A double-blind, randomized, sham-controlled, exploratory trial of immunoadsorption in patients with chronic fatigue syndrome (CFS) including patients with Post-acute COVID-19 CFS (PACS-CFS)

Statistical Analysis Plan

Version *2,* of November 26, 2025

Investigational medicinal product: Therapeutic apheresis with immunoadsorption

Comparator: sham Immunoadsorbtion (IA) (apheresis unit with a pre-saturated adsorber with immunoglobulins)

Indication: Post-COVID ME/CFS and ME/CFS

Sponsor: Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin

Financial support: Bfarm, Miltenyi

Study registry identification: ClinicalTrials.gov ID NCT05710770

Development phase: Post-Marketing (Exploratory), Phase IV

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1 Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
BMI	Body Mass Index
BP	blood pressure
BVMT-R	Brief Visuospatial Memory Test - Revised
CCC 2003	Canadian Consensus Criteria 2003
CFS	chronic fatigue syndrome
CI	confidence interval
CRO	Contract Research Organisation
CRP	C-reactive protein
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
EAS	effectiveness analysis set
ECG	electrocardiogram
EMG	electromyogram
EOS	end-of-study visit
EOT	end-of-treatment visit
eCRF	electronic Case Report Form
FAS	full analysis set
FAZ	Foveal Avascular Zone
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GCIPL	Ganglion Cell-Inner Plexiform Layer
IA	Immunoadsorption
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
LPS 50+	Leistungsprüfungssystem (performance testing system) for 50 to 90 years old
mITT	modified intention-to-treat set
MBL	mannose binding lectin
ME	myalgic encephalomyelitis
MoCA	Montreal Cognitive Assessment
NFL	neurofilament
OCB	oligoclonal IgG bands
OCT	Optical coherence tomography
PACS-CFS	Post-acute COVID-19 chronic fatigue syndrome
PBMC	peripheral blood mononuclear cells
PEM	post exertional malaise
PI	Principal Investigator
POTS	Postural Tachycardia Syndrome
PPS	per-protocol set
PR	pulse rate
PROMIS	patient-reported outcomes for health-related quality of life

pRNFL	peripapillary Retinal Nerve Fiber Layer
Qalb	CSF/serum quotient of total albumine
QoL	quality of life
RWT	Regensburger Wortflüssigkeits-Test (Regensburg Word Fluency Test)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety analysis set
SDMT	Symbol Digit Modalities Test
SoA	schedule of assessments
TAP	Test of attentional performance
Temp	body temperature (tympanic)
TMT-A / B	Trail Making Test A / B
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VLMT	verbal learning and memory test
WAIS-IV	Wechsler adult intelligence scale
WST	Wortschatz-Test (Vocabulary test)

2 Background

There is an accumulation of evidence that a post-viral autoimmune reaction with the presence of autoantibodies targeting different neuronal tissues is involved in the pathogenesis of CFS/ME. Similarly, elevations of neurotransmitter receptor antibodies in patients with PACS- CFS have been observed. Furthermore, IA has shown clinical improvement in various types of autoimmune diseases associated with autoantibodies. Based on these findings, immunoadsorption may offer an effective treatment option for patients with CFS/ME, including patients with PACS-CFS. Results from first small studies indicate a beneficial therapeutic effect of IA in patients suffering from CFS/ME (Scheibenbogen et al., 2018; Tölle et al., 2020).

However, placebo-controlled trials investigating the effectiveness of IA in patients suffering from CFS/ME, including patients with PACS-CFS are lacking, although the procedure is generally well tolerated and safe. Having in mind the current number of confirmed COVID-19 cases, we might be facing a huge number of chronically ill severely disabled patients in the near future, underlining the ethical and economic urgency to develop effective therapeutic options for this devastating condition. Already before the association of the pandemic with a possible large outbreak of the disease became evident, an EU resolution from June 2020 indicated that more research is needed into this complex illness, supporting projects focusing on diagnostic tests and treatment in CFS/ME including PACS-CFS.

3 Trial objective

Due to the high number of patients suffering from CFS/ME, including PACS-CFS, the huge economic burden related to it, and the profound impairment of affected patients, there is an immense medical need to effectively treat patients with CFS/ME, including PACS-CFS. **Therefore, in the present RCT, the effect of IA will be examined for the treatment of CFS/ME**. Based on the assumed autoimmune pathogenesis underlying severe CFS/ME, it is tempting to hypothesize that this patient population will show clinical improvement (measured by the chalder fatigue score) after five treatments with immunoadsorption.

4 Trial design

This is a double-blinded, randomized, sham-controlled post-marketing (exploratory) trial to evaluate the therapeutic effect of five cycles of immunoadsorption every other day in 66 patients with CFS/ME, including patients with PACS-CFS. Two patient groups will be included (2:1), one receiving IA, one receiving a sham-apheresis.

A screening visit is planned up to max. 3 weeks (Day -42 to Day -21) before enrolment in the study to screen patients for eligibility (including blood and urine samples for safety parameters such as viral serology, pregnancy, drug and alcohol tests) and to assess demographics and medical history (table 1). In addition, cerebrospinal fluid and blood samples are taken to test for autoantibodies and markers of neurodegeneration or neuroinflammation. If a lumbar puncture was performed as part of the clinical routine within 6 months prior to the screening visit, it will not be repeated at screening. Patient reported outcome measurements such as Chalder Fatigue Scale, physical and autonomic function, quality of life and (in case of PACS-CFS) Post-COVID-19 Functional Status Scale questionnaires as well as Cognitive (MoCA and SDMT), physical (hand grip strength evaluation, 6MWT), and autonomic (Schellong-Test) assessments are performed at

screening or baseline visit. At baseline visit a detailed neuropsychological examination, and an assessment of physical function will be conducted.

Baseline assessments will be performed between Day -20 and -1 and in any case before the first IA cycle. These include a general and neurological physical examination assessing vital signs, ECG, body weight, repeating safety check for pregnancy. Blood samples for chemistry, hematology, coagulation and immunoglobulin titers are taken.

Patients are randomized either on Day -1 or Day 1 and a peripheral venous access (or Shaldon catheter) is implemented before the first IA cycle on Day 1 or Day 2 (Figure 1). Patients will be hospitalized at the clinical site from Day 1 to Day 9 or Day 10 and receive five IA treatments and medical visits including monitoring of coagulation every other day (i.e., on Days 1, 3, 5, 7, and 9 OR on Days 2, 4, 6, 8, and 10). If delays occur, the option to extend the in-hospital stay is available. Immunoadsorption can be postponed by one or more days.. Daily study nurse visits are scheduled including control of vital signs as well as questioning for AE(s).

After the last IA cycle, a blood sample for immunoglobulin titers is collected, the peripheral venous access (or Shaldon catheter) is removed and patients are discharged from the hospital if the investigator has no concerns. At EOT visit, patients will also complete the Chalder Fatigue Scale (Chalder et al., 1993), Fluge Score (Fluge et al., 2011; Fluge et al., 2015), and PEM questionnaires. In addition, patients will be instructed how to complete all of the requested questionnaires at home at follow up time points. If the IA treatments are performed according to the planned schedule, the end of treatment visit (EOT) will take place on Day 10. However, the EOT visit may vary between Day 9 and 12. If treatment needs to be terminated, the EOT can occur as early as day 2. In such cases, all examinations originally scheduled for day 10 will be conducted on the corresponding day. In addition, two of the four follow-up visits scheduled at month 2 (Day 60) and month 6 (Day 180; EOS, End of Study visit) will take place at the neurological wards and outpatient clinics respectively. Patients will be asked to bring all requested questionnaires (including Chalder Fatigue Scale), which they completed at home, to both follow-up visits, where further assessments and laboratory tests will be conducted. An optional second cerebrospinal fluid sample may also be taken on Day 60. The remaining two follow-up visits, scheduled at month 1 (Day 30) and month 4 (Day 120), will be conducted via telephone. During these visits, patients will be asked about any adverse events (AEs), concomitant medications, and questionnaires.

Figure 1 Schematic illustration of the study design

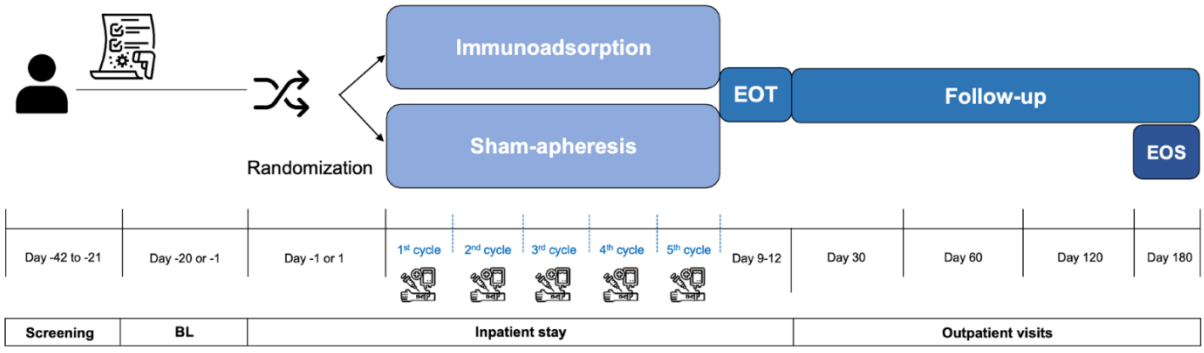

Table 1: Schedule of Assessments

Period/Visit name	**SCR**	**BL[6)]**	**Treatment period (inpatient)**										**Follow-up**			
											EOT	**US**				**EOS**
Study Days	**-42 to -21**	**-20 to -1**	**1**	**2[8)]**	**3[8)]**	**4[8)]**	**5[8)]**	**6[8)]**	**7[8)]**	**8[8)]**	**9-12[8)]**		**30*[6)]**	**60[6)]**	**120*[6)]**	**180[6)]**
Time windows (days)													+/- 7	+/- 7	+/- 7	+/- 7
Status																
Admission to hospital			X													
Discharge from hospital											X					
Discharge from study																X
History																
Informed consent	X															
Inclusion/Exclusion Criteria	X															
Demographics	X															
Medical & Medication History	X															
Safety Assessments																
Neurologic and general physical examination	X	X									X			X		X
Electrocardiogram (ECG)	X	X									X					
Vital signs (BP, PR, and Temp)	X	X	X	X	X	X	X	X	X	X	X					X
Body height	X															
Body weight, BMI	X										X			X		X
Blood pregnancy	X	X														
Urine test (dip sticks, drugs), alcohol test	X															
Blood samples for chemistry, hematology	X [(5)]	X									X			X		X
Thyroid hormone (TSH)	X															
QuantiFERON ®-TB-Gold Plus-Test[5)] and Viral Serologies[5)]	X															

Period/Visit name	**SCR**	**BL[6)]**	**Treatment period (inpatient)**										**Follow-up**			
											EOT	**US**				**EOS**
Study Days	**-42 to -21**	**-20 to -1**	**1**	**2[8)]**	**3[8)]**	**4[8)]**	**5[8)]**	**6[8)]**	**7[8)]**	**8[8)]**	**9-12[8)]**		**30*[6)]**	**60[6)]**	**120*[6)]**	**180[6)]**
Time windows (days)													+/- 7	+/- 7	+/- 7	+/- 7
Safety Assessments (cont.)																
Blood samples for monitoring of coagulation	X [(5)]	X									X			X		
Monitoring of IA (IgG)			Before each and after last IA treatment													
Blood samples for immunoglobulin titers (IgA, IgG, IgM)		X									X			X		X
Adverse event questioning		X	< ---------- >													
Concomitant Medications		X	< ---------- >													
Procedures																
Randomization		X														
PVA or Shaldon catheter implementation			X													
Chest X-ray after Shaldon catheter implementation (if applicable)			X													
Cranial MRI		X[9)]												X		
TheraSorb - Ig omni 5 adsorber cycles (IA active or IA sham)			5 IA treatments every other day													
OCT		X												X		
Removal of Shaldon catheter after last IA cycle											X					
Lumbar puncture samples[5)]	X													X[3)]		
Blood samples for: - autoantibodies[5] - inflammatory markers (CRP, Ferritin, MBL, C3, C4), LDH, ACE - SARS-CoV-2 antibody-status	X													X		X
SARS-CoV-2 PCR from nasopharyngeal swab	X	X														
SARS-CoV-2 Antigen rapid test	As required by current hospital regulations															

Period/Visit name	**SCR**	**BL[6)]**	**Treatment period (inpatient)**										**Follow-up**			
											EOT	**US**				**EOS**
Study Days	**-42 to -21**	**-20 to -1**	**1**	**2[8)]**	**3[8)]**	**4[8)]**	**5[8)]**	**6[8)]**	**7[8)]**	**8[8)]**	**9-12[8)]**		**30*[6)]**	**60[6)]**	**120*[6)]**	**180[6)]**
Time windows (days)													+/- 7	+/- 7	+/- 7	+/- 7
Questionnaires																
Chalder Fatigue Scale	X[4)]										X		X[4)]	X[4)]	X[4)]	X[4)]
Fluge Score		X[4)]											X[4)]	X[4)]	X[4)]	X[4)]
Assessment of post exertional malaise		X[4)]									X		X[4)]	X[4)]	X[4)]	X[4)]
Bell Score	X[4)]										X		X[4)]	X[4)]	X[4)]	X[4)]
Quality of life assessment (PROMIS)		X[4)]											X[4)]	X[4)]	X[4)]	X[4)]
Physical function SF-36		X[4)]									X		X[4)]	X[4)]	X[4)]	X[4)]
Post-COVID-19 Functional Status Scale (PACS- CFS patients only)		X[4)]											X[4)]	X[4)]	X[4)]	X[4)]
COMPASS-31		X[4)]											X[4)]	X[4)]	X[4)]	X[4)]
Physical assessment (-), hand grip strength)	X										X			X		X[3)]
6 Minute Walking Test (6MWT)		X												X		
Schellong Test		X									X			X		X[3]
Detailed neuropsychiatric examination (optional), VLMT, BMVT-R, WAIS-IV, TAP, LPS 50+, TMT-A / B, RWT, WST		X												X		
Cognitive assessment (MoCA, PROMIS Cognitive Function Short Form 4a, SDMT)		X												X		

Abbreviations: BMI = Body Mass Index [kg/m2]; BP = blood pressure; OCB = oligoclonal IgG bands; PR = pulse rate; CRP = C-reactive protein; MBL = Mannose binding lectin, Qalb = CSF/Serum quotient of total albumine; EOS = end-of-study visit; EOT = end-of-treatment visit; PBMC = Peripheral Blood Mononuclear Cells; PVA = Peripheral Venous Access; Temp. = body temperature (tympanic); TSH = Thyroid-stimulating hormone; US = unscheduled visit.

*No on-site visit

[3)] Only if requested by the investigator

[4)] Completion by the patient at home

[5)] If not available in the 6 months prior to screening

[6] Assessments can be done on several days; site personnel will schedule appointments with patients
[7] In case of using results of lumbar puncture from clinical routine (up to 6 months prior to screening) these parameters cannot be collected at screening or baseline and therefore do not fall under a protocol deviation
[8] If EOT occurs either before or after day 9-12, any examinations that were originally scheduled to take place on days 9-12, will be rescheduled to coincide with EOT that was determined at the time
[9] at day -60 to -1

4.1 Inclusion and exclusion criteria

Table 2: Inclusion Criteria

Nr.	Inclusion Criterion	Variable	Values
1	Male and female subjects ≥18 years and < 65 years at time of informed consent	inex_0020	yes/no
2	Body weight of ≥ 45 kilograms (kg) and ≤100 kg and must have a body mass index (BMI) within the range of 16-39.9 kg/m².at screening. BMI is calculated as Body weight (kg) / [Height (m)]^2	inex_0030	yes/no
3	Signed and dated informed consent prior to any study-mandated procedure	inex_0040	yes/no
4	Chronic fatigue determined by the Chalder Fatigue Scale at screening	inex_0050	yes/no
5	Diagnosis of chronic fatigue syndrome /myalgic encephalomyelitis (CFS/ME) under the 2003 Canadian Consensus Criteria (CCC) for ME/CFS syndrome and prolonged post-exertional malaise (PEM) including patients with CFS/ME due to Covid-19 (PACS-CFS) at screening. These criteria will be assessed by obtaining clinical histories and using appropriate symptom checklists.	inex_0060	yes/no
6	Bell Score ≥ 20 and ≤ 50	inex_0070	yes/no

Table 3: Exclusion Criteria

Nr.	Exclusion Criterion	Variable	Values
1	Severe arterial hypotension (systolic BP < 100 mmHg, diastolic BP < 60 mmHg) at screening	inex_0080	yes/no
2	Moderate to severe renal insufficiency (e.g., estimated glomerular filtration rate < 40 mL/min/1.73 m2, calculated by the Cockcroft-Gault formula or similar equation)	inex_0090	yes/no
3	Cardiac insufficiency with an LVEF lower than 40% and/or uncontrolled cardiac arrhythmia	inex_0100	yes/no
4	Coronary heart disease	inex_0110	yes/no
5	Currently medication with ACE inhibitors and unable to switch to another antihypertensive drug class within 2 weeks prior to baseline visit (treatment with ACE inhibitors not allowed within 24 hours prior to immune adsorption)	inex_0120	yes/no
6	Malignant disease within the last 5 years	inex_0130	yes/no
7	Clinically meaningful laboratory abnormalities at screening that would affect subject safety, as determined and documented by the investigator including but not limited to: Abnormal hematology: Hemoglobin < 8.0 g/dL, White Blood Cells count < 2.5/nL or >12/nL, Platelet count < 100/nL Abnormal liver function tests: ASAT/ALAT > 3 x higher than upper limit of reference (ULN), GGT, alkaline phosphatase > 3 x ULN,	inex_0140	yes/no

	Total bilirubin > 2.0 mg/dL or PT-INR > 1.5 Note: Any parameter exceeding the above defined ULN should be re-checked once more as soon as possible, and in each case, prior to enrollment/randomization, to rule out lab error.		
8	Any comorbidity bearing risk that patient might not tolerate treatment as judged by investigator	inex_0150	yes/no
9	Medical, psychiatric or other conditions rendering patient incapable to understand the patient information and to give informed consent and maintain compliance during the trial	inex_0160	yes/no
10	Fatigue duration for more than 5 years	inex_0170	yes/no
11	Patients unwilling to have pseudonymized data recorded, analyzed and anonymously published	inex_0180	yes/no
12	Participation in another clinical interventional trial within the last 6 months (or five half- lives, if longer than 6 months) previous to informed consent	inex_0190	yes/no
13	Any surgical procedure requiring general anesthesia within 3 months prior to screening, or planned elective surgery during the study	inex_0200	yes/no
14	Inmates of prisons or patients in psychiatric wards, or other state institutions	inex_0210	yes/no
15	Employee of the Sponsor, investigator or study site	inex_0220	yes/no
16	Patient unable or unwilling to comply with study restrictions or procedures as described in Section 4.	inex_0230	yes/no
17	Patient with known substance abuse or drug dependence currently or within one year prior to study participation, excluding nicotine and caffeine. This is determined through clinical history at screening.	inex_0240	yes/no
18	Acute critical illness (intubation, ongoing Intensive Care Unit stay at the point of study involvement)	inex_0250	yes/no
19	Acute or severe psychiatric disease (such as dementia, eating disorders, major unstable depression, bipolar affective disorder, schizophrenia, somatization disorders). Note: Follow-up by professionals will be offered when indicated.	inex_0260	yes/no
20	Presence of other conditions or differential diagnosis better explaining the symptoms of the patient then the suspected ME/CFS, i.e., neuroendocrine diseases (such as thyroiditis or diabetes)	inex_0270	yes/no
21	Ongoing immunomodulatory or immunosuppressive therapy or prior treatment with Rituximab (anti-CD20- antibody).	inex_0280	yes/no
22	Clinical conditions that prohibit transitory volume changes or loss of plasma constituents other than Ig (e.g., serum albumin, electrolytes), equivalent to a plasma loss of about 10% per 1-fold processed plasma patient volume.	inex_0290	yes/no
23	Indications that prohibit anticoagulation using Heparin and/or Anticoagulant Citrate Dextrose (ACD-A) solutions	inex_0300	yes/no
24	Severe Hypercoagulability	inex_0310	yes/no

25	Infection requiring hospitalization or intravenous administration of antibiotics/antimycotics or disease requiring administration of antivirus drugs (e.g., herpes zoster) within 4 weeks before starting the study treatment.	inex_0320	yes/no
26	Acute infection with Cytomegalie Virus (CMV) or Eppstein-Barr Virus (EBV)	inex_0330	yes/no
27	History of tuberculosis or evidence of active tuberculosis infection (positive QuantiFERON®-TB Gold Test).	inex_0340	yes/no
28	Tested positive for any of the following in the Screening Phase: Human Immunodeficiency Virus (HIV), hepatitis B virus surface antigen (HBs antigen), hepatitis B virus core antibody (HBc antibody), and hepatitis C virus. Note: Patients positive for anti-HBs after Hep B vaccination but negative for hBsAg and anti-HBc are eligible (Hepatitis B serology: Appendix II).	inex_0350	yes/no
29	Positive SARS-CoV-2 PCR test result at screening or baseline visit	inex_0360	yes/no
30	Severe immune deficiencies (e.g., AIDS)	inex_0370	yes/no
31	Suspected allergies against camelid antibodies or agarose	inex_0380	yes/no
32	Pregnancy or breastfeeding at screening	inex_0390	yes/no
33	Vaccination with live vaccines within 12 weeks prior to randomization and during study participation until 12 weeks after completion of immunoadsorption treatment	inex_0400	yes/no
34	Non-live vaccination including vaccination against SARS-CoV-2 within 2 weeks prior to randomization and during the IA treatment period. Note: During the follow-up period, vaccination against SARS-CoV-2 will be allowed if in line with local regulations and if there are no concerns by the investigator.	inex_0410	yes/no
35	Positive serum alcohol test	inex_0420	yes/no
36	Positive test for drugs of abuse as per local standard at screening.	inex_0430	yes/no
37	Donation of blood over 500 mL or 200 mL of plasma within 3 months prior to screening	inex_0440	yes/no
38	Patient who has previously participated in this study and completed IA treatment	inex_0450	yes/no
39	Any comorbidity bearing risk that patient might not tolerate treatment as judged by investigator	inex_0460	yes/no

4.2 Power consideration

In this study, a total of 66 patients (allocated in a 2:1 ratio: immunoadsorption (IA) group: 44 patients vs. sham group: 22 patients) will be included. Limited data from 2 small pilot studies, investigating IA in 10 patients with CFS/ME, is available to date. Consequently, data is lacking about precise effects, clinical outcomes, and effect sizes in this group of patients.

The justification of the sample size is based on the primary endpoint (change from baseline of the Chalder Fatigue Scale). The Chalder Fatigue Scale measures fatigue in patients using the overall score (range from 0 to 33) derived from a questionnaire with 11 questions (each scored from 0 to 3, see (Cella & Chalder, 2010; Chalder et al., 1993) for more details). Based on Cella & Chalder 2010, the mean score in a population of patients

suffering from CFS is 24.4 (with a standard deviation of 5.8) and for a healthy sample a mean value of 14.2 (with a standard deviation of 4.6) was observed. A difference of 10 points cannot be expected in this study since only patients suffering from CFS are included. In the systematic review of Nordin et al. 2016 a minimal important difference for the global change ranges between 2.3 and 3.3.

In an earlier study (Cleare et al. 1999) examining the efficacy of various treatments for CFS/ME, the difference in means of the Chalder Fatigue Scale was 4.5 points (Likert score) between the active and the control group. However, no sham-controlled study evaluating the effect of IA on CFS/ME has been conducted so far, but first pilot studies suggest a positive effect of IA in patients with CFS/ME.

To explore the expected precision obtained from the planned study, the distance from the mean group difference of the primary endpoint (change from baseline in Chalder Fatigue Scale) to the limits is calculated using its 95% confidence interval (CI) and a common standard deviation of 5.8 as provided for patient with CFS/ME in (Cella & Chalder, 2010). Using these assumptions and the given group sample sizes of 44 patients and 22 patients, the distance from mean to the limits of the 95%-CI is 3.03 points in the Chalder Fatigue Scale. Assuming an expected drop-out rate of 20% (resulting in expected group sample sizes of 35 and 18 patients, respectively) the distance from the mean to the limits of the 95%-CI increases to 3.37 points in the Chalder Fatigue Scale.

5 Analysis sets

5.1 Definitions

The modified **full analysis set (FAS)** consists of a modified intention-to-treat (mITT) population and will include all patients that were randomized and underwent at least one IA cycle (active or sham IA intervention).

The **per-protocol set (PPS)** comprises all subjects who completed five cycles of their assigned intervention (IA or sham IA) as planned and who completed the study without critical protocol deviations.

The **safety analysis set (SAS)** will include all patients that underwent at least one IA cycle (active or sham IA intervention). Patients will be analyzed according to the intervention they received.

5.2 Application

The primary analysis is performed using the full analysis set (FAS), including the estimated values from multiple imputations for missing values. An analysis of the primary outcome using the PPS is used as a sensitivity analysis. All safety analyses will be done using the SAS (Safety analysis set).

6 Trial centres

This is a single centre study with 66 patients.

7 Analysis variables

7.1 Demography and baseline characteristics

The following variables are assessed at baseline as additional patient characteristics:

Table 4: Demography and baseline characteristics

Characteristic	Variable	Values
demographics		
Age at inclusion (years)	dm_0010	number
sex	dm_0020	male, female, diverse
Body weight (kg)	dm_0031	number
Body height (cm)	dm_0032	number
BMI (kg/m^2)	dm_0033	number
Employment status	dm_0040	employed, self-employed, currently unable to work, pension, student, unknown
Educational achievement	dm_0050	No school-leaving certificate, lower secondary school leaving certificate (Hauptschule), higher secondary school leaving certificate (Realschule), grammar school (Gymnasium), completed vocational training, degree of a university of applied sciences, University, unknown
Self-reported predominant race	dm_0061 / dm_0062 (other specified)	Caucasian, African, Asian, Unknown, Other, please specify
Medical history		
Pre-existing diseases	mh_0010	yes, no
Pre-existing diseases: chapter	mh_0021	e.g. diseases of the circulatory system
Pre-existing diseases: group	mh_0022	e.g. Pulmonary heart disease and Diseases of the pulmonary circulation
Pre-existing diseases: subgroup	mh_0023	e.g. Pulmonary embolism
Pre-existing diseases: ICD-Code	mh_0024	e.g. I26.-
Pre-existing diseases: ICD-Description	mh_0026	e.g. Pulmonary embolism
Concomitant medications	cm_0021-cm_0026	Anatomical, therapeutically, chemical, ATC Code, active substance
Smoking		
Smoking status	mh_0051	Current smoker, former smoker, never smoker, unknown
Years of smoking	mh_0052, mh_0054	

Type of smoking	mh_0056	e-cigarette, cigarette, other, unknown
Number of cigarettes per day	mh_0058	
Known allergies	mh_0071	yes, no
Type of allergy	mh_0072-mh_0083	Pollen allergy, House dust mite allergy, Animal allergy, Hives, Sun allergy, Cross allergies, Insect venom allergy, Drug allergy
Anamnesis of infections		
SARS-Cov-2 diagnosis in connection to fatigue	imh_0011	yes, no
Other infection in connection to fatigue	imh_0021	yes, no
Date of onset fatigue	imh_0031	

7.2 Primary variable

The primary outcome variable is the Chalder Fatigue Scale (Chalder et al., 1993) (range 0-33) at day 60.

7.3 Secondary variables

Safety related endpoints:
Occurrence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuation due to TEAEs
Assessment of physical examinations, laboratory parameters, vital signs, and ECGs

Clinical effectiveness related endpoints

- Chalder Fatigue Scale (Chalder et al., 1993) at End of Treatment (EOT) visit and at month 1, 4, and 6 after the completion of IA
- Post-COVID-19 Functional Status (PCFS) scale (Klok et al., 2020) at month 1, 2, 4, and 6 after IA completion (only in patients with PACS-CFS)
- the SF-36 physical domain (Ware & Sherbourne, 1992) at EOT visit and at month 1, 2, 4, and 6 after IA completion
- Fluge questionnaire (Fluge et al., 2011; Fluge et al., 2015) at month 1, 2, 4, and 6 after IA completion
- PEM frequency, strength and severity by PEM questionnaire (Cotler et al., 2018) at EOT visit and at month 1, 2, 4, and 6 after IA completion
- the Bell disabling scale (Bell, 1995) at EOT visit and at month 1, 2, 4, and 6 after IA completion
- the Compass-31 questionnaire (Sletten et al., 2012) at month 1, 2, 4, and 6 after IA completion
- Schellong Test (Fanciulli et al., 2019) at EOT visit and at month 2 and optional month 6 after IA completion
- hand grip strength test, at EOT and at month 2 and optional at month 6 after IA completion
- the 6 Minute Walking Test (6 MWT) ("ATS statement: guidelines for the six-minute walk test," 2002) at month 2 after IA completion
- optional neuropsychiatric assessment at month 2 after IA completion

- neurocognitive assessments (MoCA and SDMT) (Nasreddine et al., 2005) (Strober et al., 2020) at month 2 after IA completion
- quality of life (QoL) determined by the PROMIS questionnaire at month 1, 2, 4 and 6 after IA completion (Cella et al., 2019; Yang et al., 2019)
- PROMIS cognitive function short form 4a
- VLMT (verbal learning and memory test) (Helmstaedter et al., 2001)
- BVMT-R (brief visuospatial memory test revised) (Benedict, 1997)
- WAIS-IV (Wechsler adult intelligence scale) (Wechsler, 2008)
- TAP (Test of attentional performance) (Zimmermann & Fimm, 2004)
- LPS 50+ (Leistungsprüfungssystem (performance testing system) for 50 to 90 years old) (Sturm et al., 2015)
- TMT-A / B, Trail Making Test A / B (Reitan & Wolfson, 1993)
- RWT, Regensburger Wortflüssigkeits-Test (Regensburg Word Fluency Test) (Aschenbrenner et al., 2000)
- WST, Wortschatz-Test (Vocabulary test) (Schmidt & Metzler, 1992)

Biomarker related endpoints:

- biomarkers of autoimmune activity (autoantibody titers against neurotransmitter receptors; among others ß2-adeno-receptor- and muscarine- receptor-antibodies) in blood at month 2 and 6 and optional in cerebrospinal fluid at month 2 after IA completion
- immunostatus (differential blood, IgG, IgM, IgA fractions) in blood at EOT, at month 2 and 6 after IA completion
- immunoglobulin levels (including SARS-CoV-2 antibody titers and PCR, if applicable) at month 2 and 6 in blood and optional in cerebrospinal fluid at month 2 after IA completion
- inflammatory biomarkers in blood (CRP, ferritin, MBL, white blood cell count, complement factors, immunoglobulin level and subtype) at month 2 and 6 after IA completion
- autoantibodies against known or unknown neuronal epitopes (Stöcker- autoimmune-encephalitis panel and screening via immunofluorescent staining on mouse brain sections – in cooperation with separate project EA1/258/18) in blood and optional in cerebrospinal fluid after IA completion .
- neurofilament (NFL) in cerebrospinal fluid at month 2 after IA completion
- auto-antibody and vaccine titers in serum and cerebrospinal fluid as well as intrathecal synthesis (CFS) at month 2 after IA completion
- inflammatory biomarkers in cerebrospinal fluid (white cell count, total protein, CSF/serum quotients of albumin (Qalb), lactate, oligoclonal IgG bands (OCB), cytokines)) at month 2 after IA completion
- MRI parameter: grey matter volume, white matter volume, thalamus volume left and right, thalamic functional connectivity to sensomotoric cluster left and right, thalamic functional connectivity to visuo-occipital cluster left and right, EndoPAT Reactive Hyperemia Index (RHI). Volumetry is based on a high-resolution T1-weighted MPRAGE sequence (voxel size 1 mm isotropic, FOV 256 mm, TR = 2500 ms, TE = 2.64 ms). The functional connectivity measures are derived from a BOLD-sensitive resting-state EPI sequence (720 volumes, voxel size 2 mm isotropic, TR = 800 ms, TE = 37 ms, FOV 208 mm).
- OCT parameter: ganglion cell-inner plexiform layer (GCIPL), peripapillary retinal nerve fiber layer (pRNFL), foveal avascular zone (FAZ), vessel density
- CD11c-Expression: Mean fluorescence intensity (MFI) on total $CD19^+$ B cells, Percentage of $CD11c^-$ cells within the $CD19^+$ gate, CD11c MFI and $\%CD11c^-$ specifically on IgD^-CD27^+ memory B cells ($CD19^+IgD^-CD27^+$ gate)
- IgM Expression: Mean fluorescence intensity (MFI) on total $CD19^+$ B cells, Percentage of IgM^- cells within the $CD19^+$ gate, IgM MFI and $\%IgM^-$ specifically on

$IgD^{-}CD27^{+}$ memory B cells ($CD19^{+}IgD^{-}CD27^{+}$ gate), Activated Canonical Class-Switched Memory B Cells (aCSM), $CD19^{+}IgD^{-}IgM^{-}CD27^{+}CD11c^{-}$, Frequency quantification within total B cells or parent gates, Activated canonical class-switched memory B cells

Table 5: primary and secondary outcome variables

Characteristic	**Variable**	**Values**
Primary outcome variable		
Chalder Fatigue Scale at 2 months	cfs_0001-cfs_0011	11 items with levels 0-3 each, sum score has to be calculated
Secondary outcome variables Efficacy related outcomes		
Chalder Fatigue Scale at End of Treatment (EOT) visit and at month 1, 2, 4, and 6 after the completion of IA	cfs_0001-cfs_0011	11 items with levels 0-3 each, sum score has to be calculated
Post-COVID-19 Functional Status (PCFS) scale	pcfs_0020-pcfs_0050	Ordinal scale, range 0 to 4 (0: no limitations, 4: severe limitations),
SF-36 physical domain	sf_0041-sf_0050	10 items, each scored with: no limitations (0 points), some limitations (5 points), severe limitations (10points), the sum will be calculated
Fluge questionnaire	ccc_0011-ccc_0131	5 domains with different number of items, domains: fatigue, pain, cognition, circulation, each item is scored from 0 to 10 according to the severity (10: highest severity), domains will be analyzed separately
Post-Exertional Malaise (PEM)	pem_0021-pem_0110	11 items, 5 items scored 0 to 4 for frequency, 5 items scored 0 to 4 for severity, 1 item scored 0 to 6 for duration, sum score from 0 to 46
Bell Score	bell_0020	1 item with 11 statements, 0-100

		points (100: no symptoms, 0: severe symptoms)
Compass-31	com_0001-com_0031	31 items in 6 domains, score by domain are rescaled ranging from 0 to 100
Schellong Test /POTS	pst_0021-pst_0080	Using items to evaluate if POTS is present (Increase in heart rate within 10 minutes of standing by at least 30 beats/minute above the level when lying down or, to at least 120 beats/minute absolutely, no pathological drop in blood pressure (i.e., systolic drop not more than 20 mm Hg and diastolic drop not more than 10 mm Hg), increasing symptoms of orthostatic intolerance)
6 Minute Walking Test (6 MWT)		
MoCA	moca_0011-moca_0110	Score items, sum of maximum 30 or 31 points dependent on educational level
Symbol Digit Modalities Test, SDMT	sdmt_0020	Item on number of correct remembered words after 90 seconds
PROMIS-29, physical function, anxiety, depression, pain interference, pain severity, fatigue, sleep disturbance, ability to participate in social roles and activities	pfa11-pfa53, edanx01-edanx53, eddep04-eddep41, hi7, an3, fatexp41, fatexp40, sleep109, sleep116, sleep20, sleep44, srpper11_caps-srpper46_caps, pain9-pain34, global07	each of the 7 domains will be scored separately, transformation in standardized t-values
PROMIS cognitive function short form 4a	pc2r-pc42r	Sum score converted to t score
Additional secondary outcome variables		
VLMT (verbal learning and memory test)	vlmt_0011 – vlmt_0220	total score: addition of the learning achievements of the 5

		rounds; delayed recall: number of words correctly recalled from the word list after a time delay; loss after delay: subtraction of the number of correctly recalled words in learning session 7 from the number of correctly recalled words in learning session 5; correct recognition: subtraction of the number of false positives and interference items from the number of correctly recognised words in the first list (i.e.: 18. recognition performance (W) - (19. interference + 20. false positives)).
BVMT-R (brief visuospatial memory test revised)	bmvt_0011 – bmvt_0150	total score: addition of the points from all three trials; delayed recall: number of correctly remembered figures. (correct figure and correct place); percent retained: [delayed recall / (higher of trial 2 and trial 3)] x 100; recognition discrimination index: (recognition hits) - (recognition false alarms)
WAIS-IV (Wechsler adult intelligence scale)	wais_0011 – wais_0070	forward: number of correctly repeated number sequences; backwards: number of number sequences correctly recited backwards; sequential: number of correctly sequenced number sequences.
TAP (Test of attentional performance)	tap_0011 – tap_0100	median of the reaction time. (runs without warning tone); standard deviation of the reaction

		time. (runs without warning tone); number of omissions in the sustained attention task; number of omissions of auditory stimuli; number of omissions of visual stimuli.
LPS 50+ (Leistungsprüfungssystem (performance testing system) for 50 to 90 years old)	lps_0010 – lps_0040	number of correctly solved lines.
TMT-A / B, Trail Making Test A / B	tmt_0011 – tmt_0060	number of seconds to complete the task A; number of seconds to complete the task B; TMT B/A ratio = time TMT-A / time TMT-B
RWT, Regensburger Wortflüssigkeits-Test (Regensburg Word Fluency Test)	rwt_0011 – rwt_0080	number of animals or first names mentioned within 60 seconds; number of S-words or M-words mentioned within 60 seconds.
WST, Wortschatz-Test (Vocabulary test)	wst_0010-wst_0050	raw score (sum of correct values)
Biomarker related endpoints		
biomarkers of autoimmune activity (autoantibody titers against neurotransmitter receptors; among others ß2-adeno-receptor- and muscarine- receptor-antibodies), autoantibodies against known or unknown neuronal epitopes	stoe_0023-stoe_0025, ak_0011-ak_0063	
immunostatus (differential blood, IgG, IgM, IgA fractions)	ig_0011-ig_0063	
immunoglobulin levels (including SARS-CoV-2 antibody titers and PCR, if applicable)	inf_0121-inf_0140, imh_0011, imh_0012, ig_0011-ig_0023	

inflammatory biomarkers in blood (CRP, ferritin, MBL, white blood cell count, complement factors, immunoglobulin level and subtype)	inf_0161-inf_0173	
neurofilament (NFL)	liq_0161-liq_0163, liq_0171-liq_0173	
auto-antibody and vaccine titers in serum and cerebrospinal fluid as well as intrathecal synthesis (CFS)	ak_0011-ak_0063	
inflammatory biomarkers in serum and cerebrospinal fluid (white cell count, total protein, CSF/serum quotients of albumin (Qalb), lactate, oligoclonal IgG bands (OCB), cytokines))	haem_0051-haem_0273, chem_0011-chem_0083, liq_0011-liq_0173	
MRI measures: grey matter volume, white matter volume, thalamus volume left and right, thalamic functional connectivity to sensomotoric cluster left and right, thalamic functional connectivity to visuo-occipital cluster left and right, EndoPAT Reactive Hyperemia Index (RHI)	gm_volume, wm_volume, thalamus_l_ volume, thalamus_r_ volume, thalamic_motor_l__fc, thalamic_motor_r__fc, thalamic_occiptial_l__fc, thalamic_occiptial_r__fc, endopat_rhi	
OCT: ganglion cell-inner plexiform layer (GCIPL), peripapillary retinal nerve fiber layer (pRNFL), foveal avascular zone (FAZ), vessel density	gcipl, prnfl, faz, vessel_density_full	
CD11c Expressions (CD19+ B cells, $IgD^{-}CD27^{+}$ memory B cells), IgM Expressions, Activated canonical class-switched memory B cells	z_cd11c_exp_cd19pl, z_cd11c_exp_igdmin_cd27plus_cd19pl, perc_cd11cpl_cd19pl, perc_cd11cpl_igdmin_cd27pl_cd19pl, z_igm_exp_cd19pl, z_igm_exp_igdmin_cd27pl_cd19pl, perc_igmpl_cd19pl, perc_igmpl_igdmin_cd27pl_cd19pl, perc_acsm_igdmin_igmmin_cd27pl_cd11cmin_cd19pl, perc_cl_acsm_igdmin_cd27pl_cd19pl	
Safety related endpoints		

Adverse events and severe adverse events	ae_0053, sae_0123	

8 Handling of missing values

Missing data will be categorized according to Rubin as “missing completely at random”, “missing at random” and “missing not at random” (MCAR, MAR and MNAR) (RUBIN, 1976). For missing data in outcome variables, data will be imputed using multiple imputation by chained equations (mice) (Van Buuren & Van Buuren, 2012) with the R package MICE (van Buuren & Groothuis-Oudshoorn, 2011) with 30 imputed data sets, where appropriate is the assumption of MAR or MCAR is reasonable. It is planned to perform sensitivity analyses, in which the robustness of the inference will be investigated. Sensitivity analyses will be done using complete data without any imputation. The following variables will be used for the imputation process: all outcome variables, demographic variables age, sex, and BMI.

9 Statistical analyses / methods

9.1 Demography and baseline characteristics

Demography and baseline characteristics will be reported for the total population and by treatment arm using descriptive statistical summary measures. No statistical test will be performed to compare baseline characteristics between randomized treatment groups. For continuous variables, mean with standard deviation (SD), median, interquartile range (IQR), minimum, maximum will be given depending on the distribution of the respective characteristic. For categorical data absolute and relative frequencies are given for each category.

9.2 Primary analysis

For the primary outcome, the Chalder Fatigue Scale at 2 months, descriptive statistics will be presented for both treatment arms. This will include the number of participants (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum for the continuous total score. Additionally, for the categorical responses (e.g., presence/absence of fatigue), frequencies and percentages will be reported.

Confirmatory analysis of the primary outcome will be conducted based on the full analysis set. An analysis of covariance (ANCOVA) will be conducted. The dependent variable is the Chalder Fatigue Score at day 60, independent variables include baseline Chalder Fatigue Score, treatment group (intervention / control), and age at baseline. The effect estimate for the treatment variable and the corresponding 95%CI will be reported. Sensitivity analysis will be done using the PPS without imputation of missing values.

9.3 Secondary analyses

For all secondary endpoints, descriptive statistics will be calculated and presented at each time point of measurement for both treatment groups. For continuous secondary outcomes, this will include the mean, standard deviation, median, interquartile range, minimum, and maximum. For categorical or ordinal secondary outcomes, frequencies and percentages will be reported. These descriptive summaries will be presented in tabular format, and appropriate graphical representations, such as line plots for longitudinal data, bar charts, or box plots, will be utilized to visually depict trends, distributions, and differences between treatment arms across all assessment time points. For all secondary endpoints, analysis of

covariance (ANCOVA) models will be employed, analogous to the approach for the primary outcome. The choice of link function will be tailored to the specific nature of each outcome variable (e.g., linear for continuous outcomes, binary logistic for dichotomous outcomes, or ordinal for ordered categorical outcomes). In instances of repeated measures, mixed-effects regression models will be utilized, incorporating random intercepts for individual participants to account for within-subject correlation. Each model will include the respective baseline value of the endpoint, age at baseline, and treatment group as fixed effects. Effect estimates for the treatment variable, along with their 95% confidence intervals (CI), will be reported. All analyses will be conducted using the Full Analysis Set (FAS). Sensitivity analyses will be performed using the Per-Protocol Set (PPS), without imputation of missing values, to assess the robustness of the findings.

Responder analysis: Explorative analyses comparing responders and non-responders in both groups regarding PCS-associated signature at baseline: CD11c and IgM expression and an aCSM frequency. For this analysis a binary logistic regression model will be implemented with the responder (yes/no) variable as the dependent variable, the PCS-associated signature at baseline, the group and the interaction term between PCS-signature at baseline and group as independent variables.

9.4 Safety Analysis

Descriptive methods will be used for analysis of safety parameters, adverse events and their intensity in total and reported separately for the intervention groups. Incidence rates and 95% confidence intervals (CI) will be calculated using Poisson regression models that consider the different observation periods for each participant. Group comparisons will be made using incidence rate ratios and their 95% CIs. The safety analysis results will be carefully interpreted and discussed, even for minor group differences, as statistical significance is not the main focus in this context. A comprehensive listing of all individual patient adverse events (AEs) and severe adverse events (SAEs) will be presented. This will include, for each event, the patient identifier, treatment arm, AE/SAE term (coded using Medical Dictionary for Regulatory Activities [MedDRA]), verbatim term, onset date, resolution date, severity (e.g., mild, moderate, severe), seriousness criteria (if applicable), causality assessment (e.g., related, not related to study drug), action taken with study drug, and outcome. Separate listings will be generated for AEs and SAEs. Furthermore, any AEs leading to study drug discontinuation or study withdrawal will be specifically highlighted. These listings will serve as a detailed and transparent record for safety monitoring and will facilitate thorough review by medical monitors and regulatory authorities.

9.5 Planned subgroup analyses

For the statistical analyses of the subgroups, the models defined in the sections above will be used for the respective outcome, additionally with an interaction term of the treatment group variable with the subgroup, in order to obtain indications of differential treatment effects in the subgroups. We will report effect estimates of interaction effects with corresponding 95%CI. In addition, marginal effect estimates for each subgroup and 95% confidence intervals will be provided.

Sub-group (levels)	**Outcomes**
Sex (male, female, diverse)	Primary endpoint and efficacy related secondary endpoints
Age (< 40 years, ≥ 40 years)	Primary endpoint and efficacy related secondary endpoints

Sub-group (levels)	Outcomes
Education (higher education meaning A-levels or higher, medium or lower educational achievement)	Primary endpoint and efficacy related secondary endpoints
Employment status (retired/ currently unable to work, employed/ self-employed / student)	Primary endpoint and efficacy related secondary endpoints
Body-mass index (BMI) (< 30 kg*m^{-2}, ≥ 30 kg*m^{-2})	Primary endpoint and efficacy related secondary endpoints
ME/CFS vs. Post-COVID-ME/CFS	Primary endpoint and efficacy related secondary endpoints, OCT outcome: Retinal vascular and perfusion density in the superficial vascular plexus (SVP)
Disease duration (≤2.5 years, >2.5 years)	Primary endpoint and efficacy related secondary endpoints
Bell Score at baseline (≤30, >30)	Primary endpoint and efficacy related secondary endpoints
Chalder Fatigue Scale at baseline (≤20, >20)	Primary endpoint and efficacy related secondary endpoints
Focal neurological deficit at baseline (yes, no)	Primary endpoint and efficacy related secondary endpoints
Antineuronal autoantibodies (yes, no)	Primary endpoint and efficacy related secondary endpoints
Subgroups by 7 PROMIS 29 sub domains (T-score cut offs of 30-40)	Primary endpoint and efficacy related secondary endpoints
Baseline detection of GPCR-Autoantibodies (pos. result from Labor Celltrend; yes, no)	Primary endpoint and efficacy related secondary endpoints
Subgroups by the presence of specific B-cell subpopulations at baseline (incl. activated plasma blasts, memory like and activated naïve like cells identified in CyTOF analysis)	Primary endpoint and efficacy related secondary endpoints
Subgroups by baseline retinal nerve fibre layer (pRNFL) thickness (median split)	Primary endpoint and efficacy related secondary endpoints

Sub-group (levels)	Outcomes
Subgroups by baseline retinal ganglion cell layer (GCIPL) thickness (median split)	Primary endpoint and efficacy related secondary endpoints

10 Interim analysis

An interim analysis is not planned.

11 Software

R (version 4.4.2 or later) will be used. For multiple imputation of missing values, the package mice will be used (van Buuren and Groothuis-Oudshoorn (2011)). For mixed models, the R package lme4 will be used (Bates et al. (2015)). For marginal mean estimates, the R package emmeans will be used (Lenth (2024)).

12 List of Changes in Version 2 of this SAP

- *MRI and OCT added in tables for scheduled measures*
- *MRI and OCT variables added in outcome and variable tables and listings,*
- *Additional immunological biomarkers: CD11c-Expression, IgM-Expression, Activated canonical class-switched memory B cells*
- *Additional subgroup analysis by OCT parameters (Subgroups by reduced peripapillary retinal nerve fibre layer, pRNFL/ganglion cells or inner plexiform layer; GCIPL at baseline)*
- *Additional OCT Outcome for subgroup analysis on subgroup defined by ME/CFS vs. Post-COVID-ME/CFS.*
- *Responder analysis in section 9.3: Explorative analyses comparing responders and non-responders in the intervention group regarding PCS-associated signature at baseline: CD11c and IgM expression and an aCSM frequency.*

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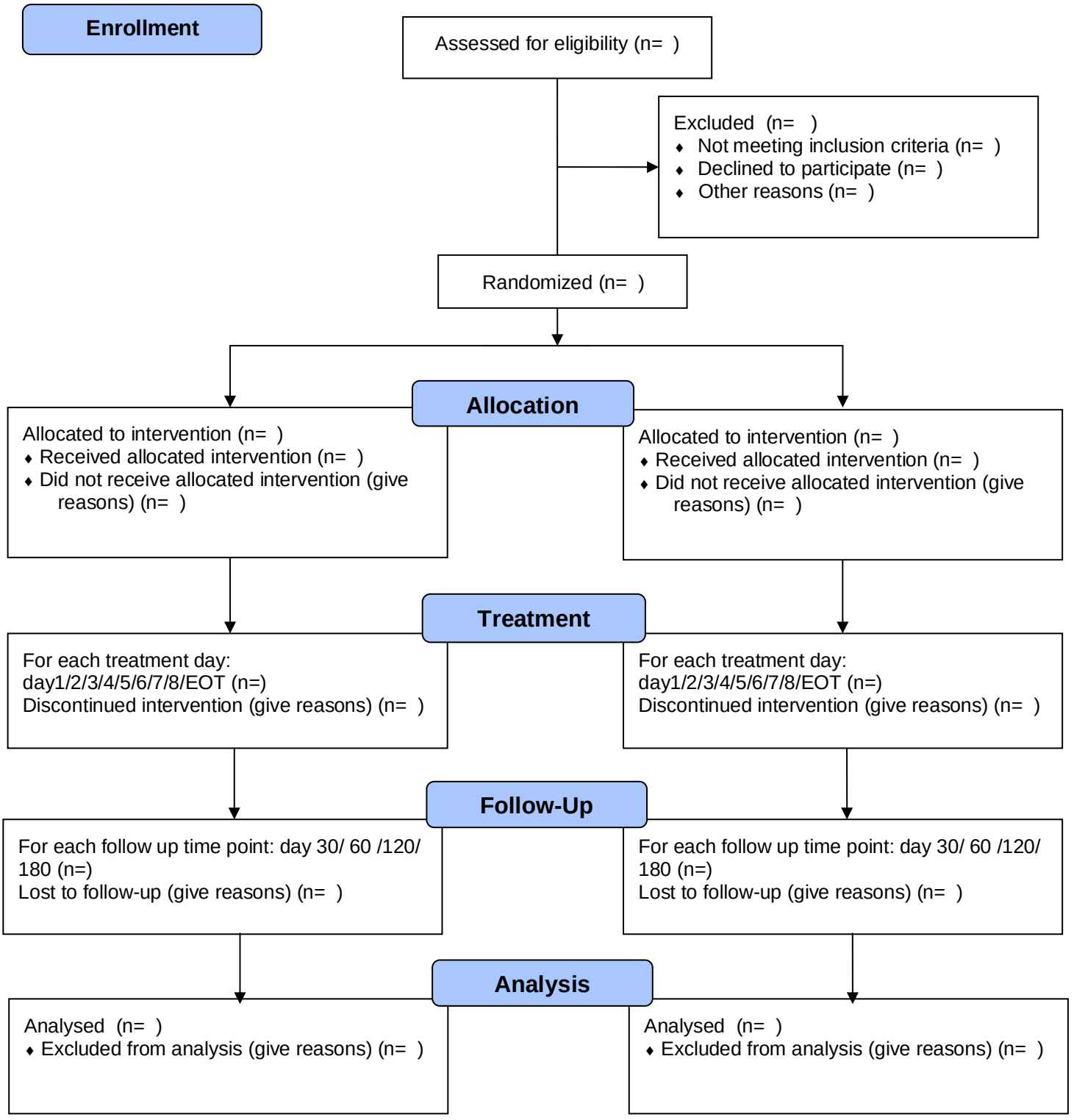
14 Appendices

14.1 Flow Chart

CONSORT 2010 Flow Diagram



14.2 Planned tables sample

Table 14.2.1 Baseline characteristics

Baseline characteristics	In total (n=…)	Intervention group (n=…)	Control group (n=…)
Age at randomization (years) Mean (SD), Median (IQR), [Min, Max]			
Sex, n (%)			
male			
female			
diverse			
Ethnicity, n (%)			
Caucasian			
African			
Asian			
Other			
Unknown			
BMI (kg/m^2), Mean (SD), Median (IQR), [Min, Max]			
Education, n (%)			
No school-leaving certificate, lower secondary school leaving certificate (Hauptschule), higher secondary school leaving certificate (Realschule), grammar school (Gymnasium), completed vocational training, degree of a university of applied sciences, University, Unknown			
Employment status, n (%)			
employed			
self-employed			
currently unable to work			
pension			
student			
unknown			
Pre-existing Comorbidities, n (%)			
Diseases of the circulatory system			
Diseases of the urogenital system			
Diseases of the genitourinary system			
Diseases of the digestive system Endocrine,			
Diseases of the musculoskeletal system and connective tissue			
Endocrine, nutritional and metabolic diseases			
Injuries, Poisoning and certain other consequences of external causes			
Smoking status, n (%)			
Current smoker			

former smoker
never smoker
unknown

Known allergies, n (%)

SARS-Cov-2 diagnosis in connection to fatigue, n (%)

Other infection in connection to fatigue, n (%)

Time from fatigue onset to study inclusion in days, Mean (SD), Median (IQR), [Min, Max]

Table 14.2.2 primary and secondary outcomes descriptive tables (examples)

	Intervention group (n=…)	**Control group (n=…)**
Chalder Fatigue score, Mean (SD), Median (IQR), [Min, Max]		
baseline		
EOT		
1 month		
4 months		
6 months		
PCFS Scale, Mean (SD), Median (IQR), [Min, Max]		
Baseline		
1 month		
2 months		
4 months		
6 months		
SF 36 physical domain, Mean (SD), Median (IQR), [Min, Max]		
Baseline		
1 month		
2 months		
4 months		
6 months		
…		

Table 14.2.3 Primary endpoint - **Chalder Fatigue score after 2 months**

Study group	**Chalder Fatigue score after 2 months mean (95% CI)**	**Mean difference (Intervention – Control) (95% CI)**	**p-value**
Intervention			
Control			

Table 14.2.4 Secondary endpoints (examples)

EORTC	Mean (95%CI)		Mean difference (IG – KG) (95% CI)	p-values
	Intervention group (IG)	Control group (CG)		
Chalder Fatigue score				
EOT				
1 month				
4 months				
6 months				
PCFS Scale				
1 month				
2 months				
4 months				
6 months				
SF 36 physical domain				
1 month				
2 months				
4 months				
6 months				
…				

14.3 Planned listings sample for AEs SAEs

Patient ID	Treatment Arm	Age at baseline	Sex	MedDRA Preferred Term	Onset Date (YYYY-MM-DD)	Resolution Date (YYYY-MM-DD)	Duration (Days)	Severity	Causality	Action Taken	Outcome

14.4 Planned graphics sample

Figure 1: Chalder Fatigue scale over time, simulated data (n=44 intervention group, n=22 control group)

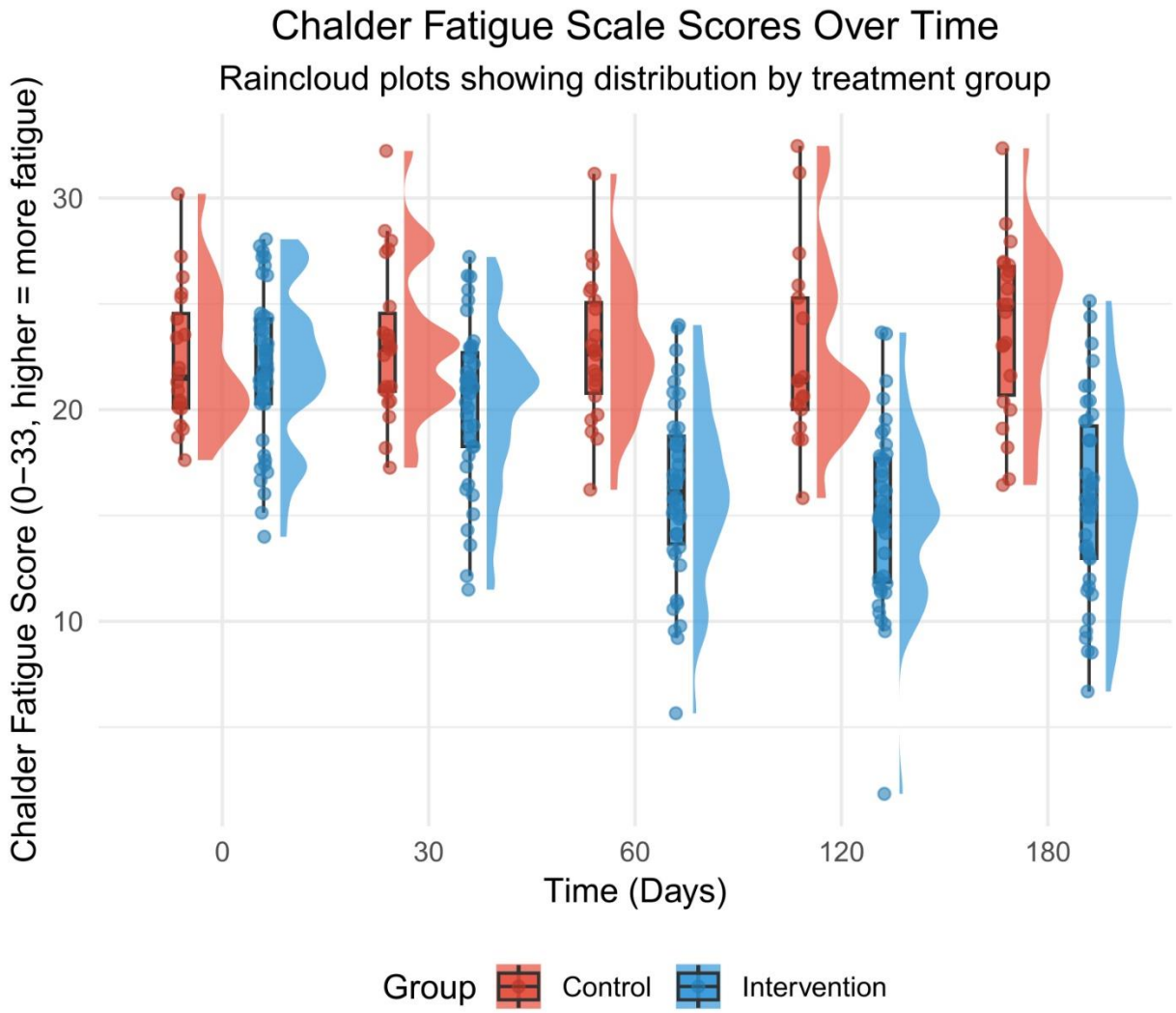


Figure 2: effect estimates for intervention for Chalder Fatigue Scale (n=44 in intervention group, n=22 in control group), (simulated data)