CLINICAL STUDY PROTOCOL

An Interventional, Double-Blinded, 2-Arm Study to Investigate the Efficacy of Orally Administered Nirmatrelvir/Ritonavir Compared With Placebo/Ritonavir in Non-hospitalized Adult Participants suffering from post-COVID

PROLIFIC

imPROving quality of LIFe In the long COVID patient

Study code:	KI-PROLIFIC-2023
EudraCT number:	2022-003855-32
Version number:	Version 2.0
Date:	10 March 2023
Sponsor:	Karolinska Institutet Nobels väg 5, SE171 77 Stockholm, Sweden
Principal Investigator:	Michael Runold, M.D., Ph.D.
Co-ordinating Investigator:	Judith Bruchfeld, M.D., Ph.D.

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Signature page

Sponsor

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this study. I will submit the protocol and all other important study-related information to the responsible investigator(s) so that they can conduct the study correctly. I am aware that it is my responsibility to hold the staff members who work with this study informed and trained.

Sponsor's signature Date

Petter Brodin

Printed name

Principal and Coordinating Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature Date

Michael Runold

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List of used acronyms and abbreviations

Abbreviation	Term/Explanation
AE	Adverse event = any untoward medical occurrence
CAT	Chronic obstructive disease assessment test
CIOMS	Council for international organizations of medical sciences
CRF	Case report form
CRP	C-reactive protein
CT	Computer tomography
DSUR	Development safety update report = annual safety report
eGFR	Estimated glomerular filtration rate
EMR	Electronic medical record
EQ5D	A standardized measure of health-related quality of life
EPM	Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)
ESR	Erythrocyte sedimentation rate
ET	Early termination
FSS	Fatigue severity scale
GCP	Good clinical practice
HDPE	High-density polyethylene
HRCT	High resonance computerized tomography
ICD	Informed consent document
ICH	International council for harmonization
IRC	Interim review committee
KI	Karolinska Institutet
KS	Karolinska university hospital
LVFS	Läkemedelsverkets författningssamling (English: Swedish Medical Products Agency's statutes)

MAPS	Malmo POTS score
mMRC	Modified Medical Research Council
MFS	Mental fatigue scale
MIP	Maximal inspiratory pressure
MoCa	Montreal cognitive assessment
MVD	Microvascular dysfunction
MWT	Minute walk test
SAE	Serious adverse event = serious untoward medical occurrence
SAP	Statistical analysis plan
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SPC or SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
PACS	Post-acute COVID-19 syndrome
PEM	Post exertional malaise
POTS	Postural orthostatic tachycardia syndrome
WHO	World health organization
WOCBP	Woman of childbearing potential

1. Synopsis

EudraCT number: 2022-003855-32		
Title: An Interventional, double-Blinded, 2-Arm Study to Investigate the Efficacy of Orally Administered Nirmatrelvir/Ritonavir Compared With Placebo/Ritonavir in Non-hospitalized Adult Participants suffering from post-COVID		
Brief title: **PROLIFIC** - imPROving quality of LIFe In the long COVID patient		
Study code:	KI-PROLIFIC-2023	
Short background/ Rationale/Aim:	There is still a significant unmet need for patients with Post-Acute COVID syndrome. This study, a 15-day twice daily dosing of Nirmatrelvir/Ritonavir (300/100 mg) or Placebo/Ritonavir (100mg) will evaluate the potential ability to provide sustained improvement in quality of life, by using EQ-5D-5L questionnaire, in patients suffering from post-COVID.	
Study objectives and endpoints:	**Objectives**	**Endpoints**
	Primary	**Primary**
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir at Day 16 on quality of life	Change from baseline on the EQ-5D-5L VAS scale at day 16
	Secondary	**Secondary**
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir in patients with post-COVID-19 symptoms over time on quality of life	Change from baseline on the EQ-5D-5L VAS scale at day 45 and on Day 90
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on hemodynamic response (**only patients diagnosed with POTS)**	Change from baseline over time as measured in delta maximum heart rate during active standing test
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on fever **MAPS (only patients diagnosed with POTS)**	Change from baseline over time in POTS-specific symptoms as measured by MAPS

	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on reactive hyperemia index	Change from baseline endothelial function measured by the EndoPat® device on Day 45
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir in 24-h average heart rate	Change from baseline over time in heart rate by ECG monitoring device
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir fever	Change from baseline over time in body temperature
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on physical capacity	Change from baseline over time as measured by 6-minute walk test
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on handgrip strength	Change from baseline over time as measured by JAMAR
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on physical activity	Change from baseline over time as measured by accelerometer
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on post exertional malaise	Change from baseline at Day 90 in total score as measured by Post-Exertional Malaise short form
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on fatigue	Change from baseline over time as measured by fatigue severity scale (FSS) and mental fatigue scale (MFS)
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on cognitive dysfunction	Change from baseline over time as measured by MoCA test
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on dyspnea	Change from baseline over time in respiratory symptoms measured by CAT and mMRC
	To evaluate the effect of oral administration of	Change from baseline over time in Njimegen questionnaire.

	nirmatrelvir/ritonavir on dysfunctional breathing patterns, maximum inspiratory pressure, and lung function	Change from baseline over time in maximal inspiratory pressure (MIP) Change from baseline over time in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on plasma biomarkers	Change from baseline over time in the following plasma biomarkers: D-dimer, CRP, ESR, ferritin, NTproBNP, LD
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on dysautonomia symptoms	Change from baseline over time as measured by Compass31
	Tertiary/Exploratory	**Tertiary/Exploratory**
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on **l**ong-term measurement of breathing pattern	Change from baseline over time in Dynamic spirometry
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on **p**ersistence of SARS-CoV-2 virus	Description at baseline and Day 16 of • Protein profiling using Olink Explore Inflammation panel • Nucleosome-profiling (using Volition) and circulating spike (using SIMOA™, Quanterix) • PBMC profiling for scTCR-sequencing (using BD Rhapsody) with assessment of Super-Ag mediated T-cell activation • Assessment of immune system signatures associated with disease states using mRNA-sequencing of stabilized whole blood (PaxGene).
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on changes in immune cell function	Immune cell assessment by high-dimensional cytometry
	To evaluate the effect of oral administration of nirmatrelvir/ritonavir on the relationship between genotypes and immune function at the molecular level	Circulating protein levels adjusted for DNA-variants

Study design:	Double-blinded randomized controlled trial
Study population:	Patients with post-COVID according to WHO definition
Number of subjects:	400
Main inclusion criteria:	Patients, ≥18 years of age, diagnosed with post-acute COVID-19 syndrome, with reported EQ-5D-5L VAS<50
Main exclusion criteria:	Acute COVID-19 infection, other non-related conditions with post-acute COVID-19 syndrome like symptoms, previous treatment with Paxlovid
Investigational product(s), dosage, administration:	Oral Nirmatrelvir/Ritonavir (Paxlovid®) 300/100 mg twice daily for 15 days Oral Placebo/Ritonavir 100 mg twice daily for 15 days. Randomization 2:1
Study period:	April 2023 – April 2024

2. Background and rationale

More than 3 years into the COVID-19 pandemic, there are still significant knowledge gaps within the umbrella definition of Post-Acute COVID-19 syndrome (PACS). Patients with PACS experience a wide variety of symptoms related to physical and cognitive function, including fatigue, dyspnea, “brain fog” or other cognitive symptoms, pain, depression, and gastrointestinal issues which significantly impact quality of life. While conclusive findings based on X-ray and blood sampling may be lacking, measurable deviations such as increased heart rate at rest, oxygen saturation upon physical activity, long-term low-grade temperature are often seen in the PACS patient.

At present there is no curative treatment for PACS at hand. Treatment is focused on symptom management and individualized rehabilitation.

We are proposing an interventional, randomized and placebo-controlled clinical intervention trial of Nirmatrelvir/Ritonavir compared with Placebo/Ritonavir in patients with post-COVID (as defined by WHO) from a database of n=988 post-COVID patients seen at the KI/KS post-COVID clinics since May 2020, and in which extensive clinical and biochemical examinations have been performed. The study will further include deep exploratory investigations of the immune phenotypes in post-COVID patients, including changes upon Nirmatrelvir/Ritonavir (Paxlovid®) treatment at the molecular and cellular level.

2.1. Post-acute COVID-19 syndrome (PACS) and Postural orthostatic tachycardia syndrome (POTS)

Hospitalized patients with severe COVID-19 generally show rapid improvement of the widespread radiological abnormalities seen during the acute phase of COVID-19 pneumonia. However, at six-month follow-up in patients hospitalized för COVID-19 “fibrotic-like” changes have been reported on chest CT. Caruso et al [1] found that 72% of the study participants had signs of “fibrotic-like” changes, whereas only 35% was seen in the study by Han et al [2]. Within the UPPCOV and RECOV research projects [3] of patients with long COVID, many hospitalized patients exhibit residual fibrotic changes as well as bronchiectasis (manuscript in preparation). Restrictive lung function impairment and reduced diffusion capacity is relatively common with prolonged oxygen dependency over time in the most advanced cases. A common finding in the hospitalized patient cohort, and to a lesser extent also in the non-hospitalized cohort, is an uneven parenchymal attenuation in expiratory images with high-resolution computer tomography (HRCT).
Non-hospitalized patients with severe PACS often exhibit dysfunctional breathing patterns with or without hyperventilation triggered by mild/moderate mental and/or physical effort. The level of activity necessary to provoke this abnormal breathing is generally very modest. Moreover, the degree of symptoms varies over time without any obvious triggers. Studies regarding correlation with respiratory symptoms and physiological function as well the pathophysiological mechanism are ongoing as well as rehabilitative interventions.
Another frequent objective disease manifestation is post-COVID POTS, which has within our UPPCOV and RECOV research projects mainly been seen in non-hospitalized patients (currently ~200 patients, or 25-30%) (unpublished observation). Unlike classical POTS patients, post-COVID POTS patients often have dyspnea with desaturation upon walking and pulmonary changes (mosaic pattern) in expiratory HRCT imaging suggestive of an overlap among multiple phenotypes. Also, other cardiovascular manifestations e.g., microvascular dysfunction and inappropriate sinus tachycardia, have been diagnosed predominantly in the non-hospitalized cohort.
Fatigue, post-exertional malaise, brain fog, cognitive impairment and breathlessness are common symptoms across all phenotypes and are also commonly reported symptoms reported in other studies [4].

2.2. Post-COVID cohort at the Karolinska University Hospital

The multidisciplinary and multi-professional post-COVID clinic at Karolinska University Hospital assessed its first patient May 11, 2020. To date, more than 1500 patients have been systematically assessed and followed, of which 2/3 have been previously hospitalized with severe COVID-19 and 1/3 were never hospitalized and referred from primary care. Study inclusion is ongoing with 988 patients enrolled as of now (2022-11-18) in the integrated research projects UPPCOV and/or RECOV of which around half were hospitalized. Our cohorts are unique due to a broad and in-depth clinical investigation over time according to our initial hypothesis that long term effects of COVID-19 could possibly be multi-systemic and impact daily function and health related quality of life.
To improve clinical management of the PACS patient, Karolinska University Hospital established in 2020 two post-COVID clinics with specialists in infection, respiratory medicine, cardiology, neurology, renal medicine, psychiatry, psychologists, and physiotherapists, and

developed a tailored battery of clinical examinations for in-depth diagnoses. Patients are followed over time and integrated in the research projects UPPCOV and/or RECOV, which have now included n=988 patients.
Investigating long-term PACS effects and increasing the understanding of the various phenotypes and underlying mechanisms will generate effective ways to inform on novel treatment strategies, develop better protocols for clinical follow-up and design interventions for prevention. Studies and case reports have indicated that viral persistence contributes to PACS and POTS, suggesting that SARS-CoV-2 anti-viral treatment may have beneficial effects in this group of patients [5, 6].

2.3. Previous clinical experience with Paxlovid®

Nirmatrelvir (PF-07321332) is an orally bioavailable Mpro inhibitor of the SARS-CoV-2 Mpro main protease, which is an enzyme that is critical for viral replication and transcription. Nirmatrelvir demonstrated cell culture antiviral activity in a wide range of in-vitro cell cultures but has more importantly demonstrated significant clinical efficacy in the EPIC-HR randomized controlled trial, which enrolled 2,246 adults with laboratory-confirmed diagnosis of mild to moderate SARS-CoV-2 infection within a five-day period and were required to have at least one characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 [7].

Nirmatrelvir will be co-administered with ritonavir, which is a strong CYP3A4 inhibitor, and is being co-administered with nirmatrelvir to achieve exposures sufficient to suppress viral replication through the entire dosing interval. Ritonavir is not expected to have any antiviral activity against the SARS-CoV-2 virus. However, the present protocol also describes the procedures for managing drugs that may interact with Ritonavir through CYP3A4 or through other cytochrome P450 enzymes, such as CYP2D6, which are described in section 6.3, 7.9 and with references to safety information in Section 9.

The safety and tolerability of nirmatrelvir has been evaluated in over 5,000 participants with acute COVID-19 with risk factors for severe COVID-19 in the EPIC-HR, in a post-exposure prophylaxis study -the 1006 EPIC-PEP trial (NCT05047601), as well as in 1,153 participants with a standard risk profile in the EPIC-SR trial, which was stopped early for futility (NCT05011513). The collective evidence from the trials supports the safety and tolerability profile of a treatment regimen of nirmatrelvir / ritonavir 300/100 mg twice daily for 5 days. Adverse (mostly mild) and serious adverse events were similar in the Paxlovid® and placebo arms of the trials.

The PROLIFIC study will recruit adult patients who were never hospitalized for acute COVID-19, in which the burden of comorbidities and prevalence of chronic medication is lower than in the group of patients suffering from long COVID who were hospitalized in the acute stage. The baseline profile of the subjects should therefore not be dissimilar to EPIC-HR, which justifies keeping the dose at 300/100 mg twice daily as in the acute COVID setting.

The pharmacokinetic profile of nirmatrelvir has been investigated in patients with normal and impaired renal function [8]. In patients with normal renal function or mild impairment, a single dose of 100 mg of nirmatrelvir / ritonavir peaked within 1 hour of administration and was

nearly completely absent in plasma at 24 hours after administration. This suggests that accumulative effects of nirmatrelvir / ritonavir are unlikely. The overall T1/2 was similar in patients with normal and mild renal impairment at ~7 hours. Analysis of urinary excretion data suggests incomplete oral absorption of nirmatrelvir.
Given the differences between acute- and long COVID-19, a prolonged 15 Day treatment period can be motivated by the beneficial observed safety profile of the nirmatrelvir / ritonavir 300/100 mg twice daily dose up to 10 days in safety data [7, 9], and the theoretical need for tissue dissemination of nirmatrelvir / ritonavir to treat potential viral reservoirs.

Hypothesis: Paxlovid® improves health-related quality of life measured with EQ-5D-5L VAS scale vs. placebo/ritonavir in objective and pre-defined clinical phenotypes: POTS, Microvascular dysfunction, inappropriate sinus tachycardia, persistent fever, PEM, fatigue, brain fog, dyspnea, dysfunctional breathing patterns or inflammatory phenotypes (increased D-dimer, CRP, ESR, ferritin)

The purpose of this study is to evaluate the efficacy of nirmatrelvir/ritonavir for the treatment of non-hospitalized patients with post-COVID 19 - a patient group with high unmet medical need. The PROLIFIC study will include non-hospitalized patients only since a) accepted therapies in that group of patients are lacking, b) there are fewer comorbidities, c) there have been indications of persistently ongoing pathology in that patient group, and in some cases viral persistence [5, 6].

3. Benefit-risk evaluation

Specific for this study, there is at present no curative treatment for post-COVID which for the intended study population is a severe condition which affects day to day life with a profound impact on functional capacity and health-related quality of life. It is at present not entirely clear what this condition will contribute to regarding long term organ dysfunction, but several studies indicate long term effects such as the development of diabetes and kidney dysfunction. Any treatment with a curative capacity would be greatly beneficial and outweigh the possible risks.

To summarize nirmatrelvir/ritonavir in the acute COVID patient, the appraisal of the benefit-risk for nirmatrelvir/ritonavir is considered positive for treatment of symptomatic mild-to-moderate COVID-19 in non-hospitalized adult and pediatric patients who are either vaccinated or unvaccinated and at high risk for progression to severe illness, including hospitalization and/or death. An NDA seeking approval for nirmatrelvir/ritonavir 300/100 mg twice daily (q12h) administered orally for 5 days for the treatment in adults and pediatric patients (12 years of age and older weighing at least 40 kg) diagnosed with mild-to-moderate COVID, and who are at high risk for progression to severe COVID-19, including hospitalization or death was submitted in June 2022. The EPIC-PEP trial showed good safety and tolerability measures in up to 10 days of dosing (NCT05047601). The observed benefit-risk profile for nirmatrelvir/ritonavir is also considered favorable for continued study in additional sub-populations of patients who may benefit from treatment with an oral antiviral agent directed against SARS-CoV-2.

Ritonavir in the comparative arm is chosen, as ritonavir may cause adverse effects such as nausea and may thus make it unblind to both study participant and study team. Possible interactions will be considered on an individual level for each patient .

Active standing test: An active standing test will be performed at the baseline visit and on Day 45 and 90 of follow-up. Heart rate (ECG) and blood pressure (Arm-cuff) will be measured after 10 minutes bed rest and for ten minutes standing as well as 5 minutes bed rest after return to supine position. ECG and blood pressure measurements are non-invasive and do not imply any risk for the study subjects. The orthostatic challenge itself is not associated with any foreseeable risk for bodily harm but may be uncomfortable and may produce new or worsening symptoms including lightheadedness, dyspnea, chest pain, syncope, headache, blurred vision, and palpitations. To mitigate the risk for serious symptoms the test will be performed by staff trained in active standing tests and study subjects may abort the test and return to supine position if he or she chooses to.

Endothelial function test: Endothelial function will be measured at baseline and day 45 during follow-up using an EndoPAT® device (Itamar medical). The procedure is non-invasive and takes approximately 20 minutes. After a stabilization period an arm cuff will be inflated to supra systolic pressure for five minutes, The cuff is then deflated, and endothelial function is measured as reactive hyperemia index in the index finger. The procedure is not associated with any foreseeable risk for bodily harm. However, it may be uncomfortable and in rare cases even painful. The procedure will be performed by staff trained in the procedure and the study-subject can opt to abort the measurement at any time.

Physical function tests: 6-minute walk test, maximal inspiratory pressure, hand grip strength, accelerometer (Active PAL) will be performed at baseline, and at Days 16, 45 and 90. The tests are non-invasive and constitute a minimal or no risk of injury and take approximately 30 minutes to perform. The physical tests that will be used are also used in the regular clinical follow-up of long COVID and for other conditions. Participants may experience fatigue during the test session, but the test procedure will be adapted to reduce this risk. The benefits of performing the measurements will outweigh the inconvenience for patients.

Patient reported outcomes: A battery of questionnaires, PRO’s, will be distributed to the participants at each visit. As these can be exhausting to fill in, the possibility to bring them home for finalization will be offered, as well as the option to fill in prior to next visit.

Nasal swabs and venipuncture: Nasal swabs for antigen tests, performed at screening and baseline visits, and venipuncture for routine blood sampling as well as research blood samples will be performed at baseline, day 16, 45 and 90. They are standard procedures in routine health care and constitute no risk to the patient but may cause minor pain and discomfort.

In summary, the potential benefits of nirmatrelvir/ritonavir treatment are considered to outweigh the foreseeable risks.

4. Study objectives

4.1. Primary objective

The primary objective of this study is to evaluate the efficacy of twice daily oral administration of nirmatrelvir/ritonavir compared with that of placebo/ritonavir in patients with post-COVID-19 symptoms.

4.2. Description of Objectives, Endpoints and Estimands

The primary, secondary and tertiary/exploratory objectives and endpoints assessed (as described in the schedule of activity) to assess the effect of oral Administration of nirmatrelvir/ritonavir in patients with post-COVID-19 symptoms are summarized in the table below.

Objectives	Endpoints	Estimand
Primary	**Primary**	**Primary**
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir at Day 16 on quality of life	• Change from baseline on the EQ-5D-5L VAS scale at day 16	Estimand 1: This estimand is intended to provide a population-level estimate of the mean treatment effect (nirmatrelvir/ritonavir relative to placebo) on a continuous endpoint over time for all randomized/evaluable participants. • The difference of Day 16 on EQ-5D-5L VAS scale between the nirmatrelvir/ritonavir and placebo arms in participants with long COVID estimated with a longitudinal analysis that controls for baseline assessment
Secondary	**Secondary**	**Secondary**
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir in patients with post-COVID-19 symptoms over time on quality of life	• Change from baseline on the EQ-5D-5L VAS scale at day 45 and on Day 90	• Estimand 1 (see above)

• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on hemodynamic response (**only patients diagnosed with POTS)**	• Change from baseline over time as measured in delta maximum heart rate during active standing test	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on fever **MAPS (only patients diagnosed with POTS)**	• Change from baseline over time in POTS-specific symptoms as measured by MAPS	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on reactive hyperemia index	• Change from baseline endothelial function measured by the EndoPat® device on Day 45	• Estimand 2: This estimand is intended to provide a population-level estimate of the mean treatment effect (nirmatrelvir/ritonavir relative to placebo/ritonavir) on a continuous endpoint at a given time point for all randomized/evaluable participants. The difference of Day 45 on endothelial function test between the nirmatrelvir/ritonavir and placebo/ritonavir arms in participants with long COVID estimated with an ANCOVA model that controls for baseline assessment
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir in 24-h average heart rate	• Change from baseline over time in heart rate by ECG monitoring device	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir fever	• Change from baseline over time in body temperature	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on physical capacity	• Change from baseline over time as measured by 6-minute walk test	• Estimand 1 (see above)

• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on handgrip strength	• Change from baseline over time as measured by JAMAR	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on physical activity	• Change from baseline over time as measured by accelerometer	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on post exertional malaise	• Change from baseline at Day 90 in total score as measured by Post-Exertional Malaise short form	• Estimand 2 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on fatigue	• Change from baseline over time as measured by fatigue severity scale (FSS) and mental fatigue scale (MFS)	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on cognitive dysfunction	• Change from baseline over time as measured by MoCA test	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on dyspnea	• Change from baseline over time in respiratory symptoms measured by CAT and mMRC	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on dysfunctional breathing patterns, maximum inspiratory pressure, and lung function	• Change from baseline over time in Njimegen questionnaire. • Change from baseline over time in maximal inspiratory pressure (MIP) • Change from baseline over time in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)	• Estimand 1 (see above) • Estimand 1 (see above) • Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on plasma biomarkers	• Change from baseline over time in the following plasma biomarkers: D-dimer, CRP, ESR, ferritin, NTproBNP, LD	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on dysautonomia symptoms	• Change from baseline over time as measured by Compass31	• Estimand 1 (see above)

Tertiary/Exploratory	**Tertiary/Exploratory**	**Tertiary/Exploratory**
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on **l**ong-term measurement of breathing pattern	• Change from baseline over time in Dynamic spirometry	• Estimand 1 (see above)
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on **p**ersistence of SARS-CoV-2 virus	Description at baseline and Day 16 of • Protein profiling using Olink Explore Inflammation panel • Nucleosome-profiling (using Volition) and circulating spike (using SIMOA™, Quanterix) • PBMC profiling for scTCR-sequencing (using BD Rhapsody) with assessment of Super-Ag mediated T-cell activation • Assessment of immune system signatures associated with disease states using mRNA-sequencing of stabilized whole blood (PaxGene).	N/A
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on changes in immune cell function	• Immune cell assessment by high-dimensional cytometry	N/A
• To evaluate the effect of oral administration of nirmatrelvir/ritonavir on the relationship between genotypes and immune function at the molecular level	• Circulating protein levels adjusted for DNA-variants	N/A

5. Study design and procedures

5.1. Overall study design

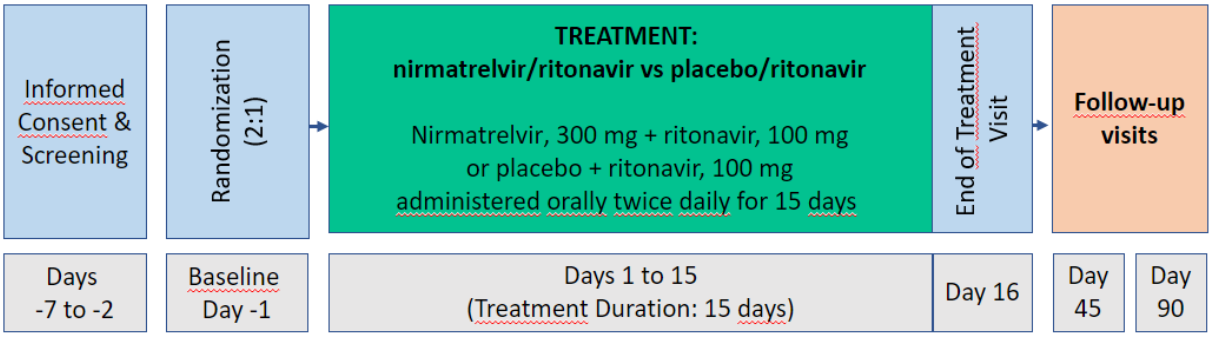
This is a phase II, interventional, randomized, parallel group, double-blind, placebo-controlled, single-center study of nirmatrelvir/ritonavir (300/100 mg) or placebo/ritonavir (100mg), administered orally twice daily for 15 days in non-hospitalized patients with post-COVID conditions.

A total of 400 patients with post-COVID conditions will be enrolled in this study. Patients will be randomized in a ratio of 2:1 to receive either nirmatrelvir/ritonavir or placebo/ritonavir. For details, see Section 7, Study treatments.

The planned length of participation in the study for each patient is a maximum of 90 days, with potential for long-term clinical follow-up at 6 and 12 months through Electronic Medical Records and national registries. The study consists of a maximum of five visits.

The study design is outlined in Figure 1 and the planned schedule of assessments at each visit are detailed in Table 1.

Figure 1 Study design



5.2. Procedures

5.2.1. Schedule of assessments

Table 1 Schedule of assessments

Visit	Screening	Baseline	Start of Treatment	End of Treatment	Follow-up	Early Termination[a]	Follow-up
Study Day	Day -7 to Day -2	Day -1	Day 1	Day 16	Day 45	Prior to Day 90	Day 90
	Up to 7 days before baseline[b]	± 0 days		± 0 days	± 7 days		± 7 days
Informed consent	X						
Demography	X						
Medical history	X						
Physical examination	X	X		X	X	X	X
Vital signs	X	X		X	X	X	X
Weight and height[c]	X						
Prior and concomitant therapy	X	X		X	X	X	X
Adjunctive therapeutic procedures	X	X		X	X	X	X
Pregnancy test	X			X		X	X
Rapid antigen testing[d]	X	X[e]					
Collect/update secondary contacts[f]		X		X	X		
Randomization		X					
Physical function tests[g]	X	X		X	X		X
Active standing test[h]		X		X	X		
Endothelial Function Test		X			X		
Dynamic spirometry		X		X	X		X

Visit	Screening	Baseline	Start of Treatment	End of Treatment	Follow-up	Early Termination[a]	Follow-up
MIP		X		X	X		X
ECG [i]		X		X	X		X
CAT [j]		X		X	X		X
Compass 31 [j]		X			X		X
EQ-5D-5L [j]	X	X		X	X	X	X
FSS [j]		X		X	X		X
MAPS [h, j]		X			X		X
MFS [j]		X		X	X		X
mMRC [j]		X		X	X		X
MoCa [j]		X		X	X		X
Nijmegen [j]		X		X	X		X
PEM [j]		X					X
Participant-completed study intervention log			X ---------- X				
Staff review of study diary				X		X	
IMP administration			X ---------- X				
PK				X			
Collection of IMP material (unused IMP, empty blisters, and cans)				X	[X]	X	[X]
Hematology, biochemistry, coagulation, and other analyses [k]	X	X		X	X		X

Visit	Screening	Baseline	Start of Treatment	End of Treatment	Follow-up	Early Termination[a]	Follow-up
Retained Research Sample for Plasma protein biomarkers		X		X	[X]		[X]
Retained Research Sample for Genetics		X		X	[X]		[X]
Retained research samples for other biomarkers		X		X	[X]		[X]
Adverse events [l]	X			X	X	X	X
Long term follow up via EMRs [m]							X

[a] In case of Early Termination of treatment, the assessments should be completed as soon as possible after decision of treatment withdrawal. When possible, all study assessments should continue in accordance with the Schedule of Assessments until completion of the Day 90 visit.
[b] Failure to include within 7 days may trigger repeat screening for otherwise eligible patient.
[c] Height may be self-reported.
[d] Only required if a participant does not have results of a positive SARS-CoV-2 test that was obtained within 5 days prior randomization. If the test is positive, subject can be re-screened at a later stage.
[e] At baseline, an NP swab will be collected by the investigational site staff to confirm SARS-CoV-2 infection by RT-PCR. This test will not be used to determine study eligibility. Subsequent NP or nasal swabs will be collected on Days 1, 16 and 45.
[f] The investigator will capture contact information for at least 2 individuals who the site can contact if the participant is unable to be reached after multiple attempts.
[g] Includes grip strength, 6-minute walk test, and accelerometer. At Screening only accelerometer assessment will be initiated.
[h] Only patients diagnosed with POTS.
[i] Apply Days 16 and 45 for up to 5 days registration.
[j] PROs will be administered for the option to complete at home prior to next visit.
[k] Laboratory tests at Days 45 and 90 are required only if clinically relevant abnormal laboratory values were present from a sample drawn at the previous study visit when laboratory assessments were performed.
[l] SAE (s) are reported from the time point ICF is signed until Day 90 visit. AE's are reported from first intake of study treatment until Day 90 visit.
[m] Potential for long-term clinical follow-up at 6 and 12 months through EMR and national registries

5.2.2. Screening period (up to 7 days before Baseline visit)

All assessments during the study are performed as listed in Table 1.

The screening assessments are initiated after completion of the informed consent process, including provision of signed consent for participation.

SAEs are reported from the time point when the ICF has been signed.

5.2.3. Baseline - Day -1

A patient study diary in paper format will be provided for the study participants where intake of investigational product is to be recorded.

Patients will be instructed who to contact in case of study related emergencies and will be provided with a study specific patient card.

The questionnaires will be distributed to fill in at the site, but if too burdensome, the option to complete at home will be given.

The option to distribute questionnaires to fill in prior to next visit will be given, and the forms will be supplied.

Patients will be informed to pay attention to changes in health during the study, to be able to report adverse events on their next visit.

5.2.4. Start of Treatment - Day 1

Patients will start treatment and register intake of investigational product. Patients will be instructed to keep empty blisters and bottles, and bring together with unused IMP, to the clinic on Day 16 visit.

Adverse event reporting starts from intake of the first dose of investigational product.

5.2.5. Visit - Day 16

Remaining IMP as well as empty blisters and bottles are collected for drug accountability. The patient study diary will be collected and reviewed.

The questionnaires will be distributed to fill in at the site, but if too burdensome, the option to complete at home will be given.

If questionnaires for Baseline visit and/or for Day 16 visit was supplied for finalization at home prior to the visit, these are to be collected and reviewed for quality reasons.

The option to distribute questionnaires to fill in prior to next visit will be given, and the forms will be supplied.

A PK sample will be taken for compliance purposes.

5.2.6. Visit - Day 45

Remaining IMP as well as empty blisters and bottles, and patient diary are collected, if not done at Visit at Day 16.

The questionnaires will be distributed to fill in at the site, but if too burdensome, the option to complete at home will be given.

If questionnaires for any visit up to Day 45 visit was supplied for finalization at home, these are to be collected, and reviewed for quality reasons, if not done earlier.

The option to distribute questionnaires to fill in prior next visit will be given, and the forms will be supplied.

5.2.7. Day 90

Remaining IMP as well as empty blisters and bottles, and patient diary are collected, if not done earlier.

The questionnaires will be distributed to fill in at the site, but if too burdensome, the option to complete at home will be given with instructions on how to send back to the clinic.

All questionnaires for visits up to Day 90 visit supplied for finalization at home are to be collected, if not done earlier, and reviewed for quality reasons.

5.2.8. Early Termination

In case of Early Termination of treatment, the assessments should be completed as soon as possible after decision of treatment withdrawal. When possible, all study assessments should continue in accordance with the Schedule of Assessments until completion of the Day 90 visit.

The estimated time needed for each visit is shown in the table below.

Screening	**Baseline**	**Day 16**	**Day 45**	**Day 90**
60 minutes 1,5 hours	90 minutes 2,5 hours	60 minutes 2 hours	60 minutes 2,5 hours	40 minutes 1,5 hours

5.3. Biological sampling procedures

5.3.1. Handling, storage, and destruction of biological samples

Blood samples and urine (only for pregnancy test) for safety monitoring will be taken and analyzed according to local procedures. These samples will be destroyed after analysis.

Blood samples for exploratory biomarkers will be collected on Day 1, Day 16 and Day 45. These will be handled and analyzed according to predefined and agreed procedures. The samples will be kept in the biobank for a maximum of 10 years after study completion.

Saliva will be collected for antigen testing of active SARS CoV-2 infection. The sample will be taken and analyzed according to local procedures after which it will be discarded.

Nasopharynx/nasal swab will be collected to confirm SARS CoV-2 infection given positive antigen test. The sample will be taken and analyzed according to local procedures after which it will be discarded.

Detailed sampling and handling procedures are described in a separate document.

5.3.2. Retained research sample for future biomarkers

Retained research samples may be used for research related to the study intervention and COVID-19. Genes and other analytes (e.g., drug metabolites, pharmacokinetics, proteins, RNA, nondrug metabolites) may be studied using the retained samples. Any future analysis will be conducted in accordance with the ICD and EPN approval.

5.3.3. Total volume of blood per subject

The total volume of blood taken from each subject during the study is maximum 200 ml, divided into 34 mL at each draw for safety samples, 4 mL for genetic sample, and 10 mL at each draw for exploratory analyses and the retained research sample.

5.3.4. Biobank

Samples taken in this study are registered in a biobank, Stockholms Medicinska Biobank, and handled according to the current biobank laws and regulations. The samples are coded/pseudonymized to protect the subject´s identification. All samples and the identification/code list are stored securely and separately to prevent unauthorized persons from having access to them.

5.4. End of Study

The study ends when the last subject has completed the last follow-up visit. The study may be prematurely terminated as per decision taken at the interim analysis, or by recommendation from the safety monitoring committee, or if recruitment of subjects cannot be met within reasonable time limits. If the study is prematurely terminated or suspended, the investigator should immediately inform the subjects about this and ensure appropriate treatment and follow-up. The regulatory authority should be informed as soon as possible, but no later than within 15 days.

Decision on premature termination is taken by the sponsor.

6. Subject selection

6.1. Study participants

Study participants in the PROLIFIC study will be identified from patients admitted to the Karolinska post-COVID clinic or who participate in Karolinska post-COVID research but may also be reached through advertisement in local media as needed.

6.2. Inclusion criteria

To be included in the study, subjects must meet the following criteria:

1. The subject has given written consent to participate in the study.
2. ≥18 years of age at the time of the Screening Visit
3. Post-acute COVID-19 syndrome (PACS) according to the WHO definition
4. EQ-5D-5L VAS< 50

5. All fertile participants must agree to use a highly effective method of contraception for the duration of the study and 28 days after last intake of IMP.

6.3. Exclusion criteria

General exclusion criteria

1. Other non-related conditions with PACS like symptoms
2. Renal function eGFR eGFRCysC < 60 mL/min/1.73 m^2
3. Not able to comply with the study protocol
4. Previous Paxlovid® treatment
5. Pregnancy or breastfeeding
6. Drug-drug interaction with ongoing treatment, including concomitant use of *any* medications or substances that are strong inducers of CYP3A4 within 28 days prior to first dose of nirmatrelvir/ritonavir and during study treatment
7. Participants who are planning or considering vaccination (including boosters) through Study Day 45
8. Active COVID-19 infection as verified by SARS CoV-2 positive antigen test
9. Self-reported medical conditions, including:
    a) Type 1 or Type 2 diabetes mellitus
    b) Chronic kidney disease
    c) Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
    d) Active cancer other than localized skin cancer, including those requiring treatment (including palliative treatment), as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period.
    e) Immunosuppressive disease (e.g., bone marrow or organ transplantation or primary immune deficiencies) OR prolonged use of immune-weakening medications:
        i. Has received corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry.
        ii. Has received treatment with biologics (e.g., infliximab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry';
        iii. HIV infection with CD4+ cell count <200/mm^3.
10. History of hospitalization for the medical treatment of acute COVID-19
11. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization in the clinical opinion of the site investigator.
12. Prior/Concomitant Therapy:
    a) Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of nirmatrelvir/ritonavir. List of potential interactions provided by Pfizer provided in Appendix A.
    b) Has received or is expected to receive monoclonal antibody treatment, antiviral treatment (e.g., molnupiravir), or convalescent COVID-19 plasma.

Prior/Concurrent Clinical Study Experience:

13. Is unwilling to abstain from participating in another interventional clinical study with an investigational compound or device, including those for post-COVID-19 therapeutics, through the long-term follow-up visit.
14. Previous administration with any investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
15. Known prior participation in this trial or other trial involving nirmatrelvir.

Diagnostic Assessments:

16. Known history of any of the following abnormalities in clinical laboratory tests (within past 6 months of the screening visit):
    - AST or ALT level ≥2.5 X ULN
    - Total bilirubin ≥2 X ULN (≥3 X ULN for Gilbert's syndrome)

6.4. Screening

Subject eligibility (that subjects fulfill all inclusion criteria and do not meet any exclusion criteria) is established at the screening visit before randomization.

6.5. Withdrawal criteria

Subjects can discontinue their participation in the study at any time without any consequence to his/her continued treatment. The investigator/sponsor can at any time terminate the study for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the study protocol. If the subject discontinues the study, follow-up of this subject will be performed according to the clinic's routine.

7. Study treatments

7.1. Investigational products

Treatment	Investigational product	Dosage form	Route	Strength	Dose regimen	Total Daily dose
A	Nirmatrelvir	Tablet	Oral	300 mg	Twice daily	600 mg
A	Ritonavir	Tablet	Oral	100 mg	Twice daily	200 mg
B	Placebo	Tablet	Oral	NA	Twice daily	NA
B	Ritonavir	Tablet	Oral	100 mg	Twice daily	200 mg

7.2. Description of investigational product(s)

Nirmatrelvir, placebo for nirmatrelvir and ritonavir is provided from Pfizer, packed and labelled from Almac Sounderton, Almac Souderton 25 Fretz Road Souderton Pa, 18964, U.S.A, shipped to ApoEx, for storage at room temperature (15 to 30°C).

Ritonavir is manufactured by Hetero Labs Limited under NDC 31722-597-30 (Camber Pharmaceuticals, Inc.).

Possible deficiencies related to the handling, storage and quality of the IMP should be reported to the study monitor and also directly to reklamationer@pfizer.com and GCSTempExcursionSupport@pfizer.com

7.3. Dose and administration

The safety and tolerability of nirmatrelvir and ritonavir has been extensively studied in preclinical species as well as in humans. Nirmatrelvir/ritonavir 300/100 mg twice daily (q12h) administered orally for 5 days has been approved for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients. Safety data in up to 10 days of dosing was demonstrated in the EPIC-PEP trial [9] [10] The dose to be used in the PROLIFIC trial is the same as approved for treatment in acute COVID-19. The prolonged dosing with 15 days of treatment is deemed necessary to ensure that Nirmatrelvir reaches hypothesized SARS-CoV-2 viral tissue reservoirs.

7.4. Packaging, labeling, and handling of investigational products

Nirmatrelvir will be provided in blister wallets, including 24 tablets. Each wallet will be labeled as required per country requirement, and with blinded labels.

Placebo for nirmatrelvir will be provided in blister wallets, including 24 tablets. Each wallet will be labeled as required per country requirement, and with blinded labels.

Ritonavir will be provided in high density polyethylene (HDPE) bottles, including 12 tablets. Each bottle will be labeled as required per country requirement.

Nirmatrelvir, and placebo for nirmatrelvir, will be provided by Pfizer and distributed via the hospital pharmacy.

Ritonavir will be provided by Pfizer and distributed via the hospital pharmacy.

7.5. Drug accountability and treatment compliance

The patients will be instructed to save empty blisters and bottles and bring unused investigational product for returning to the clinic at next visit after end of treatment. This to check randomization codes on the investigational products versus patient's study code,

check compliance with investigational product intake compared to the self-registered information in patient study diary and to perform drug accountability.

7.6. Randomization

Subjects are included/randomized consecutively, in accordance with a randomization list, as they are found to be eligible for inclusion in the study. Subjects will be assigned a unique identifier, allocated to either Treatment group or Control group in a 2:1 ratio.

If a subject discontinues their study participation, their subject code will not be reused, and the subject will not be allowed to re-enter the study again.

7.7. Blinding

The blinding will be maintained through the Day 90 follow-up visit. Subjects, the sponsor, investigators, monitors, all study site personnel involved in the study, carrying out study procedures, evaluating patients, entering study data, and/or evaluating study data will remain blinded to treatment allocations until all patients have completed the Day 90 follow-up assessments and the database has been locked for the analysis.

Active and placebo products will be of identical appearance.

7.8. Code breaking

Code breaking will be done after end of study and the database is closed.

When a SUSAR occurs for a subject participating in the study, Pfizer will request the unblinding of the treatment assigned. The randomization code will not be communicated to the site staff, to sponsor; unblinded SUSAR information will be provided to Läkemedelsverket (Swedish Medical Product Agency) only. SUSARs will be reported to Etikprövningsmyndigheten in a blinded fashion.

In case of a medical event, that requires medical treatment of a subject and unblinding needs to be done for further medical management, the investigator can unblind the subject by contacting ApoEx. In case of a medical event outside office hours, and the management of which would require knowledge of the blinded treatment assignment, the code can be accessed through ApoEx (assign contact person and 24/7 access email/phone number).

When code breaking is done the subject can continue in the study for follow-up visits, but not on study medication.

7.9. Concomitant medications

Medications that are considered necessary for the safety and well-being of the subject can be given at the discretion of the investigator, unless otherwise specified as an exclusion criterion. Concomitant medications will be reported in the eCRF.

All prescription and over-the-counter medications including vaccines taken by the participant within 30 days before study entry will be recorded.

Concomitant therapies and adjunctive therapeutic procedures will be collected through the Day90 visit and recorded in the eCRF. The data will be collected from study participants as well as through EMRs and national registries e.g., the registry for prescribed drugs.

7.9.1. Prohibited concomitant medication

Information of contraindications and prohibited concomitant medication is stated in the investigator brochure for Nirmatrelvir and for Ritonavir in pdf document “FDA_report_NDC 31722-597-30_March9_2023.pdf"

7.9.2. Contraceptive methods for WOCBP

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods [11] [12]

Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - injectable
  - implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomized partner [2,3]
- sexual abstinence [4]

Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with nirmatrelvir /ritonavir, and until one menstrual cycle after stopping nirmatrelvir /ritonavir.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

7.10. Destruction

The returned unused investigational product will be destroyed by local routines at the hospital’s pharmacy, after approval from the monitor.

8. Assessment of endpoints for clinical efficacy, safety, and pharmacodynamics

8.1. Demography

Demographic data consists of age, gender, and ethnicity.

8.2. Medical history

8.2.1. COVID-19 diagnosis

Information on Covid-19 diagnosis and microbiological verification are captured as well as information on vaccination status. Reinfections with Covid-19 are also captured.

8.2.2. Other diagnoses

Other current, chronic or for the study relevant diagnoses, either requiring pharmaceutical treatment or other treatment of importance will be captured.

8.3. Efficacy assessments

8.3.1. Health related quality of life

Patient reported outcomes will be captured through the questionnaires EQ-5D-5L, CAT, Compass 31, FSS, MAPS, MFS, mMRC, MoCa, Nijmegen and PEM which can be found in Appendix B. The questionnaires will be provided digitally or in a paper format, with the option to fill in prior (day before) a visit.

8.3.2. Physical function tests

Physical function tests consist of a 6-minute walk test (6 MWT), hand grip test, accelerometers and test of maximal inspiratory pressure.

The 6 MWT test is conducted on a straight 30-meter track in a corridor. Pulse and oxygen level (SpO2), Borg Cr-10 (breathlessness and leg fatigue) and Borg RPE (perceived exertion) is measured before and after the test. The patient is instructed to walk as far as possible for six minutes. To walk in normal pace to a cone and turn around and continue to walk back and forth for six minutes. If the patient stops during the test they can rest and check SpO2 and heart rate. The patient will be asked for the reason for not completing the assessment. The total distance walked in meters will be recorded.

Hand grip test is measuring the maximum hand strength, where the patient is instructed to hold a grip and press as much as long and as tightly as possible for the best result until the needle on the device stops rising. The patient will start with the right hand and then repeat the measurement with the left hand. Three measurements in kg for each hand, alternating sides will be measured.

Accelerometers is measuring the total volume of physical activity. The accelerometer will be placed on the thigh and must be on for a period up to 7 days. The accelerometer will then be removed by the patient for return to the clinic.

Maximal inspiratory pressure (MIP) is a measure of inspiratory muscle strength. The patient is asked to perform five MIP maneuvers, with a goal of matching the highest two within 10 cmH2O. The patient is in a sitting position. The patient is instructed to exhale slowly and completely, seal lips firmly around the new mouthpiece, and then “breath in hard.” and then repeat the maneuver at least 3 times.

8.3.3. Active standing test

Heart rate and blood pressure will be measured after a 10-minute resting period in the supine position and then every minute for 10 minutes after standing up. Heart rate will be measured with continuous ECG and blood pressure manually using an arm cuff. Data collected: Supine heart rate and blood pressure, Maximum heart rate during ten minutes standing, minimum blood pressure during ten minutes standing.

8.3.4. Endothelial function test

Endothelial function will be measured using an EndoPAT device. In short, an arm and finger cuff are attached to the patient and baseline blood pressure is recorded on a beat-to-beat basis while the patient rests in the supine position. The arm cuff in then inflated to 10-20mmHg above patient’s systolic blood pressure for five minutes. The arm cuff is then deflated, and the blood pressure is continuously recorded for an additional five minutes. Data collected: Reactive Hyperemia Index (RHI) and Augmentation Index (AI).

8.3.5. Dynamic spirometry

The spirometry test is performed using a spirometer. Spirometry is the most common type of pulmonary function or breathing test. This test measures the air volume when breathing in and out of the lungs, as well as how easily and fast it can be blown out of the lungs. Forced vital capacity, FVC, is the total volume of air exhaled during a rapid exhalation (from maximum inhalation). Forced expiratory volume in one second, FEV1, is the volume of air forced out of the lungs in 1 second. Peak expiratory flow (PEF) is the maximum flow achieved during a forced expiration starting from the level of maximal lung inflation.

8.3.6. ECG

24-hour ECG will be recorded using an ECG-device capable of collecting ECG for at least 24 hours. ECG-data will be stored digitally on an external server. ECG will not be used for patient safety monitoring and will not be reviewed at the time it is recorded. Data collected: Heart Rate Variability, min, max and average heart rate.

8.4. Exploratory efficacy assessments

8.4.1. Plasma protein biomarkers

Plasma protein assessment using Olink Explore panel of plasma cytokines and assessment of circulating spike levels [13] in patients before and after Paxlovid® or placebo treatment. We will also assess circulating nucleosome levels (Histone H3) in circulation as a biomarker of persistent innate immune activation.

8.4.2. Genetics

DNA will be extracted and subjected to genome-wide genotyping using the Illumina OmniExpress array. The data will be used to determine HLA types.

8.4.3. Other biomarkers

Bulk mRNA sequencing from PaxGene stabilized samples, batch combined from the same individuals and randomized across treatment groups to capture genome-wide transcriptional alterations in response to active treatment vs placebo. (Such analyses will also take cell composition into account to assess transcriptional changes not only explained by changes in cell composition.)

Single cell sequencing of VDJ + mRNA from sorted memory T-cells using BD Rhapsody platform will pe performed to assess T cell functional state and clonal expansion as a test of superantigen mediated activation.

8.5. Safety assessments

8.5.1. Laboratory safety assessments

Hematology, biochemistry, coagulation, and other analyses will be analyzed at the Hospital Laboratory at Karolinska University Hospital, Solna. The timepoints are summarized in Table 1, Schedule of assessments. The hospital regularly reviews reference values for each of the biomarkers and the reference values are provided by the hospital lab upon delivering lab results. The reference values serve as guidance for the clinician and study team, who will judge whether a value outside of the reference value is clinically significant or not.

Hematology	Chemistry	Other
Hemoglobin	BUN or urea	Ferritin
Hematocrit	Creatinine or Cystatin-C to	Procalcitonin
RBC count	enable eGFR calculation	
Platelet count	using CKD-Epi or CKD-	Haptoglobin
WBC count	EpiCysC	
Total neutrophils (Abs)	Glucose	Thyroid function
Eosinophils (Abs)	Calcium	TSH
Monocytes (Abs)	Sodium	T4 (free)
Basophils (Abs)	Potassium	
Lymphocytes (Abs)	Chloride	Coagulation
	Total CO_2 (bicarbonate)	PT/aPTT
	AST, ALT	Fibrinogen
	Total bilirubin	D-dimer
	Albumin	
	Total protein	HIV test
	NT-proBNP	Pregnancy test (βhCG)[1]
	LDH	
	hsCRP	
	ESR	

[1] A negative urine or serum (β-hCG) pregnancy test must be confirmed at screening for WOCBP only. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at Day 15 or ET visit.

The rapid antigen test will be evaluated directly at the clinic after testing.

8.5.2. Vital signs

Vital signs consist of blood pressure, heart rate, respiratory rate, body temperature and is measured as summarized in Table 1 “Schedule of assessments”.

8.5.3. Physical examination and anthropometry

A physical examination will be performed by a physician and will include examination of the following: general appearance, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological. Each component will be recorded as “normal” or “abnormal” at each visit. Abnormalities should be described.

Weight and height are assessed at screening, where height may be self-reported.

8.6. Adverse Events

8.6.1. Definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical investigation subject administered a medicinal product and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether related to the medicinal (investigational) product or not.

Serious adverse event (SAE): Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly/malformation

Medical and scientific assessment will be made to determine if an event is “serious” and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a reaction/event that is unexpected, serious, and suspected to be caused by the treatment, i.e., adverse events that are not included in the Investigator’s Brochure (IB) or SPC.

8.6.2. Assessment of Adverse Events

Assessment of causal relationship

The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational product.

Those AEs which are suspected of having a relationship to the investigational product will be followed up until the subject has recovered or is well taken care of and on their way to good recovery (see also section **Follow-up of Adverse Events**).

All AE will be categorized either as likely related, possibly related, or not related, in accordance with the definitions below:

Likely related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. It is unlikely that the event can be attributed to underlying disease or other medications but is most likely caused by the investigational product and its emergence is reasonable in relationship with use of the investigational product.

Possibly related: Clinical events, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. The event could be explained by the investigational product and its emergence is reasonable in relationship with use of the investigational product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

Not related: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational product. The event is unlikely related to the intervention/investigational product and can be explained by other medications or underlying disease.

Assessment of intensity

Each adverse event shall be classified by an investigator as mild, moderate or severe.

Mild: The adverse event is relatively tolerable and transient in nature but does not affect the subject's normal life.

Moderate: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

Severe: The adverse event causes deterioration of function or work ability or poses a health risk to the subject.

Assessment of seriousness

The investigator is responsible for assessing the seriousness (serious or non-serious). If the incident is considered serious, this should be reported as a serious adverse event (SAE) by the investigator to Pfizer, with a copy to sponsor (see also section Reporting of Serious Adverse Events (SAE) to Pfizer.

8.6.3. Reporting and registration of Adverse Events

At each study visit, adverse events (AE) are registered, starting at intake of first dose of investigational product up to 28 days following the last dose of study drug. All AE that occurs during the study and which are observed by the investigator/study nurse or reported

by the subject will be registered in the eCRF regardless of whether they are related to the investigational product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE or not will be done by the investigator directly in eCRF. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE or not, measures and outcome.

Reporting of Adverse Events (AE)

All AEs shall be registered in the eCRF within 3 working days.

Reporting of Serious Adverse Events (SAE) to Pfizer

Serious adverse events (SAE) are reported to Pfizer, in a protected email with copy to sponsor, on a designated SAE form within 24 hours from when the information received.

For life-threatening events or death, submit the SAE form immediately.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available and not later than 24 hours from when the information is received. The original should be kept in the Investigator Site File.

In addition, SAEs that occur after completion of the active reporting time period as defined above are reportable to Pfizer if the investigator suspects a causal relationship between the Pfizer product and the SAE.

Reporting of potential cases of Drug-Induced Liver Injury (DILI), Assessed Based on Hy's Law criteria

For investigational (non-authorized) medicinal products that are investigational in the United States (irrespective of being authorized elsewhere), interventional clinical study reports with elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) in addition to and/or preceding total bilirubin (TBili) elevations (>2 x ULN) are considered potential DILI- (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 x ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For subjects with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which value(s) are above the ULN at baseline.
    - Pre-existing AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Pre-existing values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks are assessed individually based on clinical judgment; any case where uncertainty remains as to whether it might represent a potential DILI case will be reviewed with the sponsor. The local Pfizer medical colleague for the ISR/CRC will be informed if such a situation occurs during the study and he/she will inform the Hepatic Injury Council that will provide the necessary support for an appropriate evaluation.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include:

- Albumin
- CK
- direct and indirect bilirubin
- GGT
- PT/INR
- total bile acids
- alkaline phosphatase

Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology.

A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities**

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

The SAEs which are assessed by sponsor as SUSAR are reported via a CIOMS form to the European Medicines Agency (EudraVigilance database) according to the specified time frames.

SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the incident has become known to the sponsor. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the sponsor's knowledge.

Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow.

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

When new, updated, or corrected information about a previously reported SAE is obtained, a follow-up report should be submitted to Pfizer on a new SAE Report Form that includes the data that is new or revised from the previous report. Follow-up information should never be added to a previously submitted report form. Ensure that any new events included on a follow-up report are marked as serious and a causality assessment is provided for each of them.

8.7. Safety Monitoring Committee

A Safety Monitoring Committee will review unblinded data to ensure the safety of participants throughout the duration of the study, as specified in the SMC Charter.

8.8. Annual Safety Report (Development Safety Update Report, DSUR)

As long as the study is in process in Sweden, the sponsor is obliged to submit an annual safety report to the Swedish Medical Products Agency. It defines for which time period the report applies and a list of all SAE that have occurred as well as possibly SUSAR. A summary assessment of the safety situation for the subjects and a benefit/risk evaluation for the study must also be described.

Note that information to EPM about SUSAR and annual safety reporting are requirements according to LVFS but not EPM.

8.9. Procedures in case of emergencies, overdose or pregnancy

The sponsor and investigator are obliged to immediately take the urgent safety measures necessary to protect the subjects from immediate danger. Examples of such measures are to temporarily suspend the clinical trial or to introduce supplementary monitoring measures. The sponsor shall inform the Swedish Medical Products Agency and EPM as soon as possible about the urgent safety measures taken by the investigator or sponsor.

In case of overdose, i.e., administration of a quantity of the medicinal product per administration of cumulatively that is above the maximum recommended dose according to the product labeling, reporting to Pfizer is done only if associated with an SAE.

If a study subject who participates in a clinical trial for investigational products becomes pregnant, the information is reportable to Pfizer regardless of whether there is an associated SAE. subject must be followed up until the birth has taken place.

A report on Exposure During Pregnancy needs to be completed and sent in within 24 h of the information received, regardless of whether there is an associated SAE in the infant or child.

If the fetus/child has any congenital malformation, this must be reported as a serious adverse event (SAE within 24 h). Further instructions to follow are in the Safety Reporting Reference Manual, version 8, provided by Pfizer.

8.10. Procedures in case of exposure during breastfeeding

Breastfeeding occurs if:

- A female is found to be breastfeeding while receiving or after discontinuing the study drug.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to the trial intervention (i.e., environmental exposure). An example of environmental exposure during breastfeeding is a participant family member or healthcare provider who reports that she is breastfeeding after having been exposed to the trial intervention by ingestion.

Exposure during breastfeeding is reportable to Pfizer regardless of whether there is an associated SAE in the infant or child.

8.11. Procedures in case of Environmental Exposure

Occupational/environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with, or exposure to, the Pfizer medicinal product. An occupational/environmental exposure is reportable to Pfizer regardless of whether there is an associated AE.

8.12. Procedures in case of Medication Error

Medication errors may result, for example, from the administration or consumption of the study drug by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving participant exposure to the study drug;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Medication errors are reportable to Pfizer only when associated with an SAE.

9. Reference Safety Information

The Investigator Brochure (IB) for Nirmatrelvir is the reference safety information used for the assessment of whether an AE is expected or not. The reference safety information for Ritonavir is found in document “FDA_report_NDC 31722-597-30_March9_2023.pdf”.

10. Statistics

Detailed methodology for statistical analyses of the data collected in this study is outlined here and further detailed in a Statistical Analysis Plan (SAP), which will be maintained by the KI (Institute of Environmental Medicine).

Statistical hypothesis

- The null hypothesis (H0) is that there is no placebo-adjusted difference in EQ-5D-5L between nirmatrelvir/ritonavir and placebo/ritonavir at Day 16.
- The alternative hypothesis (H1) is that there is a placebo-adjusted difference in EQ-5D-5L between nirmatrelvir/ritonavir and placebo/ritonavir at Day16.

Provided the primary endpoint shows positive signal for H1, additional endpoints will be tested including:

- Sustained EQ5D difference at Day 45 and Day 90.

10.1. Estimands

10.1.1. Primary estimand

- For a given endpoint, the primary estimand will be the population average treatment effect on the change from baseline over time of nirmatrelvir/ritonavir compared to placebo/ritonavir. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (e.g., laboratory failure) will have data imputed based on a missing at random (MAR) assumption. Participants with inadequate compliance will have their values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in nirmatrelvir/ritonavir arm compared to placebo/ritonavir.

10.1.2. Secondary estimands

- For a given endpoint, the secondary estimand will be the population average treatment effect on the change from baseline at a given time assessment (i.e., on Day 16, Day 45 or Day 90) of nirmatrelvir/ritonavir compared to placebo/ritonavir. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (e.g., laboratory failure) will have data imputed based on a missing at random (MAR) assumption. Participants with inadequate compliance will have their values used as-is in the analysis. The

population-based treatment effect will be the difference in the mean change from baseline in nirmatrelvir/ritonavir arm compared to placebo/ritonavir.

10.2. Analysis populations

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants completing randomization
Safety Analysis Set (SAS)	All participants randomly assigned to study intervention and who take at least 2 doses of study intervention. Participants will be analyzed according to the study intervention they received.
Modified Intent -To-Treat (mITT)	All participants randomly assigned to study intervention who complete 25 dosings up to Day16. Participants will be analyzed according to the study intervention to which they were randomized.
Full Completers (FC)	All participants in the set without major protocol violations who completed at least 25 dosings and were assessed at Day16, Day45 and Day90

10.3. Descriptive

Descriptive statistics for all efficacy and safety (AE related variables) endpoints by treatment group and visit will be provided.

The number of participants screened will be reported. The number of participants randomized to the double-blind treatment phase, completing the study drug administration, completing the study, and discontinued the study will be summarized from the FAS analysis set for each treatment group.

Baseline demographic and other characteristics will be tabulated for the FAS analysis set and summarized by treatment group. Continuous variables will be described by standard descriptive statistics (mean, standard deviation, median, interquartile range, minimum, and maximum), and categorical variables will be summarized by frequency tables with number and proportion in each category (with the corresponding sample sizes).

10.4. Statistical methods

For the primary estimand of the primary endpoint, a linear mixed model (LMM) with subject-specific random intercept will be specified to assess possibles changes over time within and among groups. LMM accounts for both fixed and random effects, can analyze data with repeated measures as well as can handle missing values. Specifically, the LMM will include treatment, time, and time*treatment interaction term as fixed effects, and subject/participant as a random effect. An unstructured correlation matrix will be used. Missing values will be imputed as part of the LMM model assumptions.

No adjustments will be made for multiplicity.

For continuous variables, differences in mean or median between groups will be assessed using Student's t-test (parametric) or Mann-Whitney test (non-parametric) depending on the

fulfillment of the distributional assumptions of approximation for a normal distribution (Kolmogorov-Smirnov test). Differences in mean or median within groups at Days 16, 45 and 90 with respect to baseline, will be assessed using paired Student's t-test (parametric) or Wilcoxon's signed-rank test (non-parametric) as appropriate.

For continuous primary estimands of secondary endpoints, analysis of covariance (ANCOVA) will be performed to assess changes from baseline on Days 16, or Day 45 , or Day 90. Specifically, the ANCOVA will include treatment as fixed effects, and baseline as a covariate.

For dichotomous variables, change in proportions within groups at Days 16, 45 and 90 with respect to baseline (pre-treatment vs post-treatment) will be assessed using McNemar's test.

For categorical variables, frequency distributions will be estimated and compared between the groups using Chi-squared test or the exact Fisher test.

With all baseline demographic and patient's medical history variables a logistic regression model will be adjusted for studying the influence of each of them in the response to treatment. No values will be imputed for missing data, and missing values will not be included in the model.

Sensitivity analyses will be detailed in the SAP prior to database lock and may be include analyses described in the a forementioned alternative study populations.

10.5. Sample size calculations

The statistical power to detect a 10-unit placebo/ritonavir adjusted improvement from baseline to Day16 (primary endpoint) was estimated using the following assumptions: a 2:1 case-control ratio, nominal significance of alpha=0.05, 1-tailed test and 90 % power. Based on these assumptions, the study population would need to be at least 207 patients. In the study, ~400 participants will be randomized to a) have at least 207 completers to account for 48% dropouts during the execution of the study and b) increase the statistical power for the secondary endpoints of the study that will only be measured in the subset of patients with POTS, and for the secondary endpoints for which the variabilities in the Swedish post-covid patient population are not well documented.

10.6. Interim analysis

Interim analysis (IA) will be performed at least once while the study is on-going. This review will include an assessment of the observed safety and observed (versus assumed) variability for the primary endpoint (i.e., EQ-5D-5L VAS) as well as key secondary endpoints hemodynamic response and fever, which is only completed in patients with POTS. The planned IA is proposed after at least 50% of the total planned randomized subjects (i.e., approximately 200 subjects), complete through at least one-third of the total duration of the study. Interim analysis results may be used for conducting a sample size re-estimation, and internal decisions using probability of technical success techniques of the trial (which is not impacting the alpha level). Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as

per the sponsor's standard operating procedures will be documented and approved by the study team.

11. Quality Control, Quality Assurance and Sponsor Oversight

This study will be conducted in compliance with this protocol, study specific procedures, the ICH Guideline for Good Clinical Practice, and applicable regulatory requirements.

The study will be monitored by an independent monitor, during the course of the study and after the study has been completed, to ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the study's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the eCRF are complete, correct, and consistent with the source data. All patients informed consent forms are reviewed. The investigator guarantees access to source documents by monitor and appropriate regulatory agencies.

The sponsor will establish a systematic, prioritized, risk-based approach to monitoring and has chosen a combination of on-site and centralized monitoring.

The investigator(s) and the study team will be available during monitoring visits and possible audits and devote the time needed to the process.

The eCRF system follows standards set up by 21CFR Part 11, EMA Annex 11, ICH GCP and GDPR.

Sponsor oversight will be performed according to the study specific Sponsor Oversight Plan.

The sponsor will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data which would affect subject safety and reliability of the data.

11.1. Source data

The investigator must keep source documents for each subject in the study. A document describing what has been classified as source data in the study should be included in the Investigator Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

Source data is defined before study start.

11.2. Deviations or serious breaches

Serious breaches and deviations from the study protocol, GCP and other regulations that significantly and directly affects, or with high likelihood could affect, the subjects in Sweden or the scientific value of the study, shall be immediately reported within 7 days (from knowledge) to the Swedish Medical Products Agency. It is the sponsor's responsibility to judge the consequences of deviations that have occurred, and thus also to decide whether the Swedish Medical Products Agency should be informed.

Minor deviations that do not affect subjects' integrity or safety, nor significantly affect the study's scientific value, are documented in the study documentation of the principal investigator and the sponsor.

11.3. Audits and inspections

Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the study site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections. The purpose of an audit or inspection is to systematically and independently review all study-related activities and documents, so as to determine whether these activities were performed, registered, analyzed and reported correctly according to protocol, GCP and applicable regulations.

12. Ethics

12.1. Compliance to the protocol, GCP and regulations

The study will be performed in compliance with the study protocol, the Declaration of Helsinki, ICH-GCP (Good Clinical Practice) guidelines and current national and international regulations governing this clinical trial. This is to ensure the safety and integrity of the study subjects as well as the quality of the data collected.

12.2. Ethical review of the study

The final study protocol for clinical trials must be approved, as a part of the application for a permit for clinical trials, by both the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) and the Swedish Medical Products Agency before the trial can be conducted. The final version of the informed consent form and other information provided to subjects, must be approved, or given a written positive opinion by EPM. EPM and the Swedish Medical Products Agency must be informed of any changes in the study protocol in accordance with current requirements.

12.3. Procedure for obtaining informed consent

The investigator shall ensure that the subject is given full and adequate oral and written information about the study, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the study at any time without having to provide a reason. Subjects should be given the opportunity to ask questions and be given sufficient time to consider the information provided. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as the informed consent form shall be provided to the subject. The subject's signed and dated informed consent must be obtained before performing any study-specific activity in the study. Each subject who participated in the study will be identified by a subject number on a subject identification list. The subject agrees that monitors, auditors, and inspectors may have access to their medical records and other source data. If new information comes up during

the course of study that affects the patient's safety, the subject has the right to reconsider whether he/she will continue their participation.

12.4. Data protection

The content of the informed consent form complies with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their study data will take place. Information that study data will be published without identification of individuals is also given.

The subject information and the informed consent form will explain how study data are stored to maintain confidentiality in accordance with national data legislation. Data will be centrally stored at servers at KI's own data center. Access will be granted by the project owner, only to persons within KI. All information processed by the sponsor will be pseudonymized. Any subject record or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the study, including the subject's medical history.

If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (GDPR) and other relevant legislation before any data transfer takes place.

12.5. Insurances

Patients are insured through Swedish Patient Insurance (Patientskadeförsäkringen), and through Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen).

13. Substantial changes to the study

Substantial changes to the signed study protocol are only possible through approved protocol amendments and by agreement from all responsible persons. Information on non-substantial changes should be clearly noted in the amended protocol.

In the event that substantial changes to the protocol (e.g., changing of the main objective, primary or secondary variables, method to measure the primary variable, changing of the investigational product or dosage) will be made during the course of the study, approval from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) as well as the Swedish Medical Products Agency (Läkemedelsverket) shall be obtained before any changes are implemented. A change that concerns a new site, new investigator or a new study patient information sheet shall only be approved by EPM.

Non-substantial changes will be recorded and later entered in documentation that is submitted, for example in any subsequent notifications of a substantial change or in connection with End of Trial reporting.

14. Collection, handling, and archiving data

Subjects who participate in the study are coded with a specific study identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject's name and personal number with a study identification number.

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. The complete Trial Master File, as well as source documents, will be archived for at least 25 years after the study is completed. Source data in the medical records system is stored and archived in accordance with the respective hospital regulations.

14.1. Case Report Form

A digital Case Report Form (eCRF) is used for data collection, in this study an eCRF will be used. The system will be a validated system for collecting data in clinical studies.

The investigator must ensure that data is registered and any corrections in the eCRF are made as stated in the study protocol and in accordance with the instructions. The investigator must ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The investigator signs the completed eCRF. A copy of the eCRF database will be archived at the study site.

Corrections will be saved in the EDC audit trail, this to be able to follow all changes in the clinical database.

15. Notification of study completion, reporting, and publication (Swedish MPA requirements)

A national Center of Excellence regarding PACS has been established. In this center, study team members involved in this study program serve as PACS experts (Michael Runold, co-applicants Marcus Ståhlberg, Judith Bruchfeld and, Malin Nygren-Bonnier) in national authorities (e.g., Guidelines for investigation and follow-up of PACS on behalf of the National Board of Health and Welfare and PACS scientific evidence review for the Swedish Agency for Health Technology Assessment and Assessment of Social Services, the latter ongoing). The team has also participated in a multidisciplinary and multi-professional national working group to provide guidelines for COVID-19 follow-up. The broad multidisciplinary and multi-professional research group involved with leading positions and excellent connections within the field of post-acute COVID-19 in health care, public health and national health authorities there is a very good position for engagement with end users as well as national and international media. Through the follow-up clinic there is a continuous contact with patients

as well as patient organizations, namely the Swedish COVID-19 patient organization and Doctors for Doctors with post-acute COVID-19.

Results will disseminate at national and international scientific conferences as well as in publications in scientific journals, KI.se etc. as health care authorities of Region Stockholm, through the Centre for Epidemiology and Community Medicine. The aim is to share results directly with the Public Health Agency of Sweden, the Swedish Agency for Health and Care Services Analysis, the National Board of Health and Welfare the European Centre for Disease Control and prevention (ECDC) and WHO.

The Swedish Medical Products Agency will be informed of the study's completion at latest 90 days after study end, through submission of a" Declaration of End of Trial Notification" form.

Within one year after the study completion, the results shall be analyzed, and completed in a clinical study report, and the study results shall also be reported in the EudraCT database.

16. References

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13. Swank, Z., et al., *Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae.* Clin Infect Dis, 2022.

Attachments

All attachments should have a version number and be dated.

Appendix A - Questionnaires – Patient Reported Outcomes

Appendix B - Patient study diary

Appendix A, March 9th 2023

Styrgruppen för utvecklingen av CAT har föreslagit några behandlingsåtgärder för varje scenario

CAT- poäng	Grad av påverkan	Bred klinisk bild om hur KOL påverkar patienten utifrån CAT-poäng	Möjliga behandlingsåtgärder
>30	Mycket hög	Tillståndet förhindrar patienterna från att göra allt de skulle vilja och de har aldrig några bra dagar. Om de klarar att ta ett bad eller en dusch, tar det mycket lång tid. De kan inte gå hemifrån för någon typ av nöje eller för att handla och kan heller inte utföra hushållsarbete. Många gånger kan de inte ta sig långt från sängen eller stolen. De känner sig invalidiserade.	Det finns stort utrymme för förbättringar. Utöver de rekommendationer som anges nedan för patienter med låga till medelhöga CAT-poäng kan man även överväga: • Remiss till specialistvård (om du är läkare inom primärvården)
>20	Hög	KOL förhindrar patienterna från att göra det mesta av det de skulle vilja göra. De blir andfådda av att gå omkring hemma eller när de tvättar sig eller klär sig. De kan bli andfådda av att prata. Hostan gör att de blir trötta och symtomen i bröstet stör nattsömnen de flesta nätterna. Att motionera känns osäkert och allt de gör kräver en kraftansträngning. De är rädda, har ofta panikkänslor och känner inte att de har kontroll över sin sjukdom	Överväg också: • Ytterligare läkemedelsbehandling • Remiss till lungrehabilitering • Använd de bästa metoderna för att minimera och hantera riskerna för exacerbationer
10 à 20	Medelhög	KOL är ett av patienternas största problem. De har några bra dagar per vecka, men har upphostningar de flesta dagarna och drabbas av en eller två exacerbationer per år. De är andfådda de flesta dagar och vaknar oftast med tryck över bröstet eller med väsljud. De blir andfådda när de böjer sig och det tar lång tid för dem att gå uppför en trappa. Hushållsarbetet går antingen mycket långamt eller så måste de ta pauser och vila.	Det finns utrymme för förbättringar - optimera omhändertagandet. Utöver de rekommendationer som anges nedan för patienter med låga CAT-poäng kan man även överväga: • Granska befintlig underhållsbehandling – är den optimal? • Remiss till lungrehabilitering • Använd de bästa metoderna för att minimera och hantera riskerna för exacerbationer • Se över förvärrande faktorer – röker patienten fortfarande?
<10	Låg	De flesta dagarna är bra, men KOL orsakar en del problem och förhindrar människor från att göra en eller ett par saker som de skulle vilja göra. De hostar vanligtvis flera gånger om dagen och blir andfådda när de idrottar och när de bär tungt. De måste sänka farten eller stanna och vila när de går uppför en backe eller om de går fort på plan mark. De blir lätt utmattade.	• Rökstopp • Årliga influensavaccinationer • Minska exponering för riskfaktorer som kan leda till exacerbationer • Val av lämplig behandling efter ytterligare klinisk bedömning

Ditt namn:	Dagens datum:

COPD Assessment Test

Hur upplever du din KOL? Utför KOL-testet (COPD Assessment Test™, CAT)

Detta frågeformulär kommer att hjälpa dig och din vårdgivare att mäta den inverkan KOL (kroniskt obstruktiv lungsjukdom) har på ditt välbefinnande och dagliga liv. Svaren och testresultatet kan användas av dig och din vårdgivare för att hjälpa dig förbättra vården av din KOL och få bästa utbyte av behandlingen.

Placera ett (X) för varje fråga i rutan som bäst beskriver hur du för närvarande mår. Välj endast ett svar för varje fråga.

Exempel:	Jag är mycket glad	0	X 1	2	3	4	5	Jag är mycket ledsen

								POÄNG
Jag hostar aldrig	0	1	2	3	4	5	**Jag hostar ständigt**	
Jag har inte något slem i bröstet alls	0	1	2	3	4	5	**Mitt bröst är helt fyllt med slem**	
Jag känner inte alls något tryck över bröstet	0	1	2	3	4	5	**Jag känner mycket tryck över bröstet**	
När jag går uppför en backe eller en trappa blir jag inte andfådd	0	1	2	3	4	5	**När jag går uppför en backe eller en trappa blir jag mycket andfådd**	
Jag är inte begränsad när det gäller att utföra några aktiviteter i hemmet	0	1	2	3	4	5	**Jag är mycket begränsad när det gäller att utföra aktiviteter i hemmet**	
Jag känner mig trygg att lämna mitt hem trots mitt lungtillstånd	0	1	2	3	4	5	**Jag känner mig inte alls trygg att lämna mitt hem på grund av mitt lungtillstånd**	
Jag sover bra	0	1	2	3	4	5	**Jag sover inte bra på grund av mitt lungtillstånd**	
Jag har massor av energi	0	1	2	3	4	5	**Jag har inte någon energi alls**	
								ANTAL POÄNG

Supplemental Appendix 2. Instrument - COMPASS 31

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?

1 Yes
2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?

1 Rarely
2 Occasionally
3 Frequently
4 Almost Always

3. How would you rate the severity of these feelings or symptoms?

1 Mild
2 Moderate
3 Severe

4. In the past year, have these feelings or symptoms that you have experienced:

1 Gotten much worse
2 Gotten somewhat worse
3 Stayed about the same
4 Gotten somewhat better
5 Gotten much better
6 Completely gone

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?

1 Yes
2 No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)

1 Hands
2 Feet

7. Are these changes in your skin color:

1 Getting much worse
2 Getting somewhat worse
3 Staying about the same
4 Getting somewhat better
5 Getting much better
6 Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?

1 I sweat much more than I used to
2 I sweat somewhat more than I used to
3 I haven't noticed any changes in my sweating
4 I sweat somewhat less than I used to
5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

1 Yes
2 No

10. Does you mouth feel excessively dry?

1 Yes
2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

1 I have not had any of these symptoms
2 Getting much worse
3 Getting somewhat worse
4 Staying about the same
5 Getting somewhat better
6 Getting much better
7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?

1 I get full a lot more quickly now than I used to
2 I get full more quickly now than I used to
3 I haven't noticed any change
4 I get full less quickly now than I used to
5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?

1 Never
2 Sometimes
3 A lot of the time

14. In the past year, have you vomited after a meal?

1 Never
2 Sometimes
3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?
    1 Never
    2 Sometimes
    3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?
    1 Yes
    2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per month
    4 Constantly

18. How severe are these bouts of diarrhea?
    1 Mild
    2 Moderate
    3 Severe

19. Are your bouts of diarrhea getting:
    1 Much worse
    2 Somewhat worse
    3 Staying the same
    4 Somewhat better
    5 Much better
    6 Completely gone

20. In the past year, have you been constipated?
    1 Yes
    2 No (if you marked No, please skip to question 24)

21. How frequently are you constipated?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per month
    4 Constantly

22. How severe are these episodes of constipation?
    1 Mild
    2 Moderate
    3 Severe

23. Is your constipation getting:

1 Much worse
2 Somewhat worse
3 Staying the same
4 Somewhat better
5 Much better
6 Completely gone

24. In the past year, have you ever lost control of your bladder function?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

25. In the past year, have you had difficulty passing urine?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

26. In the past year, have you had trouble completely emptying your bladder?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?

1 Never (if you marked Never, please skip to question 29)
2 Occasionally
3 Frequently
4 Constantly

28. How severe is this sensitivity to bright light?

1 Mild
2 Moderate
3 Severe

29. In the past year, have you had trouble focusing your eyes?

1 Never (if you marked Never, please skip to question 31)
2 Occasionally
3 Frequently
4 Constantly

30. How severe is this focusing problem?

1 Mild
2 Moderate
3 Severe

31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:

1 I have not had any of these symptoms
2 Much worse
3 Somewhat worse
4 Staying about the same
5 Somewhat better
6 Much better
7 Completely gone

DePaul Symptom Questionnaire Post-Exertional Malaise (DSQ-PEM)

(Ett frågeformulär om symptom efter ansträngning)

Ringa in ett nummer för frekvens samt ett nummer för svårighetsgrad för varje symtom nedan: Fyll i tabellen från vänster till höger.

Symptom	Frekvens: Under **de <u>senaste 6 månaderna</u>, hur <u>ofta</u>** har du haft dessa symtom? För varje symtom som anges nedan, ringa in ett nummer: 0 = aldrig, 1 = vid vissa tillfällen, 2 = ungefär hälften av tiden, 3 = för det mesta, 4 = hela tiden	Allvarlighetsgrad: Under **de <u>senaste 6 månaderna</u>, hur <u>mycket</u>** har dessa symtom besvärat dig? För varje symtom som anges nedan, ringa in ett nummer: 0 = symtom inte närvarande, 1 = lätt, 2 = måttliga symtom, 3 = svåra symtom, 4 = mycket svåra symtom
1. Tung känsla efter träningsstart	0 1 2 3 4	0 1 2 3 4
2. Ömhet eller trötthet dagen efter icke-ansträngande, vardagliga aktiviteter	0 1 2 3 4	0 1 2 3 4
3. Mentalt trött efter minsta ansträngning	0 1 2 3 4	0 1 2 3 4
4. Minimal träning gör dig fysiskt trött	0 1 2 3 4	0 1 2 3 4
5. Fysiskt dränerad eller sjuk efter lätt aktivitet	0 1 2 3 4	0 1 2 3 4

För varje fråga nedan, välj det svar som bäst beskriver dina PEM-symtom (ansträngningsutlöst försämring).

6. Om du skulle bli utmattad efter att ha deltagit aktivt i fritidsaktiviteter, sporter eller utflykter med vänner, skulle du då återhämta dig inom en till två timmar efter aktiviteten avslutats?	Ja	Nej
7. Upplever du en försämring av **din/a trötthet/orkesrelaterade besvär** efter minimal **fysisk** ansträngning?	Ja	Nej
8. Upplever du försämring av **din/a**	Ja	Nej

trötthet/energirelaterade besvär efter minimal **mental** ansträngning?	
9. Om du känner dig sämre efter aktiviteter, hur länge varare det?	≤1h 2-3h 4-10h 11-13h 14-23h ≥24h
10. Om du inte tränar, är det på grund av att träning förvärrar dina symtom?	Ja Nej

Hälsoenkät

Svensk version för Sverige

(Swedish version for Sweden)

Namn:……Personnummer…….

Kryssa under varje rubrik bara i EN ruta som bäst beskriver din hälsa IDAG.

RÖRLIGHET

- Jag har inga svårigheter med att gå omkring ❑
- Jag har lite svårigheter med att gå omkring ❑
- Jag har måttliga svårigheter med att gå omkring ❑
- Jag har stora svårigheter med att gå omkring ❑
- Jag kan inte gå omkring ❑

PERSONLIG VÅRD

- Jag har inga svårigheter med att tvätta mig eller klä mig ❑
- Jag har lite svårigheter med att tvätta mig eller klä mig ❑
- Jag har måttliga svårigheter med att tvätta mig eller klä mig ❑
- Jag har stora svårigheter med att tvätta mig eller klä mig ❑
- Jag kan inte tvätta mig eller klä mig ❑

VANLIGA AKTIVITETER *(t ex arbete, studier, hushållssysslor, familje- eller fritidsaktiviteter)*

- Jag har inga svårigheter med att utföra mina vanliga aktiviteter ❑
- Jag har lite svårigheter med att utföra mina vanliga aktiviteter ❑
- Jag har måttliga svårigheter med att utföra mina vanliga aktiviteter ❑
- Jag har stora svårigheter med att utföra mina vanliga aktiviteter ❑
- Jag kan inte utföra mina vanliga aktiviteter ❑

SMÄRTOR/BESVÄR

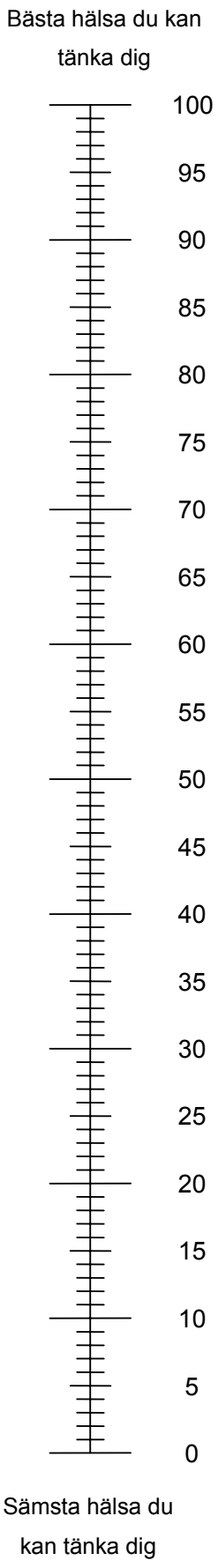
- Jag har varken smärtor eller besvär ❑
- Jag har lätta smärtor eller besvär ❑
- Jag har måttliga smärtor eller besvär ❑
- Jag har svåra smärtor eller besvär ❑
- Jag har extrema smärtor eller besvär ❑

ORO/NEDSTÄMDHET

- Jag är varken orolig eller nedstämd ❑
- Jag är lite orolig eller nedstämd ❑
- Jag är ganska orolig eller nedstämd ❑
- Jag är mycket orolig eller nedstämd ❑
- Jag är extremt orolig eller nedstämd ❑

- Vi vill veta hur bra eller dålig din hälsa är IDAG.
- Den här skalan är numrerad från 0 till 100.
- 100 är den bästa hälsa du kan tänka dig.
  0 är den sämsta hälsa du kan tänka dig.
- Sätt ett X på skalan för att visa hur din hälsa är IDAG.
- Skriv nu i rutan nedan det nummer du har markerat på skalan.

DIN HÄLSA IDAG = ☐



2005-09-21

Namn:_____ Datum:_____

Trötthetsskala (Fatigue Severity Scale, FSS) (Krupp et al 1989)

Läs igenom följande påståenden och ange i vilken grad Du instämmer i vart och ett genom att ringa in en siffra. Val av siffran 1 innebär att Du inte alls instämmer med påståendet och siffran 7 att Du instämmer helt och hållet. Du kan välja vilken siffra som helst däremellan.

1. Min motivation är lägre när jag är trött

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

2. Motion framkallar min trötthet

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

3. Jag blir lätt trött

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

4. Trötthet begränsar min fysiska aktivitet

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

5. Trötthet orsakar ofta problem för mig

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

Malin Mattsson, Sunderby sjukhus och Carina Boström, Karolinska Institutet 2005

6. Min trötthet hindrar mig från ihållande fysiska aktiviteter

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

7. Trötthet begränsar möjligheten att uppfylla vissa plikter och åtaganden

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

8. Trötthet är ett av mina tre mest funktionshindrande symtom

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

9. Trötthet begränsar mitt arbete, familjeliv eller sociala liv

1	2	3	4	5	6	7
instämmer inte alls						instämmer helt och hållet

Mattsson M, Möller B, Lundberg IE, Gard G, Boström C. Reliability and validity of the Fatigue Severity Scale in Swedish for patients with systemic lupus erythematosus. Scand J Rheumatol 2008; 37:269-77.

Malin Mattsson, Sunderby sjukhus och Carina Boström, Karolinska Institutet 2005

Symptomskattning i POTS

Skånes Universitetssjukhus Malmö
&
Lunds Universitet
2019
(Jasmina Spahic, Viktor Hamrefors och Artur Fedorowski)

Datum: ……..

Namn: ……

Personnummer: …….

Studienummer (ifylls av personal): …….

****

Hej,

Detta frågeformulär kommer att hjälpa oss skatta hur pass påverkad Du är av dina symptom härstammande från POTS. Dessutom vill vi jämföra om det finns något samband mellan dina symptom och resultat av blodprover som tagits på Dig inom en forskningsstudie om POTS som du deltager i. Av denna orsak ber vi dig fylla i följande formulär så noggrant det går.

Vänligen ringa in den siffra på skalan som bäst motsvarar hur uttalade dina symptom har varit i genomsnitt under den senaste veckan. Du ska ge ett svar för varje symptom. Om du inte har upplevt ett visst symptom, ringa in noll (0).

1. Yrsel i stående eller efter uppresning.

Inga symptom Värsta tänkbara

0 1 2 3 4 5 6 7 8 9 10

2. Svimningskänsla, upplevelse av att du kan komma att förlora medvetandet?

0 1 2 3 4 5 6 7 8 9 10

3. Hjärtklappning, hög puls eller känsla av oregelbundna hjärtslag

0 1 2 3 4 5 6 7 8 9 10

4. Besvär med andningen/andfåddhet, både vid ansträngning och i vila

0 1 2 3 4 5 6 7 8 9 10

5. Bröstsmärta.

0 1 2 3 4 5 6 7 8 9 10

6. Huvudvärk

0 1 2 3 4 5 6 7 8 9 10

7. Koncentrationssvårigheter

0 1 2 3 4 5 6 7 8 9 10

8. Muskelsmärtor

0 1 2 3 4 5 6 7 8 9 10

9. Illamående

0 1 2 3 4 5 6 7 8 9 10

10. Mag-och tarmbesvär (ont i magen, diarré, förstoppning)

0 1 2 3 4 5 6 7 8 9 10

11. Onormal trötthet som inte går över efter vila.

0 1 2 3 4 5 6 7 8 9 10

12. Sömnsvårigheter

0 1 2 3 4 5 6 7 8 9 10

Kontaktuppgifter forskare: Jasmina Medic Spahic

Mail: jasmina.medic_spahic@med.lu.se

Självskattning av mental trötthet (Mental Fatigue Scale, MFS)

Namn:_____ Datum: _____

Vi är intresserade av ditt nuvarande tillstånd, d.v.s. ungefär hur du har mått den senaste månaden.
När du ska jämföra med hur det var tidigare ska du göra det med hur det var innan du blev sjuk/skadades.
I tabellen för varje fråga finns fyra påståenden som beskriver *Inga* (0), *Lätta* (1), *Medelsvåra* (2) och *Svåra* besvär (3).
Vi vill att du markerar den siffra som står bredvid det påstående som bäst beskriver dina besvär.
Om du tycker att du hamnar mellan två påståenden finns det även siffror som motsvarar detta.

1. TRÖTTHET

Har du känt dig trött den senaste månaden? Det spelar ingen roll om det är fysisk (muskulär trötthet) eller trött i huvudet. Om det nyligen hänt något ovanligt (t.ex. en olycka eller tillfällig sjukdom) skall du försöka bortse från det.

0	Jag har inte alls känt mig trött (aldrig onormalt trött, inte behövt vila mer än vanligt).
0.5	
1	Jag har varit trött flera gånger per dag, men jag blir klart piggare av att vila.
1.5	
2	Jag har känt mig trött större delen av dagen, och vila har ingen eller liten effekt.
2.5	
3	Jag har känt mig trött all vaken tid, och vila har ingen effekt.

2. OFÖRETAGSAMHET

Har du svårt att sätta igång med saker? Känner du dig oföretagsam och tar det emot när du skall sätta igång med något, oavsett om det är en ny uppgift eller om det gäller saker du gör varje dag.

0	Jag har inga svårigheter med att ta itu med saker.
0.5	
1	Jag har svårare än tidigare för att sätta igång med aktiviteter. Jag skjuter gärna på det.
1.5	
2	Det krävs en stor ansträngning för att jag skall ta itu med saker. Detta gäller även vardagliga ting som att stiga ur sängen, tvätta mig, äta.
2.5	
3	Jag kan inte få de enklaste vardagliga saker (äta, klä på mig) gjorda. Jag måste ha hjälp med allt.

3. MENTAL UTTRÖTTBARHET

Blir du snabbt trött ”i huvudet” när hjärnan måste arbeta? Blir du mentalt trött av saker som att läsa, titta på TV eller delta i samtal med flera personer. Måste du ta pauser eller byta aktivitet?

0	Jag kan hålla på lika länge som vanligt. Min uthållighet för ”hjärnarbete” har inte minskat.
0.5	
1	Jag blir lättare trött men kan utföra lika mycket ”hjärnarbete” som är normalt för mig.
1.5	
2	Jag blir lätt trött och måste ta pauser eller göra något annat oftare än vanligt.
2.5	
3	Jag har så lätt för att bli trött att jag inte kan göra någonting, eller måste avbryta alla aktiviteter efter en kort stund (ca 5 minuter).

För mer information om MFS, se www.mf.gu.se

4. MENTAL ÅTERHÄMTNING

Hur lång tid tar det för dig att återhämta dig efter att du har arbetat tills du fullständigt tappat förmågan att kunna koncentrera dig på det du gör.

0	Jag behöver mindre än en timmes vila för att kunna fortsätta arbeta.
0.5	
1	Jag måste vila mer än en timme, men behöver inte en natts sömn.
1.5	
2	Jag behöver en natts sömn för att kunna fortsätta arbeta.
2.5	
3	Jag behöver flera dagars vila för att återhämta mig.

5. KONCENTRATIONSSVÅRIGHETER

Har du svårt att samla tankarna och koncentrera dig?

0	Jag har lika lätt som vanligt för att samla tankarna.
0.5	
1	Jag kan ibland tappa bort mig, t.ex. när jag läser eller tittar på TV.
1.5	
2	Jag har så svårt att koncentrera mig så att det besvärar mig när jag t.ex. läser en dagstidning eller deltar i samtal med flera personer.
2.5	
3	Jag har alltid så svårt att koncentrera mig att det är nästan omöjligt att göra någonting.

6. MINNESSTÖRNINGAR

Glömmer du oftare än tidigare och behöver du minneslappar, eller måste leta mer hemma eller på arbetet?

0	Jag har inga problem med minnet.
0.5	
1	Jag glömmer saker lite oftare än vad jag tycker att jag borde, men kan klara mig om jag använder minneslappar.
1.5	
2	Mitt dåliga minne orsakar regelbundet besvär (t.ex. genom att jag glömmer viktiga möten eller spisen).
2.5	
3	Jag kan nästan inte komma ihåg någonting.

7. TANKETRÖGHET

Känner du dig trög eller långsam i tankearbetet? Detta gäller känslan av att det tar ovanligt lång tid för att avsluta en tankegång eller för att lösa en uppgift som kräver tankearbete.

0	Jag känner mig inte trög eller långsam i mina tankar vid ”hjärnarbete”.
0.5	
1	Jag kan känna en viss tröghet någon eller några gånger om dagen vid krävande tankearbete.
1.5	
2	Jag känner mig ofta trög och långsam i tanken även vid vardagliga sysslor t.ex. i samtal med en person eller vid läsning av dagstidningen.
2.5	
3	Jag känner mig alltid väldigt trög och långsam i tanken.

8. STRESSKÄNSLIGHET

Har du haft svårt att hantera stress, alltså att göra många saker samtidigt och under tidspress?

0	Jag klarar stress lika bra som vanligt**.**
0.5	
1	Jag är mer lättstressad, men bara i krävande situationer som jag tidigare klarade av.
1.5	
2	Jag blir stressad lättare än vanligt. Det krävs mindre stressade situationer än tidigare för att jag skall känna av det.
2.5	
3	Jag har väldigt lätt för att bli stressad. Så fort som situationen är ovan eller påfrestande känner jag mig stressad.

9. ÖKAD KÄNSLOSAMHET

Har du ovanligt lätt för att gråta? Faller du lätt i gråt när du t.ex. ser en sorglig film eller när du pratar med dina anhöriga. Om det nyligen hänt något ovanligt (t.ex. en olycka eller sjukdom) skall du försöka bortse från det.

0	Jag är inte mera känslig än tidigare.
0.5	
1	Jag har en ökad känslighet som fortfarande är naturlig för mig. Jag har lätt att börja gråta eller får tårar i ögonen, men det händer bara för ting som engagerar mig starkt
1.5	
2	Min känslighet är besvärande eller generande. Det händer att jag börjar gråta även för saker jag egentligen inte bryr mig om. Jag försöker undvika vissa situationer på grund av detta.
2.5	
3	Min känslighet orsakar stora problem för mig. Den stör min dagliga relation även i den nära familjen och gör att jag har svårt att klara mig utanför hemmet.

10. IRRITABILITET ELLER ”KORT STUBIN”

Är du ovanligt lättretad eller lättirriterad för saker som du tidigare tyckte var bagateller.

0	Jag är inte mer lättretad eller irritabel än tidigare.
0.5	
1	Jag blir lätt irriterad men det går fort över.
1.5	
2	Jag blir väldigt fort irriterad för bagateller eller för saker som andra inte bryr sig om.
2.5	
3	Jag reagerar med en intensiv ilska, eller känsla av raseri. Jag har svårt att behärska den.

11. ÖVERKÄNSLIGHET FÖR LJUS

Är du känslig för starkt ljus?

0	Jag har ingen ökad känslighet för ljus.
0.5	
1	Ibland kan jag ha svårt för starkt ljus som t.ex. solljus, reflexer från snö eller vatten eller glasrutor, starka lampor inomhus, men det kan lätt avhjälpas, t.ex. med solglasögon.
1.5	
2	Jag är så känslig för ljus att jag föredrar att uträtta mina dagliga aktiviteter i dämpad belysning. Jag har svårt att gå ut utan solglasögon.
2.5	
3	Min ljuskänslighet är så svår att jag inte kan gå ut utan solglasögon. Jag har ständigt neddragna gardiner (eller motsvarande).

För mer information om MFS, se www.mf.gu.se

12. ÖVERKÄNSLIGHET FÖR LJUD

Är du känslig för ljud?

0	Jag besväras inte av någon ökad känslighet för ljud.
0.5	
1	Ibland kan jag ha svårt för starka ljud (t.ex. musik, ljud från TV eller radion, eller plötsliga oväntade ljud), men det kan lätt åtgärdas genom att jag sänker ljudnivån. Min ljudkänslighet stör mig inte i mitt dagliga liv.
1.5	
2	Jag är klart ljudöverkänslig. Jag måste undvika starka ljud eller dämpa (t ex med öronproppar) dem för att klara mitt dagliga liv.
2.5	
3	Min ljudkänslighet är så svår att jag har svårt att klara mig hemma trots ljuddämpning.

13. MINSKAD NATTSÖMN

Sover du dåligt om nätterna? Om din nattsömn har ökat, skattas detta som ”0”. Om du tar sömntabletter och sover normalt, skattas detta som 0.

0	Jag sover inte sämre än vanligt.
0.5	
1	Jag har lite svårt att somna eller min sömn är kortare, ytligare eller oroligare än normalt.
1.5	
2	Jag sover minst två timmar mindre än vanligt, och vaknar ofta på natten även utan yttre störningar.
2.5	
3	Jag sover mindre än två till tre timmar per natt.

14. ÖKAD SÖMN

Sover du mer och/eller djupare än vanligt? Om din sömn har minskat markeras detta som ”0”.
Obs! Räkna in även sömn dagtid.

0	Jag sover inte mer än vanligt
0.5	
1	Jag sover längre eller tyngre, men inte så mycket som två timmar mer än vanligt, inklusive tupplurar.
1.5	
2	Jag sover längre eller tyngre. Minst två timmar längre än vanligt, inklusive tupplurar.
2.5	
3	Jag sover längre eller tyngre. Minst 4 timmar längre än vanligt och behöver dessutom sova dagtid.

15. DYGNSVARIATIONER

Finns det tider på dygnet då de besvär vi frågat om (t ex trötthet, koncentration) är bättre eller sämre? Med regelbundet menar vi här åtminstone 3-4 dagar i veckan.

0	Jag har inte märkt att mina besvär är regelbundet bättre eller sämre vid vissa tider Eller jag har inga särskilda besvär.
1	Det finns en klar skillnad mellan olika tider på dygnet. Jag kan säga att jag kommer att må bättre vid en viss tid, och sämre vid andra tider.
2	Jag mår dåligt under all tid under hela dygnet.

Om det finns en dygnsvariation:

När mår du som *bäst?* Förmiddagen | Eftermiddagen | Kvällen | Natten

När mår du som *sämst*? Förmiddagen | Eftermiddagen | Kvällen | Natten

För mer information om MFS, se www.mf.gu.se

mMRC-skalan

Denna skala anger i steg 0-4 den tröskelansträngning vid vilken andningsbesvär inträder.

0	Jag blir bara andfådd när jag anstränger mig rejält, inte när jag tar en snabb promenad eller går i uppförsbacke
1	Jag blir andfådd när jag tar en snabb promenad eller går i uppförsbacke
2	Jag blir andfådd när jag går på slät mark i samma takt som en annan i min ålder
3	Jag blir så andfådd när jag går på slät mark att jag måste stanna upp trots att jag själv bestämmer takten
4	Jag blir andfådd när jag tvättar mig eller klär på mig

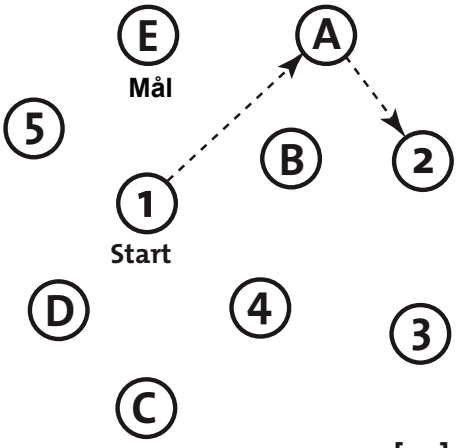
MRC–skalan (Medical Research Council Scale)
Mahler D & Wells C. Evaluation of clinical methods for rating dyspnea.Chest1988;93:580-6

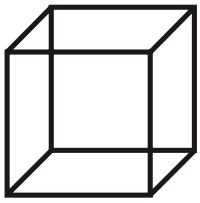
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Svensk version / Swedish version

NAMN : **Födelsedatum :**
Utbildning : **DATUM:**
Kön :

VISUOSPATIAL / EXEKUTIV





Rita av kuben

[ ] [ ]

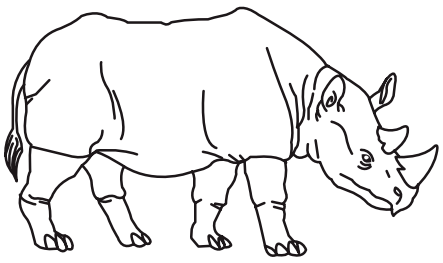
Rita en KLOCKA (tio över elva) (tre poäng)

[ ] Kontur [ ] Siffror [ ] Visare

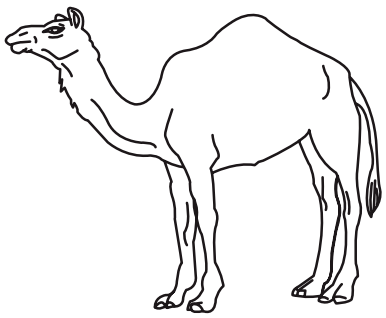
Poäng ___/5

BENÄMNING

[ ]



[ ]



[ ]

___/3

MINNE

Läs orden, försökspersonen ska återge dem. Gör 2 försök. Prova igen efter 5 minuter.

	STOL	PLÅNBOK	TÅNG	MUNSPEL	SAX
Försök 1					
Försök 2					

Inga poäng

UPPMÄRKSAMHET

Läs en nummerlista (1 siffra/sek) Försökspersonen ska repetera i samma ordning [ ] 2 1 8 5 4

Försökspersonen ska repetera baklänges [ ] 7 4 2

___/2

Läs bokstäverna. Försökspersonen knackar i bordet var gång "A" läses. (inga poäng för mer än två fel)

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Upprepa subtraktion av 7 från 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4-5 korrekta: 3p, 2-3 korrekta: 2p, 1 korrekt: 1p, 0 korrekta: 0p

___/3

SPRÅK

Upprepa: "Jag vet att det är Johan som ska få hjälp idag" [ ]

"Katten gömde sig alltid under soffan när det var hundar i rummet" [ ]

___/2

Ordflöde / Ange på en minut så många ord som möjligt som börjar på bokstaven F [ ] _____ **(N ≥ 11 ord)**

___/1

ABSTRAKTION

Likhet mellan t.ex. banan - apelsin = frukt [ ] **tåg - cykel** [ ] **klocka - linjal**

___/2

FÖRDRÖJD ÅTERGIVNING

	Måste komma ihåg orden utan hjälp	STOL [ ]	PLÅNBOK [ ]	TÅNG [ ]	MUNSPEL [ ]	SAX [ ]
Valfritt	Hjälp med kategori					
	Hjälp med alternativ					

Poäng endast för korrekta svar utan hjälp.

___/5

ORIENTERING

[ ] **Datum** [ ] **Månad** [ ] **År** [ ] **Dag** [ ] **Plats** [ ] **Ort**

___/6

Svensk översättning: Thomas Lindén MD

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Lägg till 1p om max 12 års utbildning

Administrerat av: _____

Frågeformulär dysfunktionell andning

Ringa in den siffra som bäst beskriver hur ofta Du besväras av nedanstående symtom:

	Aldrig	Sällan	Ibland	Ofta	Mycket ofta
Bröstsmärta	0	1	2	3	4
Känsla av att vara spänd	0	1	2	3	4
Dimsyn	0	1	2	3	4
Yrsel	0	1	2	3	4
Förvirring eller overklighetskänsla	0	1	2	3	4
Snabb eller djup andning	0	1	2	3	4
Andfåddhet	0	1	2	3	4
Tryckkänsla över bröstet	0	1	2	3	4
Uppblåst/uppsvälld i magen	0	1	2	3	4
Stickningar i fingrar och händer	0	1	2	3	4
Svårt att andas eller ta djupa andetag	0	1	2	3	4
Stelhet eller krampkänsla i fingrar och händer	0	1	2	3	4
Stramhet/spänning kring munnen	0	1	2	3	4
Kalla händer eller fötter	0	1	2	3	4
Hjärtklappning	0	1	2	3	4
Oro/ängslan	0	1	2	3	4

Supplemental Appendix 2. Instrument - COMPASS 31

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?

1 Yes
2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?

1 Rarely
2 Occasionally
3 Frequently
4 Almost Always

3. How would you rate the severity of these feelings or symptoms?

1 Mild
2 Moderate
3 Severe

4. In the past year, have these feelings or symptoms that you have experienced:

1 Gotten much worse
2 Gotten somewhat worse
3 Stayed about the same
4 Gotten somewhat better
5 Gotten much better
6 Completely gone

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?

1 Yes
2 No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)

1 Hands
2 Feet

7. Are these changes in your skin color:

1 Getting much worse
2 Getting somewhat worse
3 Staying about the same
4 Getting somewhat better
5 Getting much better
6 Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?

1 I sweat much more than I used to
2 I sweat somewhat more than I used to
3 I haven't noticed any changes in my sweating
4 I sweat somewhat less than I used to
5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

1 Yes
2 No

10. Does you mouth feel excessively dry?

1 Yes
2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

1 I have not had any of these symptoms
2 Getting much worse
3 Getting somewhat worse
4 Staying about the same
5 Getting somewhat better
6 Getting much better
7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?

1 I get full a lot more quickly now than I used to
2 I get full more quickly now than I used to
3 I haven't noticed any change
4 I get full less quickly now than I used to
5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?

1 Never
2 Sometimes
3 A lot of the time

14. In the past year, have you vomited after a meal?

1 Never
2 Sometimes
3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?
    1 Never
    2 Sometimes
    3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?
    1 Yes
    2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per month
    4 Constantly

18. How severe are these bouts of diarrhea?
    1 Mild
    2 Moderate
    3 Severe

19. Are your bouts of diarrhea getting:
    1 Much worse
    2 Somewhat worse
    3 Staying the same
    4 Somewhat better
    5 Much better
    6 Completely gone

20. In the past year, have you been constipated?
    1 Yes
    2 No (if you marked No, please skip to question 24)

21. How frequently are you constipated?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per month
    4 Constantly

22. How severe are these episodes of constipation?
    1 Mild
    2 Moderate
    3 Severe

23. Is your constipation getting:

1 Much worse
2 Somewhat worse
3 Staying the same
4 Somewhat better
5 Much better
6 Completely gone

24. In the past year, have you ever lost control of your bladder function?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

25. In the past year, have you had difficulty passing urine?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

26. In the past year, have you had trouble completely emptying your bladder?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?

1 Never (if you marked Never, please skip to question 29)
2 Occasionally
3 Frequently
4 Constantly

28. How severe is this sensitivity to bright light?

1 Mild
2 Moderate
3 Severe

29. In the past year, have you had trouble focusing your eyes?

1 Never (if you marked Never, please skip to question 31)
2 Occasionally
3 Frequently
4 Constantly

30. How severe is this focusing problem?

1 Mild
2 Moderate
3 Severe

31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:

1 I have not had any of these symptoms
2 Much worse
3 Somewhat worse
4 Staying about the same
5 Somewhat better
6 Much better
7 Completely gone

Patientnummer: _____

DAGBOK FÖR DELTAGANDE I PROLIFIC POST-AKUT COVID SYNDROM STUDIEN

Fyll i (kryssa) varje gång du tar studiemedicin. Du ska ta morgon och kväll med 12 timmars mellanrum. Skulle du glömma att en dos och det har gått mer än 8 timmar så ska du inte ta den glömda dosen utan du väntar till nästa schemalagda dos. Om du inte tar medicinen vid någon/några tillfällen ange det i kommentarrutan nedan.
Spara alla tablettkartor och burkar, tomma eller med överbliven medicin, och ta med dem på besöket dag 16.
Ta även med denna dagbok då och lämna till studiepersonalen.

Dag	**2 tabletter Paxlovid eller placebo + 1 tablett ritonavir**	**2 tabletter Paxlovid eller placebo + 1 tablett ritonavir**	Kommentarer *(t.ex. om dosen inte tas och varför)*
1	På morgonen ☐	På kvällen ☐	
2	På morgonen ☐	På kvällen ☐	
3	På morgonen ☐	På kvällen ☐	
4	På morgonen ☐	På kvällen ☐	
5	På morgonen ☐	På kvällen ☐	
6	På morgonen ☐	På kvällen ☐	
7	På morgonen ☐	På kvällen ☐	
8	På morgonen ☐	På kvällen ☐	

Patientnummer: _____

Dag	2 tabletter Paxlovid eller placebo + 1 tablett ritonavir	2 tabletter Paxlovid eller placebo + 1 tablett ritonavir	Kommentarer *(t.ex. om dosen inte tas och varför)*
9	På morgonen ☐	På kvällen ☐	
10	På morgonen ☐	På kvällen ☐	
11	På morgonen ☐	På kvällen ☐	
12	På morgonen ☐	På kvällen ☐	
13	På morgonen ☐	På kvällen ☐	
14	På morgonen ☐	På kvällen ☐	
15	På morgonen ☐	På kvällen ☐	