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Full-length Article

Temelimab versus placebo in patients with post-COVID condition

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ABSTRACT

Introduction: More than 400 million individuals are estimated to have been affected by post-COVID condition or long COVID. This condition can lead to significantly decreased quality of life and increased individual and societal costs. Temelimab, a monoclonal IgG4 backbone antibody targeting HERV-W ENV, may be a potential treatment for post-COVID.

Methods: In this randomized, double-blind trial, which consisted of a 24-week treatment period, we enrolled adults who had fatigue and persistent symptoms due to post-COVID and were positive for HERV-W-ENV. Participants were randomized (1:1) to receive 54 mg/kg Temelimab or placebo IV once monthly. The primary endpoint was the decline in fatigue (defined as a 3-point decrease on the PROMIS Fatigue SF 7a scale) from baseline to Week 24. Secondary endpoints included changes in cognition, anxiety, depression, functional impairment, quality of life, safety and tolerability of Temelimab.

Results: A total of 203 individuals participated in this study, 72% women, mean age 46 (standard deviation, SD 10) years. The mean initial PROMIS Fatigue SF 7a score was 26.8 (SD 3.4) in the Temelimab group and 27.1 (SD 3.8) in the placebo group. At 24 weeks, there was no difference between Temelimab (3.2 points decrease in the PROMIS score) and placebo (3.8 points decrease). Secondary outcomes also did not show differences between the Temelimab and placebo groups.

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Conclusion: In adults with persistent symptoms due to post-COVID condition, the use of Temelimab did not show improvement in fatigue compared to placebo (Funded by GeNeuro SA; ClinicalTrials.gov number NCT05497089).
Ethics and dissemination: National authorities for clinical trials on medicinal products and ethical approval was obtained in all participating countries in Europe. Trial registration numbers ClinicalTrials.gov number (NCT05497089), EudraCT (2022-000618-32). Protocol version v5.0, date 23 February 2024; CCER Geneva IRB: 2022-00658.

1. Introduction

Post-COVID condition is defined by the presence of a wide range of symptoms that persist at least three months after a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (World Health Organization). Most frequent symptoms include fatigue, cognitive impairment, dyspnea, or autonomic dysfunction, and are estimated to affect more than 400 million individuals since the COVID-19 pandemic (Davis et al., 2023). Persistence of chronic symptoms is often associated with a worsening of quality of life (QoL), decreased functional capacity, increased fatigue and neurocognitive symptoms, with an important cost to the individual and to the society (Bach, 2022; Nehme et al., 2022). This occurs independently of the severity of the disease during the acute phase of the infection (Nehme et al., 2023).

To date, some of the hypotheses behind the pathophysiology of post-COVID include immune dysfunction, low grade inflammation, endothelial dysfunction with microthromboses or persistence of viral particles (Davis et al., 2023; Couzin-Frankel, 2022). Studies have shown the presence of auto-antibodies in some of the individuals with persistent symptoms (Phetsouphanh et al., 2022; Rojas et al., 2022), others have shown endothelial dysfunction and an increase in inflammatory markers (Charfeddine et al., 2021), and other studies have shown the persistence of viral particles on gastrointestinal biopsies in individuals months after their infection (Chioh et al., 2021). Within the realm of hypotheses, the activation of endogenous retroviruses expressing a pathogenic protein, the human endogenous retrovirus envelope type W (HERV-W ENV), was evaluated (Giménez-Orenga et al., 2025).

Retroviruses have gained importance in biology and medicine in the past 50 years (Lesbats et al., 2016). Retroviruses can be pathogens, such as human T-lymphotropic virus 1 (HTLV-1) (Poiesz et al., 1980) or human immunodeficiency virus type 1 (HIV-1) (Barré-Sinoussi et al., 1983). Retroviruses can also be endogenous, and part of the human DNA (Grandi and Tramontano, 2018). Endogenous retroviruses have been integrated in genetic material via germline cells infection from thousands to millions of years (Grandi and Tramontano, 2018). They could be influencing the immune responses by modulating immunity or even protecting individuals from exogenous infections (Chuong et al., 2016; Feschotte and Gilbert, 2012). Triggering human endogenous retrovirus type Ws can lead to a dysregulated immune response as its envelope protein acts as a potent agonist of the toll like receptor 4 (TLR4) which is a critical activator of innate immunity. Subsequently, this protein was shown to be involved in the pathogenesis of diseases such as multiple sclerosis (Kremer et al., 2019; Perron et al., 1997; Perron et al., 2012), cancers (Stricker et al., 2023), or chronic fatigue syndrome (Rodrigues et al., 2019).

HERV-W ENV activation by SARS-CoV-2 was observed in about 25% of healthy donors peripheral blood mononuclear cells upon in vitro exposure to SARS-CoV-2 (Charvet et al., 2023). An increased prevalence of HERV-W ENV protein in white blood cells of COVID-19 patients compared to that of healthy donors has also been demonstrated and was correlated with markers of inflammation, T cell terminal differentiation and exhaustion, and cytokine expression (Balestrieri et al., 2021). In addition, two independent groups have now observed that HERV-W ENV is expressed in brain focal areas of patients who died from COVID-19, involving microglia and endothelial cells of certain blood vessels (Charvet et al., 2023), as well as in the blood (Garcia-Montojo and Nath, 2021). A recent study included 66 subjects (acute COVID-19 [n=22], post-COVID condition [n=12], chronic fatigue syndrome [n=17], and healthy donors [n=11]) to determine the prevalence of HERV-W ENV in patients with post-COVID condition, less than 96 weeks after their infection date (Giménez-Orenga et al., 2022). In the healthy donor group, 7 subjects were found to have anti-SARS-CoV-2 IgG antibodies and were excluded from the analysis. Results of the study showed a HERV-W ENV prevalence of 0% in healthy donors who had negative anti-SARS-CoV-2 IgG (n=4 with no exposure to the virus), a HERV-W ENV prevalence of 41% in individuals who had acute SARS-CoV-2 infection (COVID-19) (n=33), a HERV-W ENV prevalence of 58% in individuals who had post-COVID condition (n=12), and a HERV-W ENV prevalence of 18% in individuals with chronic fatigue syndrome (n=17), diagnosed prior to the COVID-19 pandemic (Giménez-Orenga et al., 2022).

The continued and self-sustained endogenous expression of pathogenic HERV-W ENV in the periphery as well as in the brain could be a key contributor to some of the neurologic and psychiatric symptoms experienced by post-COVID patients (Charvet et al., 2023). Of note, the potential identification of blood biomarkers in post-COVID patients (Charvet et al., 2023) could be a significant step forward in science and precision medicine.

To date, there are no treatment options for post-COVID condition, and no specific biomarkers associated with the disease. Several studies have evaluated the efficacy of pharmacological treatments for post-COVID condition, with mixed results (Isman et al., 2024; Couzin-Frankel, 2024; Al-Aly and Topol, 2024; Ledford, 2022; Diseases, 2023; Patrick-Brown et al., 2024; Sawano et al., 2025; Andrews et al., 2024; Finnigan et al., 2023; Geng et al., 2024). Additionally, there is lack of biomarkers to diagnose post-COVID or as targets for treatment. Temelimab, a monoclonal antibody, inhibits the activation of TLR4 by HERV-W ENV on expressing cells, preventing the activation of intracellular and inter-cellular pathways leading to abnormally activated effector functions and amplified physiological responses driven by corresponding molecular and cellular pathways (Curtin et al., 2015; Kremer et al., 2015; Madeira et al., 2016).

The present trial evaluated the efficacy and safety of Temelimab as treatment for persistent symptoms in patients with post-COVID condition compared to placebo.

2. Methods

2.1. Trial oversight

We conducted this randomized, double-blind, placebo-controlled, multicenter, phase II trial, three European countries involving 14 centers (Switzerland, Italy, and Spain). This study was approved by all the national authorities for clinical trials on medicinal products, as well as the local research ethical boards. Trial registration numbers: clinicaltrials.gov (NCT05497089), EudraCT (2022-000618-32). All study materials, including the protocol, amendments, informed consent forms, Investigator's Brochure were first approved by the institutional review board (IRB)/ethics committee (EC) prior to study initiation. Before participating, all subjects received a detailed information note and informed consent form outlining study drugs, procedures, and potential risks. Participation was voluntary, and subjects could withdraw at any

time. They were always encouraged to seek further information and ask questions before consenting. Compliance with data protection laws was maintained. subjects were informed about the use of their data and the level of disclosure, including potential reviews by the sponsor or CRO auditors, IRB/EC members, and regulatory inspectors.

2.2. Participants

Inclusion criteria included adults ≥18 years of age, able to provide a written informed consent, a SARS-CoV-2 proven infection, a positive HERV-W ENV protein in serum, post-COVID neuropsychiatric symptoms still occurring more than 12 weeks after initial symptoms, fatigue as measured by a total raw score ≥21 on the patient-reported outcomes measurement information system fatigue short form 7a (PROMIS Fatigue SF 7a) scale (Ameringer et al., 2016), and objective impairment of cognitive function or QoL as defined by the Token Motor test ≥1 Z score below the age/sex-adjusted mean (Keefe et al., 2004), the European quality of life 5-dimension-5-level (EQ5D-5L) scale (Rabin and de Charro, 2001) of at least 1 score ≥3 in any of the 5 variables questionnaire (mobility; self-care; usual activities; pain/discomfort; and anxiety/depression), or the perceived deficits questionnaire (PDQ-20) scale ≥27 (Strober et al., 2016). The HERV-W ENV assay was performed under standardized laboratory conditions with quality-control procedures to ensure analytical consistency. In multiple sclerosis, HERV-W ENV antigenemia has shown an estimated sensitivity of 73% and specificity of 96–97%, with good analytical reproducibility (Perron et al., 2012). In COVID-19 cohorts, HERV-W ENV antigenemia was detected in approximately 21% of SARS-CoV-2-positive patients and was absent in healthy and non-COVID controls, suggesting high specificity (Charvet et al., 2023; Giménez-Orenga et al., 2022). Given the relatively low prevalence and heterogeneous expression of HERV-W ENV in post-COVID populations, the assay was used as an inclusion criterion (with high specificity) to identify HERV-W ENV-positive participants rather than as a longitudinal biomarker of treatment response. The main inclusion and exclusion criteria are detailed in Table S1.

Eligible subjects were centrally randomized using an interactive voice/web response system. The system assigned a unique randomization number and encoded the subject's assignment to one of the treatment groups of the study, according to the randomization schedule generated prior to the study. Each subject was dispensed blinded study treatment, labelled with unique subject number, throughout the study. The randomization was stratified by age (≤65 years versus >65 years).

2.3. Trial procedures and end points

Temelimab is manufactured by Polymun Scientific GmbH, Austria and supplied in a sterile, preservative-free liquid solution for intravenous (IV) administration supplied in a single use, USP type 1 glass vials with a FluroTec stopper and an aluminium 20 mm flip off seal. The drug substance is formulated in histidine, sucrose, polysorbate 20, at pH 6.0. The product is dispensed based on body weight (54 mg/kg) over 2 hours. Placebo is supplied in identical vials and comprises product formulation buffer histidine, sucrose, polysorbate 20, pH 6.0, but without the active pharmaceutical ingredient. The vials were kept refrigerated (2°C to 8°C). The control group is administered with the placebo matching IV infusion. The study drug is diluted in glucose 5% solution and administrated as an IV infusion over 2 hours ±6 min. During the study period, participants received 6 IV infusions of Temelimab at a dose of 54 mg/kg or a matching placebo IV infusion every 4 weeks for a total of 24 weeks. Throughout this treatment period, from Day 1 to Week 20, all subjects continued their current standard of care (Fig. S1). Subjects were followed for a 6-month period with treatment and follow-up visits at Weeks 4, 8, 12, 16, 20, and 24. At every study visit prior to dosing, subjects underwent a physical examination, had their vital signs recorded, and provided blood and urine samples. Neuropsychological assessments (Keefe et al., 2004 Jun 1) and completion of study questionnaires were scheduled for baseline, Week 12, and Week 24. The Tower of London assessment (part of the BAC test), 40 was conducted only at baseline and Week 24. From the time of signing the informed consent form until the end of the study at Week 24, all subjects were closely monitored for adverse events (AEs).

The primary outcome of this study was the improvement in fatigue in patients with post-COVID condition, as evidenced by a decrease in ≥3 points on the PROMIS Fatigue SF 7a scale (Ameringer et al., 2016). The PROMIS Fatigue SF 7a scale is a 7-item patient-reported outcome (PRO) instrument to measure fatigue. The PROMIS Fatigue SF 7a provides a total score obtained by summing keyed scores of all items. Response options are recorded on a 5-point Likert scale (ranging from 1 to 5). Raw scores range from 7 to 35, with higher scores indicating greater fatigue.

The secondary outcomes included the improvement of fatigue (mean profile over time), cognition, anxiety, depression, functional impairment, and QoL in patients with post-COVID condition. Neuropsychological assessments were conducted using the brief assessment of cognition (BAC) test (Keefe et al., 2004) to evaluate verbal memory and learning (verbal memory test), working memory (digit sequencing test), psychomotor coordination (token motor test), verbal fluency (semantic and letter fluency), and executive function (Tower of London test). For each domain, higher scores reflect better cognition; raw scores are then converted to age and gender-corrected normalized Z-scores. The BAC composite Z-score (measure of overall cognitive functioning) is calculated as the mean of the normalized scores from the 5 domains.

The symbol digit modalities test (SDMT) (Lezak, 2004) was used to evaluate information processing speed. The SDMT involves substituting 9 different symbols for digits 1 to 9 across 110 blanks, with the first 10 serving as practice (Benedict et al., 2017). Subjects have 90 seconds to complete as many substitutions as possible. The score is compared against age- and education-specific norms. It is recorded as a ratio (e.g., 36 correct out of 39 attempts) and can range from 0 to 120, with higher scores indicating better performance.

The generalized anxiety disorder (GAD 7) (Sapra et al., 2020), is a 7-item PRO tool for identifying and assessing the severity of generalized anxiety disorder symptoms. It uses a 4-point Likert scale, with total scores ranging from 0 to 21. Higher scores indicate more severe anxiety symptoms. The patient health questionnaire (PHQ-9) (Kroenke et al., 2001) is a 9-item PRO tool for measuring depression severity and diagnosing depressive disorders. It includes an additional item for questionnaire feedback. The global score ranges from 0 to 27, with higher scores indicating more severe depression.

The PDQ-20 (Strober et al., 2016), a 20-item PRO tool, was used to gauge cognitive difficulties perceived by patients in daily life (Strober et al., 2016). It covers 4 domains: attention/concentration, retrospective memory, prospective memory, and planning/organization, each with five items. Responses are on a 5-point scale, with total scores ranging from 0 to 80. Higher scores reflect a greater perceived level of cognitive difficulty. The SDS is a 3-item PRO measure evaluating functional disability in work, social, and family life (Sheehan and Sheehan, 2008). It includes a global score and three domains, with optional items for days lost or underproductive due to symptoms. Scores range from 0 to 10 and can be converted to percentages, with total scores from 0 to 30. Higher scores suggest greater impairment. The EQ5D-5L is a PRO measure for health description and valuation (Herdman et al., 2011). It includes a 5-dimension descriptive system and a visual analogue scale (VAS). Each dimension is rated on a 5-point scale, and the overall health state is represented by a 5-digit number. The VAS measures self-rated health on a 20-cm scale, with higher scores indicating better QoL. The PCFS is a scale assessing functional limitations post-COVID-19 (Klok et al., 2020). It covers signs, symptoms, and activities of daily living on a 5-point scale. The total score, ranging from 0 to 4, reflects the worst functional status reported. Higher scores denote greater COVID-19 impact. Phenotypes were defined as fatigue dominant if the PROMIS Fatigue SF 7a scale was ≥23 points and the BAC composite z-score was higher than −1.5; cognitive dysfunction dominant if

the PROMIS Fatigue SF 7a scale was below 23 points and the BAC composite z-score was ≤ -1.5; or multisystemic for those who were not fatigue nor cognitive dysfunction dominant. The secondary outcomes also included the safety and tolerability of Temelimab.

Adverse events were evaluated by looking at clinical signs, symptoms, and laboratory measurements, and using non-leading question such as ""How are you feeling today?" or "Have you had any health concerns since last asked?". AEs were recorded from the moment of informed consent to completion of the study participation. Subjects were also encouraged to spontaneously report AEs occurring at any other time during the study. Anti-drug antibodies (ADAs), pharmacokinetic (PK) concentrations displaying standard PK parameters, such as minimum serum concentrations (Cmin) and accumulation factor, were also measured.

Exploratory assessments included biomarkers (neurofilament light protein [NfL] and glial fibrillary acidic protein [GFAP]), immune response and inflammation (cytokines [IL-1b, IL-6, IL-8, IL-10, TNF-alpha, IFNa, GM-CSF], endothelin), COVID-19 serology as well as changes in the levels of HERV-W ENV over the 24-week period.

2.4. Statistical analysis

We calculated a target sample size of 182 participants based on 80% power to detect a 0.2 increase in the proportion of participants achieving the primary endpoint (defined as a $\geq$3 points reduction in PROMIS Fatigue SF 7a score from baseline to Week 24) in the Temelimab group compared to the placebo group. To observe this difference, 182 subjects (91 in each group) were required, assuming a 0.3 proportion in the placebo group and a 2-sided alpha level of 0.05. This calculation was based on a 2-sided Z-test with un-pooled variance.

The statistical analysis was conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines (Fig. S2). Primary and secondary end points were analyzed according to the intention-to-treat principle.

The primary analysis evaluated the difference in the proportion of subjects with PROMIS Fatigue SF 7a score improvement (primary outcome) in the Temelimab versus placebo groups at 24 weeks, quantified by relative risk. Relative risk estimates were used although the protocol had prespecified odds ratios as the primary analysis. The choice of using relative risk was to address any potential concerns of overestimation or misinterpretation with odds ratios. Relative risk was calculated using logistic regression models in the overall sample and in subgroups of participants by sex, age, baseline scores of the different scales, and baseline biomarkers levels. Regression models were adjusted on the age randomization stratification factor, except when age subgroups were tested.

Secondary analyses evaluated the difference in the secondary outcomes from baseline to 24 weeks in the Temelimab versus placebo groups using linear mixed models. There was no missing data for the primary outcome. Models included change from baseline in score at each scheduled post-baseline visit as response variable, baseline score as covariate and the treatment arm, the visit, the treatment-by-visit interaction and age stratification ($\leq$65 versus >65 years old) as fixed effects. Subject effect was assumed to be random, and an unstructured covariance structure was used. Least square means of changes from baseline to Week 24 were estimated with 95% confidence interval (CI) in each arm as well as differences in LS means between groups with associated 95% CI. Considering the directionality of each scale, lower scores were considered as a favorable outcome using the Fatigue SF7a, PDQ-20, GAD-7, PHQ-9, SDS and PCFS scales; while higher scores were considered as a favorable outcome using the BAC score, SDMT, and EQ-5D-5L scales.

Relative risks showing secondary outcomes results at week 24 were calculated using logistic regression models. Results were categorized based on medians of each outcome, both at baseline and Week 24. Relative risks ratios estimated the proportion of patients with improvement in secondary outcomes in the Temelimab versus Placebo groups between baseline and week 24. Improvement was defined as moving from an unfavorable outcome at baseline (according to median) to a favorable outcome at week 24.

The statistical analysis plan did not include a provision of correction for multiplicity. Results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals should not be used to infer definitive treatment effects. Additional details regarding the statistical analysis are provided in the supplementary appendix.

3. Results

3.1. Trial participants

Overall, n=203 individuals participated in this study (50% Temelimab), 72% women, mean age 46 (standard deviation, SD 10) years. The characteristics of participants were similar in the two groups (Table 1).

3.2. Treatment

The mean initial PROMIS Fatigue SF 7a score was 26.8 (SD 3.4) in the Temelimab group and 27.1 (SD 3.8) in the placebo group. At 24 weeks, participants receiving the Temelimab treatment had 3.2 points decrease in the PROMIS score, compared to 3.8 in the placebo group. Fig. 1 shows the mean changes in the PROMIS score between baseline, week 12 and week 24. At week 24, a decrease in the PROMIS score $\geq$3 was observed in 47 of 96 participants in the Temelimab group (49%) and in 51 of 94 participants in the placebo group (54%). Overall, the difference between the Temelimab and Placebo group was 0.39 (−0.98, 1.77) at Week 12, and 0.62 (−0.78, 2.01) at week 24. Fig. 1 shows the percent change in the PROMIS score per participant in the Temelimab and placebo groups. There were no significant adverse events reported in this study.

At baseline, participants exhibited a substantial multidimensional disease burden across secondary outcomes, including impaired cognitive performance on the composite BAC score and across individual neurocognitive tests (Verbal Memory Test, Digit Sequencing Test, Token

Table 1
Baseline characteristics per treatment group.

	Temelimab N = 102	Placebo N = 101
Age in years, mean (SD)	46 (11)	46 (10)
Age groups – N(%)		
18–30	8 (7.8%)	9 (8.9%)
31–50	58 (57%)	60 (59%)
51–65	33 (32%)	30 (30%)
>65	3 (2.9%)	2 (2.0%)
Sex – N(%)		
Female	71 (70%)	75 (74%)
Male	31 (30%)	26 (26%)
Race or ethnic group – N(%)		
White	92 (91%)	100 (98%)
Black	2 (2.0%)	0 (0%)
Hispanic or latino	4 (4.0%)	1 (1.0%)
Other	1 (1.0%)	1 (1.0%)
Unknown	2 (2.0%)	0 (0%)
BMI, mean (SD)	25.7 (5.0)	26.3 (4.8)
HERV-W-ENV levels, log2- mean (SD)	0.58 (0.63)	0.52 (0.48)
PROMIS Fatigue S7a score, mean (SD)	27.13 (3.80)	26.83 (3.39)
Composite BAC score, mean (SD)	−0.78 (0.78)	−0.54 (0.80)
Duration of post-COVID condition in days, mean (SD)	649 (307)	653 (316)
Comorbidities – N(%)	46 (45%)	49 (49%)
Pre-existing psychiatric conditions – N(%)	1 (1%)	0 (0%)

BMI: body mass index. Comorbidities included anemia, cardiac disease, endocrine and gastrointestinal disorders.

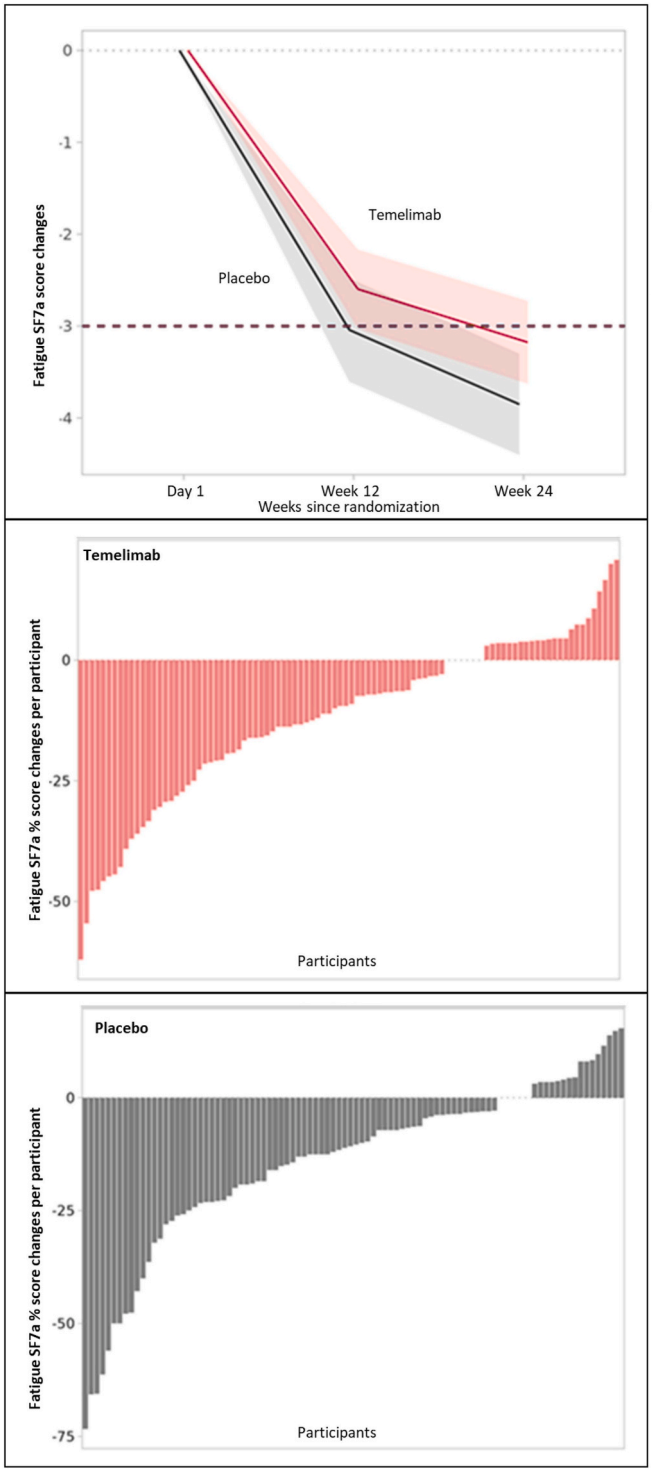

Fig. 1. Changes in mean score of the PROMIS Fatigue SF7a scale between day 1, week 12 and week 24 comparing Temelimab and the placebo group. At week 24, a decrease in the PROMIS score ≥3 was observed in 47 of 96 participants in the Temelimab group (49%) and in 51 of 94 participants in the placebo group (54%). Overall, the difference between the Temelimab and Placebo group was 0.39 (-0.98, 1.77) at Week 12, and 0.62 (-0.78, 2.01) at week 24.

Motor Test, Semantic and Letter Fluency Test, Tower of London Test, and SDMT), as well as high levels of self-reported cognitive complaints measured by PDQ-20. Participants also reported elevated GAD-7 and PHQ-9 scores, alongside reduced quality of life on the EQ5D-5L and functional impairment (SDS, PCFS). Across the 24-week follow-up period, both the Temelimab and placebo groups demonstrated modest improvements across most secondary outcomes, including cognitive performance, perceived cognitive deficits, mental health, quality of life, and functional status measures. Improvements were generally of similar magnitude between groups, with no consistent pattern suggesting superior benefit with Temelimab treatment.

The mean composite BAC score changed by 0.44 (SD 0.50) and 0.48 (SD 0.63) in the Temelimab and placebo groups respectively. The token motor test score changed by 0.27 (0.86) and 0.13 (0.99); the SDMT score by 4.48 (12.11) and 6.41 (14.23) respectively in the Temelimab and placebo groups. The GAD-7 score decreased by 1.24 (4.46) and 2.52 (4.79), and the PHQ-9 score decreased by 1.95 (4.26) and 3.38 (5.32) respectively in the Temelimab and placebo groups. There were no differences in the Sheehan disability scale, numbers of days lost or number of unproductive days between the Temelimab and placebo groups. Exploratory assessments showed no differences in the change of biomarkers, including HERV-W ENV, GFAP, NfL, IL-6, and TNF-alpha between the Temelimab and placebo groups at 24 weeks. Changes in HERV-W ENV levels are shown in Fig. S4, there were no further differences in HERV-W ENV levels between baseline and week 24 when comparing individuals with an improved outcome in fatigue or cognitive dysfunction. Table 2 shows the mean changes of all outcomes (primary and secondary) at week 12 and week 24 compared to baseline, in the Temelimab and placebo groups.

When looking at relative risk, there were no differences between the two groups for the primary outcome of fatigue (relative risk RR 0.9; 95% CI 0.6–1.2), including in subgroups by sex, age, duration of post-COVID condition, baseline scores for fatigue, neurocognitive impairment, disability, anxiety, depression, quality of life and biomarkers levels. Fig. 2 shows the relative risk of a change in the fatigue score between Temelimab and placebo overall and in subgroups of participants. Fig. S3 shows the changes in the fatigue scores stratified by phenotype with no differences in the subgroups. Analyses of secondary outcomes also revealed relative risks that were similar in the Temelimab and placebo groups. When comparing Temelimab to placebo groups, the relative risk of improvement in BAC score was (RR 1.0; 95%CI 0.5******–1.9), SMDT (RR 0.7; 95%CI 0.3-1.5), PDQ-20 (RR 1.1; 95%CI 0.5-2.1), GAD-7 (RR 0.9; 95% CI 0.4-1.6), PHQ-9 (RR 0.4; 95%CI 0.2-0.8), EQ5D-5L (RR 0.8; 95%CI 0.4-1.6), SDS (RR 1.1; 95%CI 0.5-2.3) and PCFS (RR 0.7; 95%CI 0.3-1.5). Fig. 3 shows the relative risk of the secondary outcome improvements, comparing Temelimab to the placebo group at week 24.

4. Discussion

In this trial involving 203 patients with post-COVID condition, there was no improvement in fatigue in the group of individuals who received Temelimab compared to placebo. Results were consistent overall and in subgroup analyses of participants, showing no treatment effect. There were also no differences in the change in secondary outcomes including cognition, anxiety, depression, functional impairment, and QoL when comparing Temelimab to placebo, and both groups improved overall over the 24 weeks. Participants did not experience any significant adverse effects and there was no difference in the adverse effects reported in the Temelimab and placebo groups.

To date, there is no specific treatment nor biomarker for post-COVID condition, leaving millions of patients with chronic symptoms and significant disability (Davis et al., 2021). This is especially important because of the number of individuals affected by this condition and most at the same time, and because insights into treatment for post-COVID condition could help in better understanding and treating post-viral conditions in general. Earlier research showed that persistent immune activation could be associated with post-COVID condition (Peluso et al., 2021; Schultheiß et al., 2022). Current studies include trials targeting potential SARS-CoV-2 viral persistence (Couzin-Frankel, 2024), others are targeting potential dysregulations in the immune pathways leading to potential pro-inflammatory responses or endothelial dysfunctions (Al-

Table 2
Mean change (SD) from baseline in primary and secondary outcomes in the Temelimab and Placebo groups.

Endpoint	Temelimab baseline	Placebo baseline	Temelimab Week 12 change	Placebo Week 12 change	Temelimab Week 24 change	Placebo Week 24 change
Fatigue SF7a score[a]	26.83 (3.39)	27.13 (3.80)	−2.60 (4.24)	−3.04 (5.46)	−3.18 (4.41)	−3.85 (5.34)
Composite BAC score[b]	−0.54 (0.80)	−0.78 (0.78)	0.21 (0.51)	0.22 (0.58)	0.44 (0.50)	0.48 (0.63)
Verbal Memory Test Z-score[b]	−0.17 (1.32)	−0.48 (1.37)	0.26 (0.82)	0.46 (1.08)	0.31 (1.11)	0.56 (1.22)
Digit Sequencing Test Z-score[b]	−0.87 (1.28)	−1.09 (1.20)	0.28 (1.07)	0.36 (0.96)	0.35 (1.09)	0.52 (1.00)
Token Motor Test Z-score[b]	−0.89 (1.35)	−1.19 (1.40)	0.56 (0.92)	0.32 (1.09)	0.86 (0.93)	0.75 (1.00)
Semantic and letter fluency Test Z-score[b]	−0.69 (1.00)	−0.92 (1.04)	0.19 (0.63)	0.30 (0.71)	0.41 (0.81)	0.42 (0.94)
Tower of London Test Z-score[b]	−0.09 (1.09)	−0.21 (0.95)			0.27 (0.86)	0.13 (0.99)
Symbol Digit Modalities Test [SDMT][b]	46.98 (18.72)	47.82 (20.75)	1.54 (11.81)	3.47 (13.56)	4.48 (12.11)	6.41 (14.23)
Perceived Deficits Questionnaire [PDQ-20][a]	47.16 (13.41)	48.69 (13.69)	−6.47 (11.14)	−8.77 (13.13)	−9.01 (12.74)	−12.07 (13.20)
Generalized Anxiety Disorder [GAD-7][a]	8.64 (5.10)	10.06 (5.79)	−1.36 (4.18)	−1.52 (4.67)	−1.24 (4.46)	−2.52 (4.79)
Patient Health Questionnaire [PHQ-9][a]	12.87 (4.99)	14.25 (5.23)	−1.45 (3.95)	−2.12 (5.02)	−1.95 (4.26)	−3.38 (5.32)
European Quality of Life [EQ5D-5L] [b]	43.52 (17.05)	43.59 (18.84)	4.65 (12.95)	6.61 (15.17)	7.17 (15.86)	10.59 (17.89)
Sheehan Disability Scale [SDS][a]	22.78 (5.63)	23.40 (5.59)	−2.05 (5.57)	−3.54 (6.06)	−2.88 (6.36)	−4.51 (6.51)
SDS number of lost days[a]	3.78 (2.85)	3.77 (2.83)	−0.36 (2.39)	−0.63 (2.62)	−0.59 (2.31)	−1.08 (2.84)
SDS number of unproductive days[a]	5.46 (2.07)	5.29 (2.10)	−0.82 (2.85)	−0.97 (2.69)	−1.22 (2.77)	−1.17 (2.68)
Post-COVID-19 Functional Status Scale [PCFS][a]	2.95 (0.64)	3.03 (0.67)	−0.11 (0.66)	−0.16 (0.74)	−0.10 (0.61)	−0.31 (0.76)
HERV-W ENV S/N (log2)	0.52 (0.48)	0.58 (0.63)	−0.66 (0.67)	−0.56 (0.76)	−0.66 (0.76)	−0.55 (0.81)
Serum GFAP (pg/mL) (log2)	6.13 (0.66)	6.22 (0.77)	0.01 (0.36)	−0.05 (0.43)	−0.05 (0.40)	−0.15 (0.48)
Serum NfL (pg/mL) (log2)	2.78 (0.70)	2.95 (0.64)	0.04 (0.29)	−0.04 (0.36)	0.02 (0.25)	0.01 (0.44)
IL-6 (pg/mL)	0.97 (1.24)	1.04 (0.91)			−0.15 (1.08)	−0.04 (0.87)
TNF-alpha (pg/mL)	3.35 (0.53)	3.35 (0.39)			−0.05 (0.37)	−0.13 (0.24)

The tower of London test, IL-6 and TNF-alpha were not measured at week 12 as prespecified in the protocol. [a]Scores with higher values correspond to worse outcomes; change in the negative direction corresponds to improvement in the outcome. [b]Scores with higher values correspond to better outcomes; change in the positive direction corresponds to improvement in the outcome.

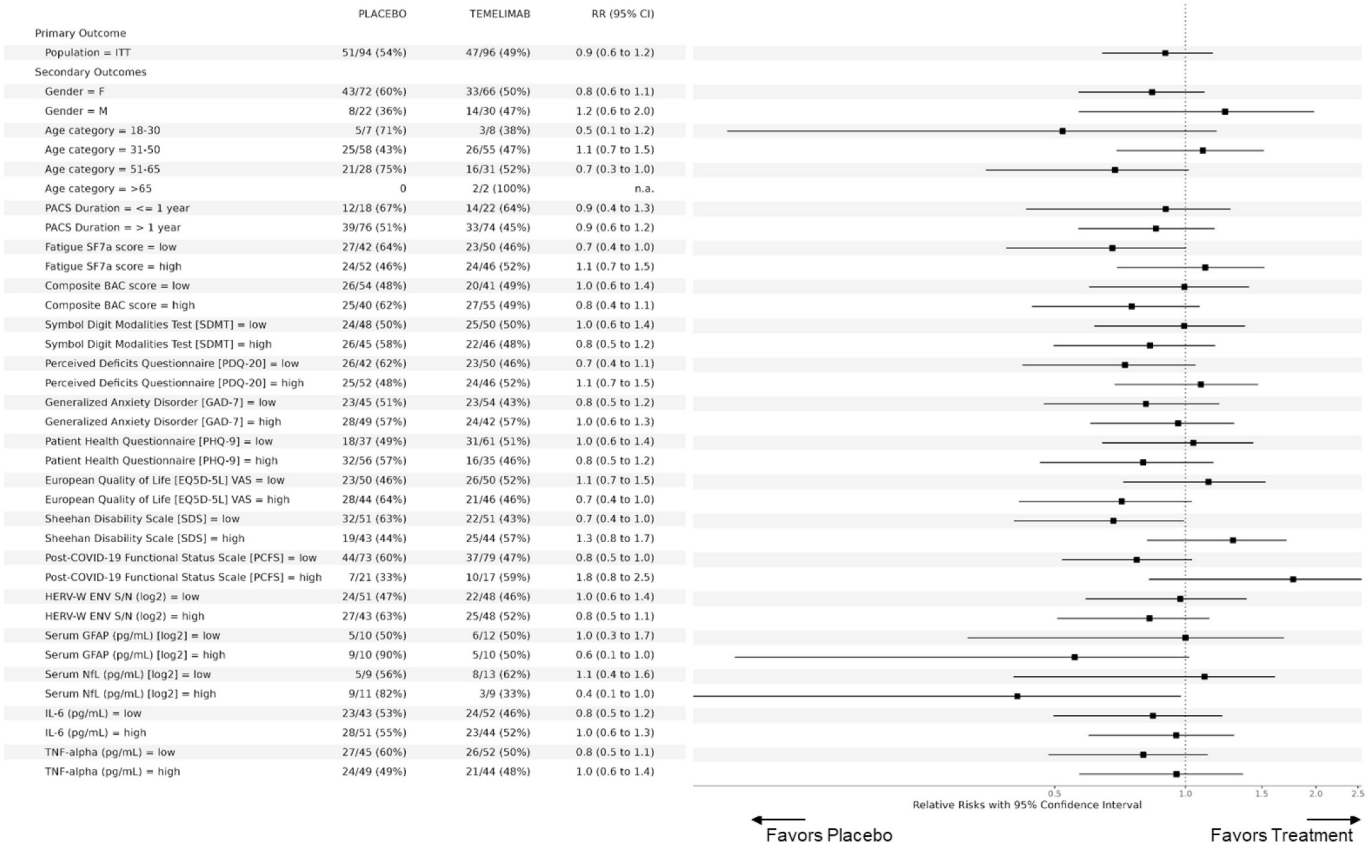

Fig. 2. Relative risk of primary outcome between Temelimab and placebo groups overall and in subgroups of participants. The primary outcome is improvement in fatigue between baseline and week 24 in Temelimab versus placebo group. The relative risk is calculated overall and in subgroups by sex, age, duration of post-COVID condition, baseline scores and baseline biomarker levels. Widths of the 95% confidence intervals were not adjusted for multiplicity.

Aly and Topol, 2024; Ledford, 2022; Diseases, 2023). Completed trials of remdesivir (Patrick-Brown et al., 2024), nirmatrelvir–ritonavir (Sawano

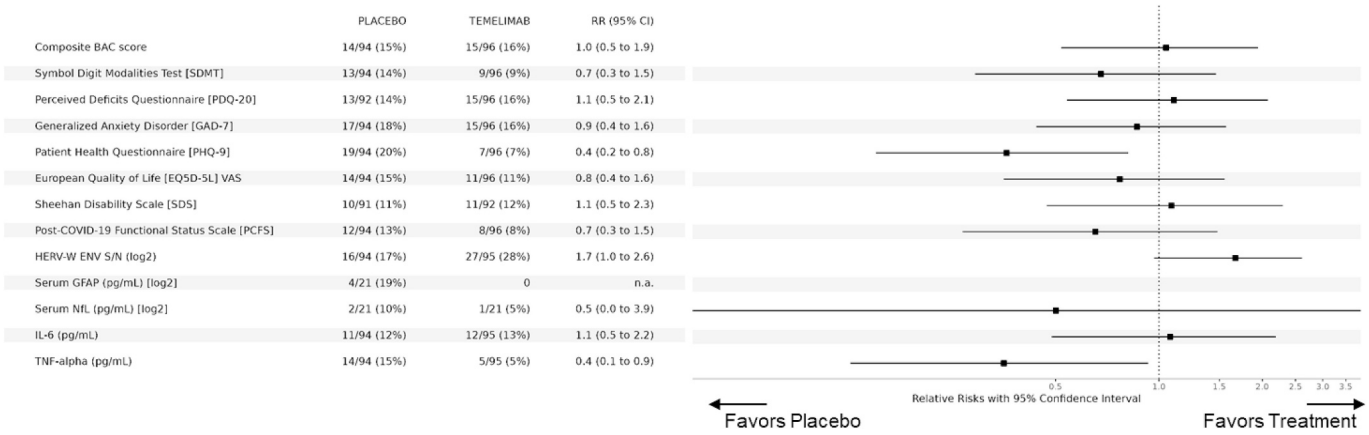

Fig. 3. Relative risk of secondary outcomes between Temelimab and placebo groups. The secondary outcomes are the proportion of patients with improvement in cognitive function (BAC score, SDMT), perceived deficits questionnaire (PDQ-20), generalized anxiety disorder (GAD-7), Patient health questionnaire (PHQ-9), quality of life (EQ5D-5L), sheehan disability scale (SDS), post-COVID 19 functional status scale (PCFS) and the biomarkers (HERV-W-ENV, serum GFAP, serum NfL, IL-6, TNF-alpha) in the Temelimab versus Placebo groups at week 24. Improvement was defined as moving from the above-median to the below-median score for the Fatigue SF7a, PDQ-20, GAD-7, PHQ-9, SDS and PCFS scales, and moving from the below-median to an above-median score for the BAC score, SDMT, and EQ-5D-5L scales. Widths of the 95% confidence intervals were not adjusted for multiplicity.

et al., 2025; Geng et al., 2024), RSLV-132 (Andrews et al., 2024), and AXA1125 (Finnigan et al., 2023) showed no consistent benefit, though AXA1125 reduced fatigue and women responded better to RSLV-132. Low-dose naltrexone with NAD+ (Isman et al., 2024 Feb) improved fatigue and quality of life in a small study, while vortioxetine showed cognitive benefits only after adjusting for CRP (McIntyre et al., 2024). While an earlier study on ivabradine for postural orthostatic tachycardia syndrome POTS (a condition that is potentially associated with post-COVID (Mallick et al., 2023) showed exploratory improvements in executive function (Abdelnabi et al., 2023), more recent results no significant improvement in POTS symptoms in adults with post-COVID receiving ivabradine versus placebo (RECOVER study, 2026). Of note, our study shows improvement in the Tower of London test Z-score in the Temelimab group compared to placebo. While acknowledging that the study was powered only for the primary outcome and that interpretations of any secondary or exploratory outcomes should be considered with caution, this could lead to a better understanding of some of the symptoms of post-COVID as executive dysfunction and difficulties with multitasking or concentration, as seen in clinical assessments. These results should be further examined in future studies. Future studies should aim to recruit large samples of participants, better define fatigue as an outcome and consider subgroup analyses.

Temelimab is a monoclonal neutralizing antibody targeting the HERV-W ENV pathogenic protein that could be detected in post-COVID patients (Curtin et al., 2015; Kremer et al., 2015). Temelimab was developed to selectively bind HERV-W ENV/MSRV-ENV with high affinity (KD approximately 2.2 nM), neutralizing its downstream pro-inflammatory effects rather than inhibiting viral replication. HERV-W ENV protein was considered as a potential pro-inflammatory component contributing to the broad spectrum of neuropsychiatric symptoms experienced by patients with post-COVID condition (Charvet et al., 2023; Balestrieri et al., 2021; Garcia-Montojo and Nath, 2021), through mechanisms involving Toll-like receptor 4 (TLR4)-mediated immune activation and neuroinflammation. The biological rationale linking HERV-W ENV to post-COVID symptoms may also differ according to clinical manifestation. HERV-W ENV has been implicated in neuroinflammatory pathways that may plausibly contribute to neurocognitive symptoms (Balestrieri et al., 2021; Garcia-Montojo and Nath, 2021). Similarly, persistent immune activation and neuroinflammation have been hypothesized to contribute to central fatigue and post-exertional symptom exacerbation (Phetsouphanh et al., 2022). The absence of a treatment effect across fatigue, cognitive, and functional outcomes in our study may suggest that HERV-W ENV-associated pathways are not dominant drivers of symptoms in an unselected post-COVID population, or alternatively that only specific biologically defined subgroups may derive benefit from targeted HERV-W neutralization. In the era of precision medicine, it is important to find biomarkers and targeted therapy for conditions. While results in this study did not show HERV-W-ENV to be a biomarker for post-COVID, research should continue to focus on finding biomarkers for this disease. It should also be noted that the HERV-W ENV test was designed primarily as an inclusion criterion to detect baseline presence of the protein and the absence of a change in group-level signal after treatment cannot be interpreted as absence of pharmacological activity.

This study was one of the first large randomized controlled trials evaluating the efficacy of a specific and targeted therapy in post-COVID condition. Although Temelimab did not demonstrate a treatment benefit, the study provides several important contributions. The study delivers high-quality evidence that helps refine therapeutic development. This prevents unnecessary exposure of patients to ineffective therapies and redirects research efforts toward more promising biological pathways. Second, the study establishes a robust methodological framework for future post-COVID interventional studies, demonstrating feasibility of recruitment, retention, and outcome measurement for a medical condition that is not easily defined or measured. Negative findings are essential for building cumulative scientific knowledge, reducing publication bias and showing complete transparency in research.

This study has some limitations including the lack of an objective measurement in the primary outcome. Unfortunately to date, there is no objective measurement of fatigue or post-COVID condition and this could be one of the limiting factors in several studies looking at treatment options. Additionally, the study was only powered for the primary outcome, leaving subgroup detection uncertain with wide confidence intervals. Future studies should focus on subgroups or some of the secondary outcomes that could be of interest according to new knowledge about the disease, such as executive function. The mean duration of post-COVID condition for participants was 651 days, raising the possibility that chronicization of symptoms may have reduced responsiveness to treatment. However, stratified analyses by duration of post-COVID condition did not reveal differences in treatment effect. Finally, our study hypothesized HERV-W-ENV as a target pathway in post-COVID condition, thus limiting the ability to evaluate treatment effect in patients with post-COVID condition who were HERV-W-ENV negative, and 98% of participants were Caucasian, reducing the generalizability of the results to more diverse populations.

In conclusion, this study was one of the first large randomized controlled trials evaluating a treatment for post-COVID condition. While the results are negative, they help guide researchers and the scientific community towards other potential treatment options and still show the enduring impact of post-COVID condition with patients having persistent symptoms and functional impairment for years after SARS-CoV-2 infection.

CRediT authorship contribution statement

Mayssam Nehme: Writing – review & editing, Writing – original draft, Investigation. **Margret Hund-Georgiadis:** Writing – review & editing, Investigation. **Esther Del Corral Beamonte:** Writing – review & editing, Investigation. **Pierre-Olivier Bridevaux:** Writing – review & editing, Investigation. **Robert Hoepner:** Writing – review & editing, Investigation. **Iris-Katharina Penner:** Writing – review & editing, Investigation. **Joana Strobel:** Writing – review & editing, Investigation. **Gregory Fretz:** Writing – review & editing, Investigation. **Mercè Boada Rovira:** Writing – review & editing, Investigation. **Francesc Puchades:** Writing – review & editing, Investigation. **Francesco Landi:** Writing – review & editing, Investigation. **Pablo Guisado Vasco:** Writing – review & editing, Investigation. **Giovanni Guaraldi:** Writing – review & editing, Investigation. **Francisco Mera Cordero:** Writing – review & editing, Investigation. **Luca Sebastianelli:** Writing – review & editing, Investigation. **Loredana Sarmati:** Writing – review & editing, Investigation. **Nathalie Berthuy:** Writing – review & editing, Project administration. **Jérôme Wojcik:** Writing – review & editing, Writing – original draft, Formal analysis. **Karim Keddad:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Anke Post:** Writing – review & editing, Project administration, Investigation. **David Leppert:** Writing – review & editing, Conceptualization. **Idris Guessous:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mayssam Nehme: speaking fees (Pfizer). Margret Hund-Georgiadis: no competing interest. Esther Del Corral Beamonte: no competing interest. Pierre-Olivier Bridevaux: no competing interest. Robert Hoepner: received speaker/advisor honorary from Merck, Novartis, Roche, Biogen, Alexion, Sanofi, Janssen, Bristol-Myers Squibb, Teva/Mepha and Almirall. He received research support within the last 5 years from Roche, Merck, Sanofi, Biogen, Chiesi, and Bristol-Myers Squibb. He also received research grants from the Swiss MS Society, the SITEM Insel Support Fund and is a member of the Advisory Board of the Swiss and International MS Society. He also serves as deputy editor in chief for Journal of Central Nervous System disease and is part of the ECTRIMS Young Investigator Committee. Iris-Katharina Penner: Honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Almirall, Bayer Pharma, Biogen, Celgene, Sanofi-Genzyme, Janssen, Merck, Neuraxpharm, Novartis, Roche, and Teva. Research support from the German MS Society, Celgene, Novartis, Roche, and Teva. Joana Strobel: no competing interest. Mercè Boada Rovira: no competing interest. Francesc Puchades: no competing interest. Francesco Landi: no competing interest. Pablo Guisado Vasco: Angelini Pharma Spain - consulting fees, Berlin Cures GmbH – advisory board fees, GlaxoSmithKline (Spain) - speaking fees and meetings grants, Pharma Mar SA (Spain) – speaking, consulting, meeting grants & advisory board fees, Pfizer (Spain) – speaking fees. Giovanni Guaraldi: no competing interest. Francisco Mera Cordero: no competing interest. Luca Sebastianelli: no competing interest. Loredana Sarmati: no competing interest. Nathalie Berthuy: employee of Geneuro. Jérôme Wojcik: statistician of the trial and consultant statistician for Geneuro. Karim Keddad: employee of Geneuro. Anke Post: employee of Geneuro. David Leppert: former Chief Medical Officer of Geneuro, consultant for Geneuro. Idris Guessous: member of the Fatigue Differential Diagnostic Aid (FDDA) study that was funded by CSL-Vifor.

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Patient consent for publication

Not applicable.

Data statement

No data are available at this stage.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2026.106892.

Data availability

Data will be made available on request.

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