment for Post Acute COVID-19 Syndrome	Pimozide in Post Acute COVID Syndrome	Pimozide	Randomized	Planned: ≈30–60; Enrolled: 50; Age: ≥18; Sex: all; Post-acute COVID syndrome	Unknown status on ClinicalTrials.gov, study has passed its completion date and status has not been verified in more than two years
NCT04904536	Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy	Atorvastatin for neurological recovery after COVID	Atorvastatin, Standard Care	Randomized, standard care comparator	Planned: ≈140–200; Enrolled: 190; Age: ≥18; Sex: all; Ongoing neurological symptoms post-COVID	Active, not recruiting. No published results yet.

NCT Number	Title	Aim	Interventions	Study design	Population	Current status (Sept. 2025) and results
NCT05497089	Temelimab as a Disease Modifying Therapy in Patients with Neuropsychiatric Symptoms in Post-COVID 19 or PASC Syndrome	Temelimab as therapy for neuropsychiatric PASC	Temelimab, Placebo	Placebo-controlled	Planned: ≈24–50; Enrolled: 203; Age: ≥18; Sex: all; Neuropsychiatric post-COVID symptoms	Completed. No peer-reviewed final results published as of September 2025; initial findings suggest further investigation warranted.
NCT05350774	Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2	IVIG, steroids, immunotherapy for neuro-PASC	IV immunoglobulin, Saline, IV methylprednisolone	Randomized	Planned: ≈120–180; Enrolled: 45; Age: ≥18; Sex: all; Neurological post-acute sequelae of COVID-19	Active, enrolling by invitation; study ongoing, no published results available as of September 2025.
NCT05430152	Low-dose Naltrexone for Post-COVID Fatigue Syndrome	Low-dose Naltrexone for post-COVID fatigue	Low-Dose Naltrexone, Placebo	Randomized, placebo-controlled	Planned: ≈150; Enrolled:160; Age: ≥18; Sex: all; post-COVID fatigue	Active, recruitment in progress
NCT05096884	Post-Acute Sequelae of Coronavirus-19 (COVID-19) With Dyspnea on Exertion And Associated TaChycardia TrEatment Study	Metoprolol for post-COVID exertional tachycardia	Metoprolol Succinate	Small cohort	Planned: ≈40; Enrolled: 14 (small cohort); Age: ≥18; Sex: all; Exertional dyspnoea/tachycardia post-COVID	Terminated, no published results available as of September 2025.
NCT05047952	Vortioxetine for Post-COVID-19 Condition	Vortioxetine for post-COVID condition	Vortioxetine, Placebo	Randomized	Planned: ≈25–60; Enrolled: 149; Age: ≥18; Sex: all; long COVID	Completed. No significant overall benefit of vortioxetine versus control in post-COVID condition; secondary analyses highlight roles of metabolic disruption, BMI, and

NCT Number	Title	Aim	Interventions	Study design	Population	Current status (Sept. 2025) and results
						inflammation in symptom persistence. Several post-hoc publications available. (62)
NCT05228899	Zofin to Treat COVID-19 Long Haulers	Zofin in COVID-19 long haulers	Zofin, Placebo	Randomised, placebo-controlled	Planned: ≈40–80; Enrolled: 18; Age: ≥18; Sex: all; long haulers/post-COVID	Completed; no published results available as of September 2025.
NCT05052307	A Real-world Evidence Study of BNT162b2 mRNA Covid-19 Vaccine in Brazil	COVID-19 vaccine effectiveness and outcomes (Brazil)	Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine, CoronaVac, ChAdOx1, Janssen	Observational cohort	Planned: population registry; Enrolled 4574: population-level; Age: ≥18; Sex: all; Vaccinated Brazilian adult population	Completed; Two doses of BNT162b2 provided moderate initial protection (effectiveness: 77.7%), waned to <30% by day 120 during Omicron. Overall adjusted effectiveness after median 94 days was 46.7% (95% CI: 19.9–64.6%). Booster vaccination is recommended for sustained protection. (63)

4.1.7. Ongoing studies

Based on a search for ongoing clinical trials for the period 2024-2025, I found 70 relevant clinical trials. This analysis of 70 long COVID therapeutic trials reveals a methodologically rigorous but evidence-limited research landscape with only 2.9% of studies reporting available results.

Confirmed scientific data

Trial portfolio metrics:

- High-quality randomised controlled trials: 27 quadruple-blind studies
- Late-phase evidence generation: 17 Phase III trials (24.3%)
- Large-scale studies: 11 trials with ≥500 participants

Therapeutic approach distribution:

- Antivirals: 9 trials (Paxlovid, remdesivir, ensitrelvir)
- Neurological interventions: 8 trials (amantadine, modafinil)
- Anti-inflammatory agents: 6 trials (baricitinib, anakinra)
- Cardiovascular therapies: 6 trials (ivabradine, atorvastatin)
- Immunomodulators: 6 trials (IVIG, monoclonal antibodies)

Most robust evidence-generating studies

Definitive Phase III Trials:

1. REVIVE Trial (NCT06128967): 1500 participants testing fluvoxamine/metformin combination
2. Baricitinib Study (NCT06631287): 550 participants evaluating Janus kinase inhibition for neurologic/cardiopulmonary symptoms
3. Allopurinol Cardiovascular Trial (NCT05943821): 1116 participants for cardiovascular risk reduction
4. RECOVER Platform Trials: Multiple coordinated studies with >2000 combined enrolment

Critical evidence limitations

Results Availability Crisis:

Only 2 of 70 trials have published results, creating a severe evidence-practice gap.

Population Coverage Gaps:

- Pediatric representation: Limited to 3 trials (4.3%)
- Trial discontinuation: 5 studies terminated/withdrawn/suspended

Detailed information on ongoing clinical trials can be found in Annex 1.

4.2. Off-label drug use for long COVID

4.2.1. Comprehensive analysis of COVID-19 off-label requests in Hungary

A total of 165 „COVID-19" off-label requests were submitted, with their yearly distribution shown in Figure 1.

2020: 145 requests (87.9%)

2021: 9 requests (5.5%)

2022: 6 requests (3.6%)

2023: 4 requests (2.4%)

2024: 1 request (0.6%)

2025 (I-V.): 0 requests (0.0%) (64)

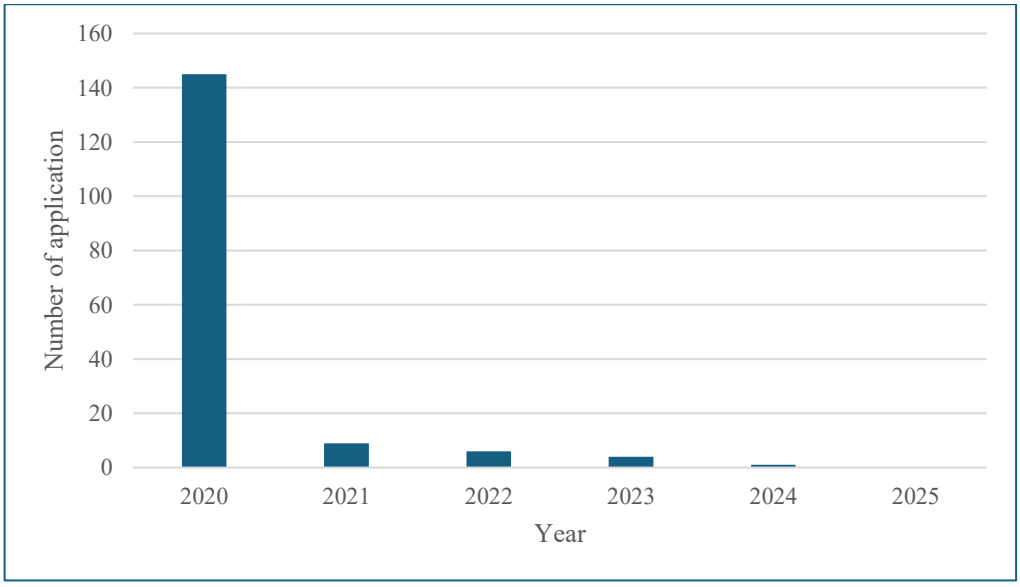

Figure 1. Number of COVID-19 off-label applications by year 2020-May 2025 (Based on NNGYK database) (64)

Demographic data

- Gender distribution: A predominance of male patients was observed (63.5% vs. 36.5%)
- Mean age: 57.0 years (median: 62 years)
- Age range: 1.9–90 years
- Paediatric cases: 9 requests (5.7%) (64)

The most frequently requested off-label active substances, along with their corresponding dosage regimens for the treatment of COVID-19, are presented in Table 4.

Table 4. List of the most frequently requested off-label active ingredients (Based on NNGYK database) (64)

Ingredient	Number of applications (%)	Main indication	Standard dosage
Tocilizumab	57 (34.5%)	COVID pneumonia, CRS (Cytokine Release Syndrome)	2×800 mg, 2 hours apart
Favipiravir	59 (35.7%)	COVID-19 infection	Day 1: 2×1600 mg, then: 2×600 mg
Ruxolitinib	10 (6.1%)	COVID-19, CRS	2×10 mg per day, for 28 days
Remdesivir	8 (4.8%)	COVID-19 pneumonia, including pediatric cases	5 mg/kg/day on day 1, then from day 2 onwards 2.5 mg/kg/day.
Chloroquine	7 (4.2%)	COVID-19 infection	2×500 mg per day

Combination therapies

In 12 cases, off-label requests involved combination therapies. Among these, the most frequently requested combinations were favipiravir + hydroxychloroquine (5 cases) and tocilizumab + dexamethasone (2 cases). (64)

Long COVID off-label requests

The analysis identified five off-label requests specifically related for long COVID indications, all of which pertained to the active substance pirfenidone. The detailed characteristics of these five relevant requests are summarized in Table 5.

Table 5. Summary of long COVID off-label applications by year 2008-May 2025 (Based on NNGYK database) (64)

Year	Patient demographics	Indications	Active ingredients	Planned dosing regimen	Approval conditions
2022	Female, 49 years old	Post-COVID pulmonary fibrosis	Pirfenidone, 267 mg	Days 1–7: 267 mg three times daily Days 8–14: 534 mg three times daily From day 15 onward: 801 mg three times daily	Pirfenidone Compared to Placebo in Post-COVID19 Pulmonary Fibrosis COVID-19 (FIBRO-COVID) ClinicalTrials.gov Identifier: NCT04607928
2023	Female, 49 years old	Post-COVID pulmonary fibrosis	Pirfenidone, 267 mg	Days 1–7: 267 mg three times daily Days 8–14: 534 mg three times daily From day 15 onward: 801 mg three times daily	Application supported by published data: Based on literature, the requested therapy may be effective in the indicated condition.
2023	Male, 72 years old	Post-COVID pulmonary fibrosis	Pirfenidone, 267 mg	Days 1–7: 267 mg three times daily Days 8–14: 534 mg three times daily From day 15 onward: 801 mg three times daily	Application supported by published data: Based on literature, the requested therapy may be effective in the indicated condition.
2023	Male, 70 years old	Progressive post-COVID pulmonary fibrosis	Pirfenidone, 267 mg	2 tablets three times daily (the patient did not tolerate 3 tablets three times daily)	Application supported by published data: Based on literature, the requested therapy may be effective in the indicated condition.
2024	Male, 75 years old	Post-COVID pulmonary fibrosis	Pirfenidone, 267 mg	Days 1–7: 267 mg three times daily Days 8–14: 534 mg three times daily From day 15 onward: 801 mg three times daily	Application supported by published data: Based on literature, the requested therapy may be effective in the indicated condition.

Off-label demand declined sharply after 2020, reflecting evolving clinical practice and regulatory trends regarding COVID-19 therapies. Despite the limited evidence for effectiveness from high-quality clinical trials, pirfenidone remained the sole off-label

treatment for post-COVID syndrome formally used in Hungary, whereas internationally, attention has shifted to other agents with better theoretical or clinical support.

Therefore, I considered it necessary to explore the international literature for evidence regarding off-label pharmacological interventions in post-COVID conditions.

4.2.2. Global review of off-label pharmacological interventions for long COVID

Table 6 summarizes the off-label pharmacologic interventions for long COVID syndrome, based on data published in the past two years (2023-2025).

Table 6. Summary table of off-label pharmacologic interventions for long COVID syndrome (peer-reviewed clinical evidence)

Active ingredient	Main indication	Inclusion criteria	Planned dosing regimen	Included patient number and method	Conclusions
Low-dose Naltrexone (LDN)	Post-acute sequelae of COVID-19' (PASC)	Adult patients with a history of SARS-CoV-2 infection confirmed by PCR, antigen, or serology prior to vaccination, who had persistent symptoms attributable to PASC for at least 28 days following infection. (65)	Low-dose naltrexone (LDN) was individualized dose-titration ranging from 0.5 mg daily to 6.0 mg daily. (65)	59 out of 468 PASC patients at the Stanford clinic who received low-dose naltrexone and completed all required questionnaires were evaluated in a retrospective observational study. (65)	The improvements in the total number of symptoms, severity of primary symptoms (fatigue, post-exertional malaise, unrefreshing sleep, abnormal sleep pattern), and functional status after low-dose naltrexone treatment were statistically significant, as evidenced by p-values less than 0.05 for these outcomes. (65)
Pirfenidone (antifibrotic)	Post-acute sequelae of COVID-19' (PASC)	18 and older patients who confirmed moderate to severe COVID-19 and had a positive reverse transcriptase-polymerase chain reaction nasopharyngeal swab. (66)	Prednisolone 20 mg once daily plus pirfenidone 267 mg three times daily (46/90), administered for at least three months within the previous six months in one group of patients; another group received steroids only. (66)	90 patients who completed follow-up in a post-COVID retrospective observational study were examined. (66)	CT scores improved markedly after six months, with no significant association observed between score changes and off-label pirfenidone use. (66)

Active ingredient	Main indication	Inclusion criteria	Planned dosing regimen	Included patient number and method	Conclusions
Molnupiravir	Acute COVID-19 and long-term post-COVID symptoms in high-risk adults. (67)	Adults ≥50 years, or ≥18 years with ≥1 comorbidity, ≤5 days symptomatic, confirmed COVID-19 by PCR or antigen, not hospitalised. (67)	800 mg twice daily for 5 days. (67)	25 783 randomised (12 821 molnupiravir + usual care; 12 962 usual care); 23 008 (89.2%) long-term follow-up 11 778 molnupiravir, 11 230 control. Multicentre, prospective, open-label, adaptive RCT in community participants (molnupiravir + usual care vs usual care), with 3- and 6-month follow-up. (67)	Molnupiravir modestly reduced severe and persistent symptoms and improved quality of life and wellness at 3 and 6 months (all $p < 0.0001$); absolute effects were small with high numbers needed to treat, and no difference in hospitalisation rates. (67)
Nintedanib, pirfenidone	Lung fibrosis after COVID-19 (post-COVID pulmonary fibrosis)	Adults (>18 years) with prior COVID-19 pneumonia, persistent cough, dyspnoea, exertional dyspnoea, reduced oxygen saturation ≥12 weeks post-diagnosis, fibrosis detected by imaging (CT), no prior idiopathic lung disease, not intubated during acute phase. (68)	Nintedanib: 300 mg/day; Pirfenidone: week 1=600 mg/day, week 2=1200 mg/day, week 3 and after=1800 mg/day, both oral for 12 weeks. (68)	30 (15 per group); randomised, prospective clinical trial. (68)	Both treatments improved lung function, exercise capacity, oxygenation, and radiology. Nintedanib was superior in improving 6MWT and saturation but had more adverse effects (mainly gastrointestinal). (68)
Amifampridine	Fatigue in post-COVID syndrome (PCS)	Adults with PCS-associated fatigue, refractory to other therapies; no major pre-existing neurological disease in most cases. (69)	Mostly 5–20 mg/day (individualized, off-label use). (69)	5; retrospective case series. (69)	Marked, reproducible improvement in fatigue and sleep need in all cases; improvement reversed on drug withdrawal; larger RCT need to confirm effect. (69)
Acyclovir	Long-haul COVID, especially neurological symptoms (encephalopathy)	Patients with confirmed prior COVID-19 infection and persistent long-haul symptoms, especially neurological (e.g., encephalopathy, brain fog), as judged by treating psychiatrist. (70)	Acyclovir 400 mg 2-4 times daily (BID/TID/QID), dose and duration individualized per case. (70)	4 (case series) (70).	All 4 patients had clinical improvement in neurological symptoms and reductions in IgG/IgM titers during acyclovir therapy, with no reported side effects; authors suggest acyclovir may be safe and effective, but further controlled studies are needed. (70)

4.2.3. Summary evaluation of potential off-label drug treatments for long COVID syndrome

Low-dose naltrexone (LDN)

The studies aim to demonstrate that LDN may be an effective and safe symptomatic treatment for post-COVID syndrome, particularly for reducing fatigue and related symptoms such as sleep disturbances and exhaustion. (65)
LDN exerts its effects primarily through the blockade of opioid receptors (mainly the μ-opioid receptor), thereby triggering immunomodulatory, anti-inflammatory, and regulatory mechanisms in the body. (65)

Completed LDN study

Stanford retrospective cohort study (N=59)

- Results: Significant improvement in fatigue (FSS score significantly decreased during treatment), post-exertional malaise, sleep disturbances, and functional status
- Dosage: 0.5–6.0 mg/day, tailored to the individual
- Safety: Well tolerated, minimal side effects (65)

Ongoing LDN study

This study is not listed in the table as it is ongoing, and no results are available yet.
British Columbia RCT (N=160)

- Study ID: NCT05430152, BMJ Open protocol
- Design: Randomised, double-blind, placebo-controlled phase II study
- Primary endpoint: Fatigue Severity Scale (FSS) after 16 weeks
- Dosage: Titrated from 1 mg to 4.5 mg
- Status: Actively recruiting participants until 2025 (71)

Antiviral agents

Molnupiravir

This study evaluates whether adding molnupiravir to standard therapy improves quality of life at 3 and 6 months after treatment.

PANORAMIC trial (N=25 783)
Trial ID: ISRCTN30448031, ISRCTN registry

- Design: Multicentre, open-label, randomised controlled trial
- Follow-up period: 6 months
- Results:
  - Symptoms such as fatigue, shortness of breath, and others occurred less frequently and were generally milder during the six-month follow-up in the molnupiravir group compared to the standard care group. However, this effect was modest, with a high number needed to treat (NNT: 40–63).
  - Quality of life improved based on the EQ-5D-5L quality of life scale. In the study, the treated group's scores were slightly but significantly more favourable.
  - Importantly, the absolute differences were small; while the molnupiravir group had statistically significantly fewer and milder post-COVID symptoms and better quality of life, the difference compared to the control group was very small. (67)

Antifibrotic agents

Pirfenidone as monotherapy

This study seeks to determine whether pirfenidone is more effective than placebo in preventing or treating post-COVID-19 pulmonary fibrosis.
FIBRO-COVID trial (N=113)
Clinical trial identifier: NCT04607928

- Design: Phase II, double-blind, placebo-controlled, Spanish multicentre trial
- Duration: 24 weeks
- Results: No significant difference compared to placebo
  - FVC improvement: 12.74% vs 4.35% (p=0.071)
  - Fibrotic score reduction: 5.44% vs 2.57% (p=0.52)
- Conclusion: Pirfenidone was not shown to be more effective than placebo (66)

Nintedanib vs. pirfenidone

This Turkish study compares the efficacy and side effect profiles of two antifibrotic drugs in patients with post-COVID pulmonary fibrosis.

Turkish comparative study (N=30)

- Design: Randomised, prospective study
- Duration: 12 weeks
- Results:
  - Both drugs were effective in PFT parameters
  - Advantages of nintedanib: Better 6-minute walk test (p=0.02), higher oxygen saturation (p=0.005)
  - Side effects: Nintedanib caused more gastrointestinal side effects (diarrhoea 80%, nausea 66.6%) (68)

Statins

The analysis identified only limited pirfenidone cases for post-COVID pulmonary fibrosis in the Hungarian NNGYK database. In contrast, international evidence suggests statins could address a broader spectrum of long COVID symptoms, including:

- Neurological symptoms (brain fog, cognitive impairment) - STRONGER trial (72)
- Systemic inflammation and vascular dysfunction - multiple mechanisms
- Fatigue and autonomic dysfunction - combination approaches
- Cardiovascular sequelae - established statin benefits

The absence of statin-related off-label requests in Hungarian long COVID treatment represents a significant gap, particularly given:

- Established safety profile - Statins have decades of clinical experience
- Multiple mechanisms of action - Anti-inflammatory, antiviral, vascular protective
- Ongoing high-quality clinical trials - STRONGER trial provides regulatory pathway
- Cost-effectiveness - Generic statins are highly affordable
- Broad applicability - Could address multiple long COVID symptom domains

The published statin research suggests that Hungarian regulatory authorities and clinicians should monitor the outcomes of the STRONGER trial and consider developing

evidence-based guidelines for statin use in long COVID conditions. Unlike treatments with limited mechanisms (such as acyclovir for neurological symptoms), statins offer multiple pathways for therapeutic benefit that align with our understanding of long COVID pathophysiology. (73)

Immunomodulators

Ongoing study

This study is not included in the table as they are ongoing, and no results are yet available.

Methylprednisolone

This trial investigates whether methylprednisolone is effective in treating persistent cognitive problems and memory complaints in adults with post-COVID syndrome.

PoCoVIT trial protocol (N=418 planned)

- Trial ID: NCT05986422
- Design: Randomised, double-blind, placebo-controlled trial
- Target population: Adults with post-COVID syndrome experiencing cognitive deficits
- Dosage: ~1 mg/kg/day for 4 weeks, then tapering
- Status: Protocol published, results not yet available (74)

Case series

Amifampridine

This study evaluates whether off-label use of amifampridine can improve refractory post-COVID fatigue.

German case series (N=5)

- Indication: Refractory post-COVID fatigue
- Dosage: 5–20 mg/day
- Results: Marked and reproducible improvement observed in all cases
- Limitation: Very small sample size (69)

Acyclovir

This study investigates whether acyclovir can improve persistent neurological symptoms associated with post-COVID syndrome, particularly in cases of encephalopathy. Neurological case series (N=4)

- Indication: Neurological complications (encephalopathy)
- Results: Clinical improvement in all 4 patients
- Mechanism: Presumed antiviral effect against persistent virus (70)

Various off-label therapies and supplements in long COVID

This German single-centre, assessor-blinded randomised controlled trial (ACUQiG study, N=235) examined adult PCS patients (18–60 years) with persistent fatigue and at least 3 out of 7 multi-systemic symptoms (sleep disturbance, headache, joint/muscle pain, anxiety/depression, concentration impairment, post-exertional malaise, anosmia) for at least 12 weeks after COVID-19 infection.

- Design: Open-label, randomised, controlled trial with acupressure plus qigong vs. waitlist; all data refer to the baseline cohort before any intervention.
- Results: Baseline medication history revealed frequent use of off-label antihistamines (9.4%), vitamin D (53.6%), minerals (50.2%), and herbal medicines (32.3%). PCS patients had a high burden of disease, long sick leave, and widespread use of unproven therapies and supplements.
- Conclusion: No strong evidence supports the effectiveness of these interventions and widespread off-label/self-medication highlights substantial clinical uncertainty and unmet needs in PCS care. (75)

4.3. Post-COVID interstitial lung disease: medication usage analysis

Demographic data

- 470 patients, mean age 53.6 ± 15.9 years
- Male predominance: 277 individuals (58.9%) vs 193 women (41.1%)
- ILD diagnosis: 52 patients (11.1%)
- Post-COVID ILD: 40 patients (8.5%)

Patient group characteristics

ILD positive patients (n=52):

- Mean age: 63.3 years
- Male dominance: 65.4%
- Medication usage: 73.1%

Post-COVID ILD patients (n=40):

- Mean age: 62.4 years
- Pronounced male predominance: 72.5%
- Medication usage: 70.0%

ILD negative patients (n=418):

- Mean age: 52.4 years
- Balanced genders: 58.1% male
- Medication usage: 57.4%

Medication Usage Analysis

Age-related Trends

Based on age distribution:

- <30 years: 32.5% take medication
- 60-69 years: 81.1%
- 80+ years: 100% (all patients take medication)

Medication Statistics

- 1076 medication prescriptions total
- 562 unique drug names
- 238 different active ingredients

The amount of medication taken by the 470 patients is summarized in Table 7. 63 patients take more than 5 medications out of 470 patients (13.4%). The 2 patients taking the most medications use 16 different preparations each. Both patients are transplant recipients.

Table 7. Number of medications taken by patients included in the study

Number of medications taken	Number of patients	Patient proportion (%)
0	195	41.5
1	66	14.0
2	62	13.2
3	30	6.4
4	28	6.0
5	26	5.5
6	17	3.6
7	12	2.6
8	9	1.9
9	3	0.6
10	5	1.1
11	3	0.6
12	4	0.9
13	6	1.3
14	2	0.4
16	2	0.4

Table 8 summarizes the five most commonly used drug groups in ILD patients. The analysis revealed significantly higher usage rates of beta-blockers (33.3% vs. 12.7%), antiplatelet agents (33.3% vs. 6.5%), angiotensin receptor blockers (16.7% vs. 6.7%), diuretics (25.0% vs. 8.1%), and anti-gout medications (8.3% vs. 3.1%) among ILD+ patients compared to ILD- cases. The largest differences were observed for antiplatelet agents (+26.9 pp) and beta-blockers (+20.7 pp), indicating pronounced cardiovascular comorbidity and associated pharmacotherapy in the ILD population. Although the discrepancy identified is significant, the sample size is small and further investigation is needed to confirm the findings.

Table 8. Most frequently used 5 drug groups in ILD patients

Category	ILD+	Post-COVID ILD	ILD-	Difference (pp)
Beta-blocker	33.3%	15.0%	12.7%	+20.7
Antiplatelet agent	33.3%	10.0%	6.5%	+26.9
ARB	16.7%	12.5%	6.7%	+10.0
Diuretic	25.0%	12.5%	8.1%	+16.9
Anti-gout medication	8.3%	10.0%	3.1%	+5.2

11 cases show inconsistencies between available medication data and medical history data.

Types of inconsistencies:

- 1 case: "Does not take medication" marked, but 6 medications listed
- 10 cases: "Takes medication" marked, but no medications listed

Respiratory medication overview

Since ILD is a respiratory disease, it is important to highlight data on medications used to treat related symptoms. Of the 470 patients included in the study, 98 are taking some form of respiratory medication, the distribution of which is shown in Table 9.

Table 9. Distribution of respiratory medications taken by the 470 patients included in the study

Category	Number of patients	Proportion (%)	Occurrences
Inhaled corticosteroids	35	7.4%	37
Antimuscarinics (LAMA/SAMA)	14	3.0%	18
Short-acting beta-2 agonists (SABA)	13	2.8%	13
Antihistamines	11	2.3%	11
Antileukotriene agents	11	2.3%	11
Combination inhalers (ICS/LABA)	11	2.3%	11
Nasal sprays	2	0.4%	2
Long-acting beta-2 agonists (LABA)	1	0.2%	1

Medication data for different patient groups

Interstitial lung disease

- Patients with ILD diagnosis: 52 patients (11.1%)
- Taking respiratory medication: 7 patients (13.5% of ILD patients)

Post-COVID ILD

- Post-COVID ILD positive patients: 40 patients (8.5%)
- Taking respiratory medication: 4 patients (10.0% of Post-COVID ILD patients)

Respiratory Disease in Medical History

- Total respiratory diseases: 79 patients (16.8%)
- Of these taking medication: 48 patients (60.8%)

Non-ILD patients based on medical history data

- Asthma: 49 patients → 37 take medication (75.5%)
- COPD: 23 patients → 11 take medication (47.8%)
- Allergy: 20 patients → 12 take medication (60.0%)

Combination Therapy

45.2% of patients taking respiratory medications use multiple medications simultaneously.

5. Discussion

5.1. Status of therapeutic trials

A small number of studies are still active or recruiting, and their results are not yet available or final statistical analysis is not available: IV immunoglobulin/methylprednisolone, low-dose naltrexone, Zofin, sirolimus, and some platform studies are currently in this status. The data are constantly being updated, but no spectacular results that would widely change treatment protocols are known yet.

Completed and discontinued studies

Several studies—e.g., lithium, cannabidiol, Paxlovid, atorvastatin, remdesivir, montelukast, metoprolol, fluvoxamine, temelimab, pimozide, vortioxetine—have been closed or discontinued, and the published or available data show consistently negative or neutral results, with no statistically significant improvement in symptoms. Some studies are undergoing further follow-up or post-hoc analysis, but no significant effect has yet been observed.

The baseline landmark is the review by Sebők et al. (2023), which reported 21 ongoing drug clinical trials for Long COVID from clinicaltrials.gov (data cut-off: November 19, 2022), targeting diverse pathomechanisms such as viral persistence, immune dysregulation, neurological sequelae, fibrosis, and chronic inflammation.

To sum up, most originally ongoing trials are now completed or inactive; very few remain in recruitment or ongoing stages. No therapeutic breakthrough has emerged among the tested agents (including lithium, cannabidiol, Paxlovid, naltrexone, atorvastatin, montelukast, metoprolol, fluvoxamine, temelimab, pimozide, vortioxetine). Outcome pattern: most trials yielded negative or statistically insignificant results, despite some having favourable safety profiles. Partial or secondary benefits were reported (e.g., Paxlovid platform, Ampligen, NAD+ combinations), but these remain insufficient for guideline-level recommendations. A minority of drugs (IV immunoglobulin/methylprednisolone, low-dose naltrexone, sirolimus, Zofin, and some platform studies) are still active/recruiting, with results pending.

5.2. Summary of the results of off-label studies

The comparative analysis of Hungarian regulatory data and international clinical evidence reveals significant disparities in off-label therapeutic approaches for post-COVID conditions. The Hungarian NNGYK database documented only five off-label requests specifically targeting post-COVID syndrome over the entire study period (2020-2025), all involving pirfenidone for post-COVID pulmonary fibrosis. This remarkably narrow therapeutic scope contrasts sharply with the diverse range of off-label interventions reported in the international literature.

Regulatory practice vs. clinical evidence

The exclusive use of pirfenidone in Hungarian post-COVID off-label applications demonstrates a conservative, indication-specific approach focused solely on pulmonary fibrosis complications. However, international clinical evidence suggests broader therapeutic potential across multiple symptom domains. Low-dose naltrexone showed the most promising results in the Stanford retrospective cohort (N=59), demonstrating statistically significant improvements in fatigue, post-exertional malaise, and functional status—symptoms that extend far beyond the respiratory focus of Hungarian practice.

Evidence quality and therapeutic efficacy

The international off-label evidence base suffers from substantial methodological limitations that constrain clinical recommendations. Most studies employed small sample sizes (ranging from 4-90 participants), utilized observational designs rather than controlled trials, and provided only short-term follow-up data. Notably, the largest controlled study of pirfenidone (FIBRO-COVID trial, N=113) failed to demonstrate significant efficacy compared to placebo, questioning the empirical basis for its continued off-label use. Conversely, molnupiravir showed modest but statistically significant benefits in the large PANORAMIC trial (N=25,783), though with high numbers needed to treat (40-63), indicating limited clinical significance.

Therapeutic landscape and unmet needs

The dramatic temporal decline in Hungarian off-label requests (from 87.9% in 2020 to 0% in 2025) likely reflects evolving clinical practices, improved standard care protocols, and reduced acute COVID-19 severity rather than resolution of long COVID therapeutic

needs. The absence of requests for agents with demonstrated international efficacy—particularly low-dose naltrexone, antivirals beyond acute treatment, or immunomodulatory approaches—suggests either under-recognition of available therapeutic options or informal prescribing practices outside regulatory oversight.

Clinical and regulatory implications

The evidence-practice gap identified in this analysis has important implications for long COVID care optimization. While Hungarian regulatory compliance demonstrates appropriate caution in off-label prescribing, it may simultaneously limit access to potentially beneficial interventions supported by emerging clinical evidence. The concentration of off-label use on a single agent (pirfenidone) for a specific complication (pulmonary fibrosis) inadequately addresses the multisystem nature of post-COVID syndrome, where neurological, cardiovascular, and systemic symptoms predominate in many patients.

Future regulatory frameworks should consider evidence-based expansion of approved off-label indications while maintaining safety standards, particularly for agents with favourable risk-benefit profiles such as low-dose naltrexone and certain statins, which are currently undergoing rigorous clinical evaluation in dedicated long COVID trials.

5.3. Medication usage patterns in the study cohort

The medication usage among patients with respiratory and interstitial lung diseases was found to be remarkably low. Overall, only 13.2% of patients were receiving respiratory medication, which raises concern regarding the adequacy of treatment coverage in this population. Among the prescribed therapies, inhaled corticosteroids represented the dominant category, used by 35 patients (7.4%). This treatment choice is consistent with current therapeutic recommendations for managing airway inflammation in respiratory diseases.

A more detailed analysis of disease-specific patterns revealed important differences. Among asthmatic patients, 75.5% were receiving appropriate respiratory medication, indicating relatively good therapeutic coverage in this subgroup. In contrast, less than half of patients with chronic obstructive pulmonary disease (COPD) (47.8%) were prescribed medications targeting airway obstruction, suggesting undertreatment and potential

underutilization of evidence-based therapies. Patients diagnosed with post-COVID interstitial lung disease (ILD) received respiratory medications at even lower rates, with only 10.0% being treated for persistent respiratory symptoms. These findings highlight a notable gap in therapeutic management, particularly in COPD and post-COVID ILD cohorts.

Combination therapy was frequently observed, with nearly half of patients receiving multiple respiratory agents simultaneously. In total, 470 patients accounted for 1076 medications, including 238 different active ingredients and 562 unique preparations. When comparing ILD and non-ILD patients, the former exhibited significantly higher medication usage rates (73.1% vs. 57.4%), especially concerning cardiovascular therapies. The most frequently prescribed drug groups for ILD patients included beta-blockers (33.3%), antiplatelet agents (33.3%), angiotensin receptor blockers (16.7%), and diuretics (25.0%). Polypharmacy, defined as the concurrent use of more than five medications, was identified in 63 patients (13.4%). Of particular note, two lung transplant patients were each receiving as many as 16 preparations, reflecting the complexity of post-transplant pharmacological management.

6. Conclusions

The thesis provided comprehensive follow-ups directly comparing the status of November 2022 trials with their situation in September 2025. This temporal comparison reveals a clear shift from active investigations to trial completion/termination, offering insight into the overall trajectory of long COVID drug development.

The updated dataset demonstrates that despite unprecedented clinical trial activity between 2022–2025, long COVID remains without an efficacious pharmacological treatment. This provides strong evidence that the field is currently at a therapeutic impasse, highlighting urgent need for novel mechanistic approaches, biomarker-driven selection of patient subgroups, and more targeted intervention strategies.

The long COVID trial portfolio demonstrates exceptional methodological quality, with 38.6% employing quadruple-blind designs, but suffers from critical evidence availability gaps. The diversity of therapeutic targets appropriately reflects the multisystem nature of long COVID pathophysiology. Definitive therapeutic guidance awaits results from ongoing large-scale Phase III trials, expected within 12-24 months.

Despite the limited evidence for effectiveness from high-quality clinical trials, pirfenidone remained the sole off-label treatment for post-COVID syndrome formally used in Hungary, whereas internationally, attention has shifted to other agents with better theoretical or clinical support.

Correlation analysis demonstrated a strong positive association between patient age and the number of medications used ($r = 0.96$, $p < 0.001$) in the study cohort. However, no significant differences were observed between the overall medication usage characteristics of ILD and post-COVID ILD patients, despite the markedly lower proportion of respiratory treatments in the latter group. This lack of distinction may reflect heterogeneity in treatment practices or incomplete adaptation of clinical protocols for post-COVID care.

7. Summary

Introduction: Long COVID is a prevalent, multifaceted syndrome causing major therapeutic challenges and affecting millions worldwide. This dissertation critically examines both approved and off-label drug approaches, highlighting that—despite extensive research—effective pharmacological solutions remain elusive.

Objectives: This work (1) updated the Sebők et al, 2023 framework by assessing current scientific evidence on post-COVID pharmacological prevention and therapy; (2) evaluated Hungarian off-label prescribing trends for COVID-related indications against international practices; (3) characterized post-COVID medication usage, focusing on links with interstitial lung disease (ILD) development.

Methods: 2023 baseline data were revisited, adding new evidence from PubMed (2024–2025) and ClinicalTrials.gov. Nationwide NNGYK records of COVID-linked off-label drug requests (2020–05.2025) were analysed. Retrospective analysis compared 470 post-COVID outpatients (ILD-confirmed versus non-ILD) by descriptive statistics.

Results: Updated meta-analyses confirmed that vaccination moderately reduces long COVID risk (effectiveness 43–70% after ≥2 doses), with evident dose-response and mRNA vaccine superiority. Among ongoing therapeutic trials, few results have emerged; all completed studies consistently reported neutral or negative outcomes across targeted mechanisms. Hungarian off-label COVID requests dropped sharply from 87.9% (2020) to 0% (2025); only five post-COVID requests—each for pirfenidone in fibrosis—were submitted. Internationally, broader off-label use included naltrexone, antivirals, and immunomodulators. Compared to controls, ILD patients had higher medication use (73.1% vs 57.4%) and greater cardiovascular therapy reliance, also showing a strong age-medication correlation ($r = 0.96$, $p < 0.001$).

Clinical Implications: Despite significant research investment, no proven pharmacotherapy exists for long COVID. The gap between Hungarian regulatory policy and broader international practice may constrain patient access to potentially beneficial options. Future advancements require innovative therapeutics and biomarker-guided patient stratification to address the complex, multisystem nature of post-COVID syndrome.

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9. Bibliography of the candidate's publications

I. Original articles published on the topic of the dissertation:

1. Sebők, S., & Gyires, K. (2023). Long COVID and possible preventive options. INFLAMMOPHARMACOLOGY, 31(6), 2807–2817. http://doi.org/10.1007/s10787-023-01204-1 IF=4.6

2. Artner, A., Diler, I., Hankó, B., Sebők, S., & Zelkó, R. (2025). A Critical Appraisal of Off-Label Use and Repurposing of Statins for Non-Cardiovascular Indications: A Systematic Mini-Update and Regulatory Analysis. JOURNAL OF CLINICAL MEDICINE, 14(15). http://doi.org/10.3390/jcm14155436 IF=2.9

II. Other original articles – published not on the topic of the dissertation:

1. Fésü, D., Bárczi, E., Csoma, B., Polivka, L., Boga, M., Horváth, G., Varga J.T., Sebők Sz., Müller, V. (2025). Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients. BMC INFECTIOUS DISEASES, 25(1). http://doi.org/10.1186/s12879-024-10398-w IF=3.0

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Annex 1

Clinical trials of medicinal products 30 November 2022–8 September 2025 (source:clinicaltrials.gov)

NCT number	Study title	Study status	Study results	Interventions
NCT06234462	A Study of Amantadine for Cognitive Dysfunction in Patients with Long-Covid	Withdrawn	No	Amantadine, Physical, Occupational, Speech Therapy, Provider Counseling, Medications for symptoms management
NCT06928272	Long Covid (LC)-REVITALIZE - A Long Covid Repurposed Drug Study	Not yet Recruiting	No	Pirfenidone, Placebo for pirfenidone, Upadacitinib, Placebo for upadacitinib
NCT05350774	Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2	Enrolling by invitation	No	IV normal saline, IV immunoglobulin
NCT07128082	The Long COVID Treatment Trial	Not yet Recruiting	No	Tirzepatide, Placebo
NCT05669261	Treatment of Long COVID Symptoms Utilizing Autologous Stem Cells Following COVID-19 Infection	Unknown	No	Adipose Tissue Harvest, ATCell
NCT06766825	Study to Evaluate the Efficacy and Safety of Plitidepsin in Adults with Post-COVID-19 Condition (PCC)	Recruiting	No	Plitidepsin, Placebo,
NCT05874037	Fluvoxamine for Long COVID-19	Active not recruiting	No	Fluvoxamine
NCT05513560	RECLAIM: Recovering From COVID-19 Lingering Symptoms Adaptive Integrative Medicine	Suspended	No	Ibudilast, Pentoxifylline, Placebo
NCT06147050	Effect of Metformin in Reducing Fatigue in Long COVID in Adolescents	Not yet Recruiting	No	Metformin, Placebo
NCT06974084	Investigating Measurable PRO Acuity Trial (IMPACT) is a Multi-Center Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Maraviroc and Atorvastatin to Improve Neurocognitive and Physical Function of Subjects With Long COVID-19/Post-Acute Sequelae of COVID-19 (PASC).	Not yet Recruiting	No	Maraviroc (MVC), Atorvastatin, Placebo, Maraviroc, Placebo, Atorvastatin
NCT05747534	AT1001 for the Treatment of Long COVID	Recruiting	No	Larazotide Acetate, Placebo
NCT06492798	Effectiveness and Safety of Mesenchymal Stem Cell Therapy in Long COVID Patients	Recruiting	No	Umbilical cord mesenchymal stem cell
NCT06511063	Antiviral Clinical Trial for Long Covid-19	Recruiting	No	Tenofovir disoproxil/emtricitabine, Selzentry, Placebo
NCT07123727	A Study to Examine Anktiva for the Treatment of COVID-19.	Recruiting	No	Anktiva (nogapendekin alfa inbakicept)

NCT number	Study title	Study status	Study results	Interventions
NCT06847191	NE3107 in Adults with Neurological Symptoms of Long COVID	Recruiting	No	NE3107 (Bezisterim), Placebo
NCT06597682	Evaluating Immunomodulatory Interventions in Post-Acute Sequelae of SARS-CoV-2 InfEction	Not yet Recruiting	No	Prednisone, Budesonide/Formoterol, Vitamin C combined with Coenzyme Q10 oral treatment, Montelukast tablets oral treatment
NCT06437223	Study of Xiflam™ Treatment in Patients Post COVID-19 Infection Suffering From What is Known as Long COVID (LC)	Recruiting	No	Tonabersat, Placebo
NCT05877508	Anti-SARS-CoV-2 Monoclonal Antibodies for Long COVID (COVID-19)	Active not recruiting	No	AER002 (monoclonal antibody), Placebo
NCT05999435	Study of LAU-7b for the Treatment of Long COVID in Adults	Completed	No	LAU-7b (fenretinide) for 3 cycles, LAU-7b for 1 cycle, then placebo, Placebo for 3 cycles
NCT05668091	A Decentralized, Randomized Phase 2 Efficacy and Safety Study of Nirmatrelvir/Ritonavir in Adults with Long COVID.	Completed	No	Nirmatrelvir, Ritonavir, Placebo
NCT07108036	A Study to Assess Anktiva in Patients With Long Covid-19.	Not yet Recruiting	No	N-803 (nogapendekin alfa inbakicept, IL-15 Superagonist)
NCT06821087	Evaluating the Neuromodulatory Effect of Ketamine in Long COVID-19	Enrolling by invitation	No	Ketamine only
NCT05911009	To Investigate Efficacy, Pharmacodynamics, and Safety of BC 007 in Participants With Long COVID	Completed	No	BC 007 (rovunaptabin) or matching placebo
NCT05764538	DAOIB for the Treatment of Brain Fog	Recruiting	No	DAOIB (Diamine Oxidase Inhibitor B)
NCT05595369	RECOVER-VITAL: Platform Protocol to Measure the Effects of Antiviral Therapies on Long COVID Symptoms	Completed	No	Experimental: Paxlovid 25 day dosing, Experimental: Paxlovid 15 day dosing, Placebo Comparator: Control
NCT06161688	Ensitrelvir for Viral Persistence and Inflammation in People Experiencing Long COVID	Active not recruiting	No	Ensitrelvir, Placebo
NCT06404099	RECOVER-SLEEP: Platform Protocol, Appendix_A (Hypersomnia)	Recruiting	No	Modafinil, Modafinil Placebo, Solriamfetol, Solriamfetol Placebo
NCT05965726	RECOVER-VITAL: Platform Protocol, Appendix to Measure the Effects of Paxlovid on Long COVID Symptoms	Completed	No	Paxlovid 25 day dosing, Paxlovid 15 day dosing, Control
NCT07021794	SARS-CoV-2 Specific Monoclonal Antibody for Post-COVID-19 Conditions (Long COVID)	Recruiting	No	Sipavibart, Placebo
NCT05926505	Safety and Efficacy of Anakinra Treatment for Patients With Post Acute Covid Syndrome	Recruiting	No	Anakinra Prefilled Syringe [Kineret], Placebo,

NCT number	Study title	Study status	Study results	Interventions
NCT06907251	Dapagliflozin for Long COVID Syndrome	Not yet Recruiting	No	Dapagliflozin (DAPA), Placebo
NCT06055244	Amantadine Therapy for Cognitive Impairment in Long COVID	Recruiting	No	Amantadine
NCT06257420	Low Dose Rapamycin in ME/CFS, Long-COVID, and Other Infection Associated Chronic Conditions	Enrolling by invitation	No	Rapamycin
NCT05823896	ImPROving Quality of LIFe in the Long COVID Patient	Completed	No	Nirmatrelvir/ritonavir, Placebo/ritonavir
NCT06404086	RECOVER-SLEEP: Platform Protocol	Recruiting	No	Modafinil, Modafinil Placebo, Solriamfetol, Solriamfetol Placebo, Melatonin, Melantonin Placebo|DEVICE: Tailored lighting (TL) Active|DEVICE: Tailored lighting (TL) Placebo
NCT05890534	Pycnogenol® in Post-COVID-19 Condition	Active not recruiting	No	Pycnogenol®, Placebo
NCT06631287	Randomized Double-Blind Placebo-Controlled Trial EValuating Baricitinib on PERSistent NEurologic and Cardiopulmonary Symptoms of Long COVID	Recruiting	No	Baricitinib, Placebo
NCT05592418	Study to Evaluate the Efficacy and Safety of Ampligen in Patients With Post-COVID Conditions	Completed	Yes	Rintatolimod, Placebo / Normal Saline
NCT06404112	RECOVER-SLEEP: Platform Protocol, Appendix_B (CPSD)	Recruiting	No	Melatonin, Melantonin Placebo| Tailored lighting (TL) Active| Tailored lighting (TL) Placebo
NCT05597800	Nivolumab/Ipilimumab and Chemotherapy Combination in Advanced NSCLC Patients With HIV, HBV, HCV and Long Covid Syndrome	Not yet Recruiting	No	Nivolumab and Ipilimumab
NCT06305806	RECOVER-AUTONOMIC: Platform Protocol, Appendix B (Ivabradine)	Active not recruiting	No	Ivabradine, Ivabradine Placebo|BEHAVIORAL: Coordinated Care|BEHAVIORAL: Usual Care
NCT06305780	RECOVER-AUTONOMIC Platform Protocol	Completed	No	IVIG + Coordinated Care, IVIG Placebo + Coordinated Care, Ivabradine + Coordinated Care, Ivabradine Placebo + Coordinated Care, IVIG + Usual Care, IVIG Placebo + Usual Care, Ivabradine + Usual Care, Ivabradine Placebo + Usual Care
NCT06590324	A Study of Apabetalone in Subjects With Long -COVID	Recruiting	No	Apabetalone
NCT05858515	REVERSE-Long COVID-19 With Baricitinib Study	Withdrawn	No	Baricitinib 4 MG, Placebo
NCT05690503	Glutamatergic Modulation as a Treatment for Depressive Symptoms Among Patients With	Active not recruiting	No	CI-581a, CI-581b (investigational drug (no INN)

NCT number	Study title	Study status	Study results	Interventions
	Post-acute Sequelae of COVID (PASC): A Pilot Trial			
NCT06171152	Study of Liraglutide (A Weight Loss Drug) in High Risk Obese Participants With Cognitive and Memory Issues	Recruiting	No	Liraglutide Pen Injector [Saxenda], Medication Diary
NCT06305793	RECOVER-AUTONOMIC: Platform Protocol, Appendix A (IVIG)	Active not recruiting	No	IVIG (intravenous immunoglobulin), IVIG Placebo|BEHAVIORAL: Coordinated Care|BEHAVIORAL: Usual Care
NCT05795816	Effectiveness of Testofen Compared to Placebo on Long COVID Symptoms	Completed	No	Testofen, Microcrystalline cellulose
NCT06792214	Antiviral Strategies in the Prevention of Long-term Cardiovascular Outcomes Following COVID-19: The paxloviD/Remdesivir Effectiveness For the prEvention of loNg coviD Clinical Trial	Recruiting	No	Nirmatrelvir/ritonavir, Remdesivir
NCT05911906	An Open-label, Clinical Feasibility Study of the Efficacy of Remdesivir for Long-COVID.	Active not recruiting	No	Remdesivir
NCT06159283	Intravenous Immunoglobulin Replacement Therapy for Persistent COVID-19 in Patients With B-cell Impairment	Recruiting	No	Immunoglobulins
NCT05986422	Methylprednisolone in Patients with Cognitive Deficits in Post-COVID-19 Syndrome (PCS)	Recruiting	No	Methylprednisolone
NCT06316843	Valacyclovir Plus Celecoxib for Post-Acute Sequelae of SARS-CoV-2	Completed	No	Valacyclovir celecoxib dose 1, Valacyclovir celecoxib dose 2, Placebo
NCT05682560	Human Umbilical Cord Blood (RegeneCyte) Infusion in Patients with Post-COVID Syndrome	Completed	No	REGENECYTE, Placebo
NCT05481177	Ivabradine for Long-Term Effects of COVID-19 With POTS Cohort	Recruiting	No	Ivabradine
NCT06597396	Study to Investigate the Efficacy of Abrocitinib in Adult Participants with Severe Fatigue from Post COVID Condition/Long COVID	Recruiting	No	Abrocitinib, Placebo
NCT05697640	Study to Investigate Improvement in Physical Function in SF-36 With Vericiguat Compared With Placebo in Participants With Post-COVID-19 Syndrome	Recruiting	No	Vericiguat Oral Tablet
NCT06960928	Low Dose Sirolimus in People With Post-Acute Sequelae of COVID-19 (PASC) Long COVID-19	Recruiting	No	Low-dose sirolimus, Placebo
NCT05430152	Low-dose Naltrexone for Post-COVID Fatigue Syndrome	Recruiting	No	Low-Dose Naltrexone,Placebo

NCT number	Study title	Study status	Study results	Interventions
NCT05947617	Safety, Efficacy, and Dosing of VIX001 in Patients With Neurological Symptoms of Post Acute COVID-19 Syndrome (PACS).	Unknown	No	VIX001 (amniotic fluid product)
NCT06128967	A Multicenter, Adaptive, Randomized, doublE-blinded, Placebo-controlled Study in Participants With Long COVID-19: The REVIVE Trial	Recruiting	No	Fluvoxamine Maleate, Placebo, Metformin Extended Release Oral Tablet
NCT05943821	The Effect of Allopurinol on the Risk of Cardiovascular Events in Patients with Cardiovascular Risk	Recruiting	No	Allopurinol, Optional intervention
NCT05876377	Use and Effectiveness of COVID-19 Vaccines Using State Vaccine Registries and Insurance Claims Data	Active not recruiting	No	Pfizer-BioNTech COVID-19 mRNA vaccine
NCT05946551	Treatment of Long CoronaVirus Disease (COVID) (TLC) Feasibility Trial	Terminated	Yes	Cetirizine, Famotidine, Cetirizine Placebo, Famotidine Placebo
NCT07090486	A Study to Understand How the Use of Paxlovid Affected Healthcare Use in People With Pre-existing Conditions.	Completed	No	Nirmatrelvir-ritonavir
NCT06204432	Sodium Citrate in Smell Retraining for People With Post-COVID-19 Olfactory Dysfunction	Active not recruiting	No	Sodium Citrate, Normal Saline, Olfactory Training Kit - "The Olfactory Kit, by AdvancedRx"
NCT05667077	The Effect of Amantadine on Post-COVD-19 Fatigue	Unknown	No	Amantadine
NCT05642923	Post-COVID-19 Chronic Fatigue Syndrome	Completed	No	Synthetic Vitamin B1
NCT05371288	The Role of Glutathione Deficiency and MSIDS Variables in Long COVID-19	Withdrawn	No	NAC (N-acetyl cysteine), Alpha lipoic acid (ALA), liposomal glutathione (GSH)
NCT05967052	Investigation of Treating Chronic Fatigue Syndrome After COVID With Pharmacotherapy (Pregabalin) or Complex Rehabilitation	Recruiting	No	Pregabalin|Independent walking training, Placebo|Gradual movement therapy in the ward| Telerehabilitation|Psychotherapy