Supplementary Appendix

Supplement to: Reis G, Silva EASM, Medeiros Silva DC, et al. Early treatment with pegylated interferon lambda for Covid-19. N Engl J Med 2023;388:518-28. DOI: 10.1056/NEJMoa2209760

This appendix has been provided by the authors to give readers additional information about the work.

Table of Contents: Supplementary Information, Figures, and Tables

Trial Infrastructure and the Extended TOGETHER investigators

The COVID-19 TOGETHER Trial initiative was designed to evaluate repurposed treatments for COVID-19 disease through an adaptive trial design in two arms being conducted in Brazil and Canada. The trial is supported by a network of primary care research centers located in the state of Minas Gerais, Brazil and several sites in Toronto, Canada, devoted to a comprehensive evaluation and treatment of patients with COVID-19. The trial was fully integrated with local public health authorities (Brazilian Unified Health System – SUS) as part of coping strategy for COVID-19 pandemic. Namely, the main institutions involved were: Cardresearch – Cardiologia Assistencial e de Pesquisa and Toronto Centre for Liver Disease, University Health Network, Michael Garron Hosptal, Sunnybrook Health Science Centre, Trillium Health Partners, Women's College Hospital. This initiative is funded by FastGrants, The Rainwater Foundation, Eiger BioPharmaceuticals and the FTX Foundation.

The TOGETHER Trial consortium is a partnership between academics and clinicians at McMaster University in Ontario, Canada, and Pontificia Universidade Catolica de Minas Gerais, Claros State University, University of Ouro Preto in Minas Gerais, Brazil and University Health Network in Ontario, Canada. Other partners include Cytel, Platform Life Sciences, MMS Holdings, WHO Therapeutic Guidelines Committee, and the Society for Clinical Trials.

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Participating Enrolling Centres

Included below are representatives from the enrolling centres at participating cities that enrolled at least 1 patient. Centres are listed in order of enrolment contribution. All study sites were located in the State of Minas Gerais, Brazil or Ontario, Canada.

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Women's College Hospital
Marc Dagher

Public health authorities and mayors

We are in debt with the following local public health authorities and mayors (listed by enrollment):

City of Ibirité

William Parreira Duarte (Mayor), Carina Bitarães (public health authority)

City of Sete Lagoas

Duílio de Castro (Mayor), Flávio Pimenta Silveira (public health authority), Alber Alípio Ribeiro (public health authority)

City of Betim

Vittorio Medioli (Mayor), Augusto Viana da Rocha (public health authority), Hilton Soares de Oliveira, Tânia Maria de Resende Amaral (public health authority)

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City of Ouro Preto

Angelo Oswaldo de Araujo Santos (Mayor), Glauciane Resende do Nascimento (public health authority)

Supplemental Methods:

Description of Prolonged ER Visits and Modification of Primary Endpoint

When we initially proposed the study, we defined one of the endpoints as emergency care extended treatment of at least 12 hours. However, during the initial weeks of the trial, we found that patients rarely stayed for more than 12 hours at emergency units for extended care and later discharged home due to the progressive overcrowding of emergency units and referral centers for COVID-19. From March 2021, the health units in Minas Gerais State in Brazil experienced a depletion of their hospital bed capacities with >90% occupancy. During the period from May to mid-July 2021, there was >100% occupancy of available hospital beds, leading to situations of "hospitalization" in the corridors of the units as there were no longer available hospital beds.

The lack of available hospitals to accommodate patients with moderate to severe COVID-19 was then reflected in the emergency units, where the only option available to frontline medical teams was to release patients as quickly as possible to give others the opportunity to be treated with a minimum decent standard of medical care.

Thus, patients presenting with O_2 saturation between 85-93% and dyspnea without overt respiratory failure (i.e. FDA criteria of severe COVID-19)[1] were treated, undergoing initial respiratory stabilization which included high-dose intravenous corticosteroids, supplemental oxygen, full inhalation therapy, and sometimes antibiotics, and a short stay at ER observation bed unit to monitor O_2 saturation and assess for progressive deterioration of respiratory status.

Usually after 4-6 hours, these patients under ER observation were re-evaluated with a decision made for being discharge home or hospitalized. In general, many ER patients were discharged home in less than 6 hours, and the majority of patients were discharged in less than 12 hours so long as they were able to maintain their O_2 saturation at $\geq$ 90%. Patients discharged after prolonged ER observation were followed at a homecare program designed especially for persons with COVID-19. Persons unable to be maintain their O_2 saturations above 90% were prioritized for hospital admission.

Rational for modification of primary endpoint: Due to the limitations in health system capacity, we realized that a minimum observation period of 12 hours was unrealistic to capture participants with moderate/severe COVID-19. For this reason, we asked the National Research Ethics Commission in Brazil to modify the protocol endpoint to be at least 6 hours of ER observation instead of 12 hours. This change, based on the real world of care provided by the public emergency services of the Health System, was approved. This change was registered on clinicaltrials.gov on March 21, 2021. No data were analyzed prior to this change, and all blinding was maintained.

These persons presenting with O_2 saturation between 85-93% and dyspnea who underwent > 6 hours of observation are consistent with the U.S. FDA definition of severe COVID-19.[1]

- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress

- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$

Representativeness of study populations

The TOGETHER data can be generalized to the US population for the following reasons:

1. Populations at risk for COVID-19 morbidity and mortality

The populations most at risk for COVID-19 morbidity and mortality are Hispanic, Black, and American Indian / Alaska Native (AIAN) peoples. Approximately 18% (50.5 million) of the US population is Hispanic and 12.4% (41.1 million) is Black, collectively making up over 30% of the total US population.

The most recent demographic data from the CDC (https://covid.cdc.gov/covid-data-tracker/#demographics) indicate the following:

- Hispanic people represent a larger proportion of COVID-19 cases relative to their proportion of the population (24% vs 18%, respectively).
- Black people account for approximately 13% of cases and 13% of deaths due to COVID-19.
- The largest number of cases are observed in the 18-64 years-old age group. When adjusted for age, Hispanic, Black, and AIAN people are about 2-times more likely to die from COVID-19 compared to White people, and Hispanic and AIAN people are 1.5-times greater risk of COVID-19 infection than White people.
- There are also large disparities in death and hospitalization for AIAN, Black, and Hispanic people. Hispanic, Black, and AIAN people are almost 3-times as likely to die from COVID-19 and about 4-times as likely to be hospitalized for COVID-19 as White people.

The population in the TOGETHER study is drawn from 12 sites in Brazil and five sites in Canada. It is primarily composed of patients from these high-risk groups:

- Black/African American: 1.9%, Brazil alone and Brazil + Toronto combined
- Hispanic/Latino: 94.8% Brazil alone, 96.4% Brazil + Toronto combined
- The majority of patients were aged 18-69 (95.6% Brazil, 95.3% Brazil + Toronto combined)

2. Risk factors for COVID-19-related morbidity and mortality

It is estimated that 41.9% of the US population is obese (https://www.cdc.gov/obesity/data/adult.html). The proportion of obese patients in the Brazil as well as Brazil + Canada combined populations was 38.1%.

3. Vaccination status and vaccine type

It is estimated that 80.3% of the US population have received at least one dose of a vaccine.

Approximately 84% of the TOGETHER study population (Brazil alone and Brazil + Canada combined) had received at least one dose of a vaccine.

Lambda was effective and improved clinical outcomes in the sub-group of vaccinated patients (primary endpoint RR 0.54, CrI [0.31, 0.91], Pr 0.991).

Directly relevant to the US population is the type of vaccine. A total of 56.6% of the vaccinated patients from Brazil received either the AstraZeneca (47.7%) or Pfizer (20.3%) vaccine. The Moderna vaccine was most common among patients from Canada. Among those patients who received the AstraZeneca or Pfizer vaccine, the RR for the primary endpoint was 0.43, CrI [0.20, 0.86].

Vaccination rates are much lower among the high-risk populations compared to White people. According to the most recent CDC data, unvaccinated people are 6-times more likely to die from COVID-19. Only 21% of Hispanics and 10% of Black people are vaccinated (https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic). Lambda was equally effective among patients who were unvaccinated: RR primary endpoint 0.45, CrI [0.18, 0.99].

4. SARS-CoV-2 Variants of Concern

The Delta and Omicron variants were the most recent variants of concern in the US, with new Omicron variants now being reported with increasing frequency. Lambda is effective against multiple variants of the SARS-CoV-2 virus. The mechanism of action makes it unlikely that resistance to treatment will emerge.

A temporal analysis of the effect of Lambda overtime accounting for different variants of the SARS-CoV-2 virus was previously submitted (IND154,118 SN0008, module 1.11.3). Briefly, three variants of concern predominated during the course of the TOGETHER study in Brazil: Delta, Gamma, and Omicron. In Canada the Omicron variant was the major variant of concern.

Lambda was effective against all three variants of concern:

- The relative risk reduction (RRR) during the Delta period (46%)
- The RRR was lower in the Gamma variant period (25%), which had a smaller sample size than the other time intervals.
- The RRR improved to 83% risk during the period in which the Omicron variant was dominant.

Collectively, these data indicate the results of the TOGETHER study are directly applicable to the US population.

Description of Statistical Methods

All analyses involving dichotomous outcomes, including the primary outcome, were performed using the Bayesian beta-binomial model with uniform prior distributions for the individual arm event rates. Relative risks and posterior efficacy were evaluated based on size 10^6 Monte Carlo samples from the resultant Beta posterior distributions. The choice of prior distribution was a Beta distribution because it is a conjugate prior for a Binomial likelihood. This was critical to allowing for interim analyses updates to be made using analyses that reflected prior interim analyses and allowing for simulations that allowed to control for multiplicity. The posterior distribution is then solved for using a closed-form equation based on its relationship to priors and posteriors. Summaries were derived using Monte Carlo samples from the posterior distributions of the two arms. The choice of uniform priors was, in part, made to minimize the impact of prior information, or lack thereof, on the statistical inference. However, given the study size, no major impact of said choice was expected on the estimation, while interim analysis decision boundaries were calibrated to meet frequentist criteria of power and type I error rate. See the statistical analysis plan for more detail.

Time-to-event analyses that were not adjusted for competing risks, and numeric secondary outcomes, were performed using the default Bayesian implementation of the Cox proportional hazards model in the *brms* R library[2] with four independent Markov Chain Monte Carlo (MCMC) chains of size 4,000 each and a flat prior distribution assigned to the treatment assignment coefficient. The likelihood is a function of the hazard rate, cumulative hazard and survival probability as described here (https://arxiv.org/pdf/2002.09633.pdf). The prior and posterior distributions for each of the parameters were Normally distributed. Posterior distributions were estimated using the Hamiltonian Monte Carlo, which ia form of Markov Chain Monte Carlo in which information about the gradient of the log posterior is used to more efficiently sample from the posterior space. This was implemented in Stan using the No-U-Turn Sampler (NUTS).

A longitudinal mixed effects linear regression, with participant entered as a random effect, was used to evaluate the antiviral effect over time. Due to the rapidly changing nature of COVID, the variant of concern changed during the study period. Therefore, we categorized patients by variant of concern when the Gamma, Delta, or Omicron variant were dominant within the sample, and carried out an exploratory subgroup analysis using these categories. This analysis is exploratory. A treatment by time interaction was used to look for differential changes in viral load from baseline between the groups accounting for variants. Ct values were converted to copies/ml using a standard curve obtained from the same machine, and analysis were carried out on log10 (copies/mL). Days since randomization was entered as a factor, with Day 0 as the reference category. We categorized baseline load, *a priori*, as high (the 15% of patients with the highest baseline load) or low as a three-way interaction with treatment and days since randomization. In addition, to account for additional variance, we included age, sex, days since onset of symptoms and vaccination status at randomization, and whether Omicron B.11529 was the dominant variant at the time of randomization. For tests where the N2 target was not detected, they were assigned a viral load of 0 for calculation purposes.

Figures S1-3 are purely descriptive and did not inform formal statistical inference.

Description of Virological Assays

SARS-CoV-2 quantification was performed at the central laboratory of Precision Medicine Labs (Belo Horizonte, MG, Brazil) using the quantitative real-time PCR CDC protocol for the N gene with N1 and N2 primers.[5] RNaseP was run on all samples to confirm sample integrity. Samples negative for RNaseP with undetectable SARS-CoV-2 RNA were counted as missing for all analyses. To convert cycle threshold (Ct) values to quantitative values, a standard curve was generated using a plasmid-derived cDNA standard. The limit of detection was determined to be 10 copies/µL for the N2 primer. Samples below the limit of detection were counted as undetectable. Samples from the Canadian cohort were quantified similarly using a protocol for the E gene[6] as well as the CDC protocol for N gene.[5]

Determination of SARS-CoV-2 variant was performed using exclusion PCR for mutational analysis according to the table below.

Variant	N501Y	E484K	K417T	K417N	L452R	E484Q	P681R	G339D
Alpha (B.1.1.7)								
Beta (B.1.351)								
Delta (B.1.617.2)								
Delta não VOC (B.1.617.1)								
Omicron (B.1.1.529)								
Zeta (P.2)								
Gamma (P.1)								
Mu (B.1.621)								

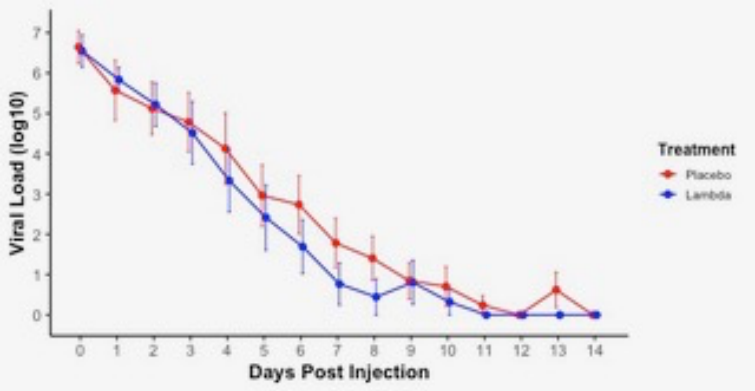
Viral kinetics Days 0-14 among patients in the Canadian cohort

Virological data are shown for the subset of participants (n=30) who did daily self-collected swabs for 14 days after treatment.

Figure S1: Mean SARS-CoV-2 viral load and viral load decline

a) Mean SARS-CoV-2 viral load and b) Mean decline in SARS-CoV-2 viral load in log copies/mL from baseline through Day 14 post-injection are shown for the peginterferon lambda and placebo groups. Error bars represent standard error of the mean.

a.



b.

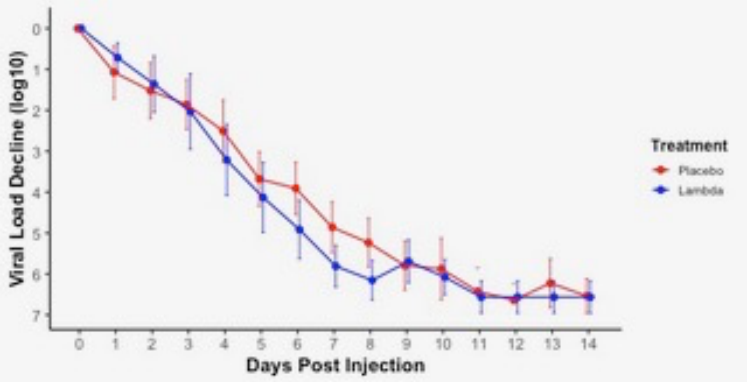
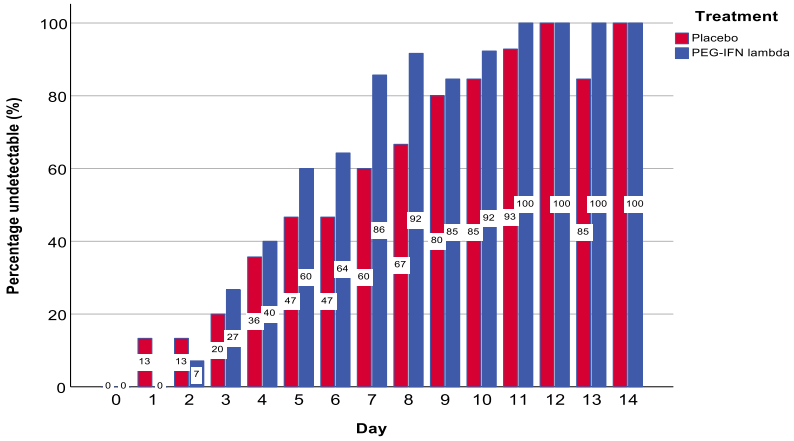


Figure S2: Proportion of patients negative for SARS-CoV-2 RNA per day after the injection
The proportion of participants who had a negative swab for SARS-CoV-2 RNA at each day post injection is shown for the peginterferon lambda (blue) and placebo (red) groups. After controlling for baseline viral load, the odds of clearance at Day 7 were higher in the peginterferon lambda than placebo group (OR 9.35, 95% CI 1.42-103.61).



570 **Figure S3: Proportion of patients negative for SARS-CoV-2 RNA per day after injection and**
571 **probability of testing negative by Day 7 based on baseline SARS-CoV-2 viral kinetics.**

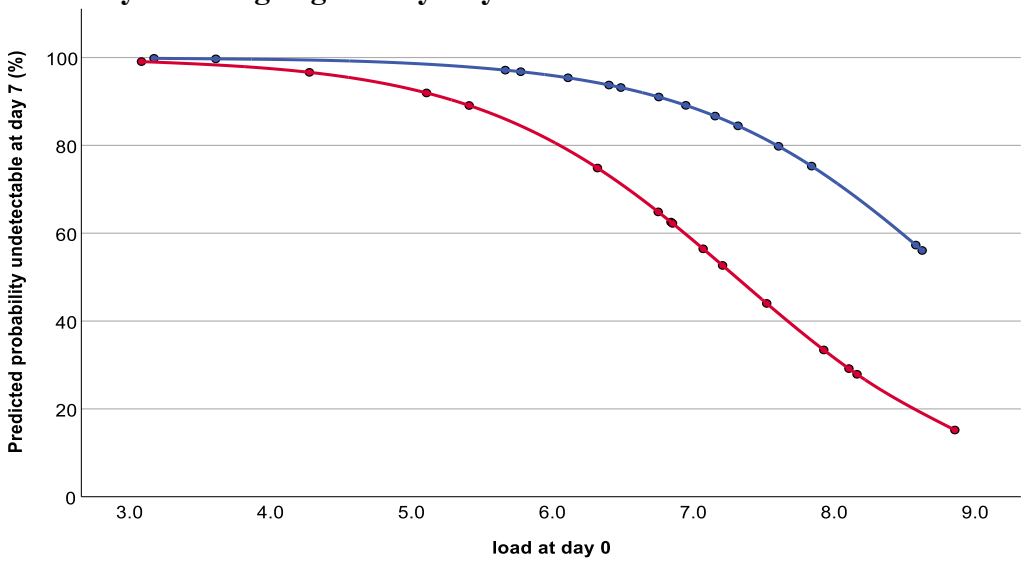


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Figure S4: Relative risk of being hospitalized or in observance in an emergency room for at least 6 hours for peginterferon lambda versus placebo (early onset [0-3 days] subgroup)

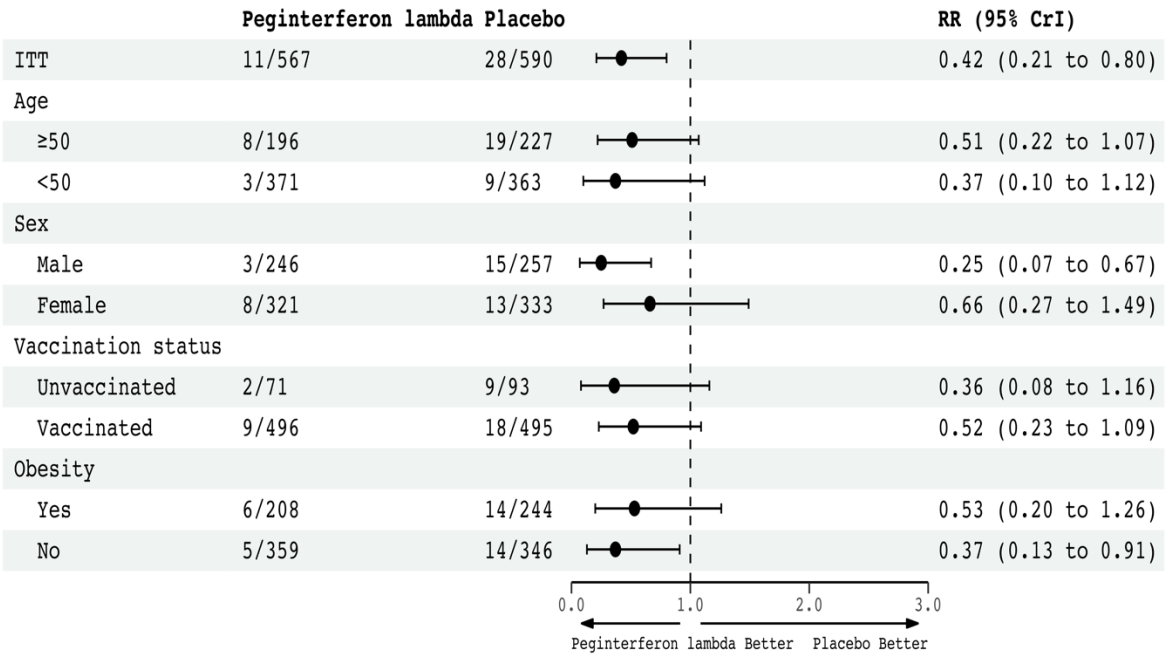
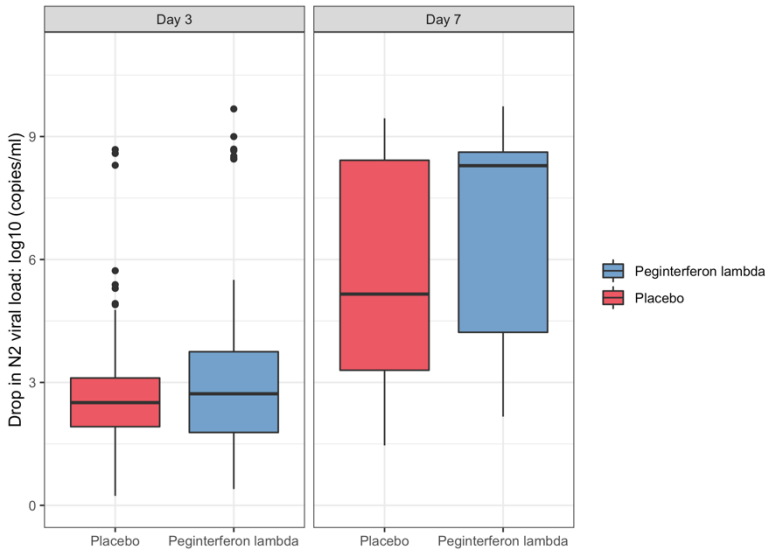


Figure S5. Change in viral load from baseline, days 3 and 7.



Legend: Box plot shows median, inter-quartile range, minimum and maximum, and outliers more than 1.5*inter-quartile range.

Table S1: Primary and secondary outcomes for peginterferon lambda versus placebo (ITT population)

	Measure	Peginterferon lambda*	Placebo*	Estimated treatment effect
		(n=916)	(n=1003)	
Hospitalization or ER > 6h for COVID-19	RR (95% CrI)	25 (2.7%)	57 (5.7%)	0.49 (0.30, 0.76)
Hospitalization or ER (any duration) for COVID-19	RR (95% CrI)	99 (10.8%)	140 (14%)	0.78 (0.61, 0.99)
Death due to COVID-19	RR (95% CrI)	1 (0.1%)	4 (0.4%)	0.40 (0.05, 1.95)
Death or hospitalization due to COVID-19	RR (95% CrI)	22 (2.4%)	40 (4%)	0.61 (0.36, 0.99)
All cause death or hospitalization due to COVID-19	RR (95% CrI)	24 (2.6%)	40 (4%)	0.66 (0.40, 1.07)
All cause ER visit, hospitalization, or death	RR (95% CrI)	124 (13.5%)	151 (15.1%)	0.90 (0.72, 1.12)
All cause ER visit >6h, hospitalization, or death	RR (95% CrI)	34 (3.7%)	59 (5.9%)	0.64 (0.42, 0.95)
Mechanical ventilation	RR (95% CrI)	4 (0.4%)	7 (0.7%)	0.66 (0.20, 2.03)
Days on mechanical ventilation	IRR (95% CrI)			-4.47 (-6.89, 3.09)
Days of hospitalization	IRR (95% CrI)			-1.02 (-3.86, 1.37)
Days to hospitalization for COVID-19	HR (95% CrI)			0.57 (0.33, 0.95)
Days to hospitalization or ER visit > 6h for COVID-19	HR (95% CrI)			0.47 (0.29, 0.73)
Days to death for COVID-19	HR (95% CrI)			0.22 (0.01, 1.64)
Days to hospitalization or death for COVID-19	HR (95% CrI)			0.59 (0.35, 0.97)
Days to recovery	HR (95% CrI)			0.94 (0.85, 1.05)

*For categorical outcomes, totals and percentages are shown. For time-to-event outcomes, medians and 95% CIs are shown. For continuous outcomes, medians and ranges are shown. CI, confidence interval; CrI, credible confidence interval; HR, hazard ratio; RR, relative risk; TEAE, treatment emergent adverse events.

Table S2: Primary and secondary outcomes for peginterferon lambda versus placebo (Treated within 3 days of symptom onset population)

	Measure	Peginterferon lambda*	Placebo*	Estimated treatment effect
		(n=567)	(n=590)	
Hospitalization or ER > 6h for COVID-19	RR (95% CrI)	11 (1.9%)	28 (4.7%)	0.42 (0.21, 0.80)
Hospitalization for COVID-19	RR (95% CrI)	8 (1.4%)	23 (3.9%)	0.38 (0.17, 0.79)
Hospitalization or ER (any duration) for COVID-19	RR (95% CrI)	54 (9.5%)	79 (13.4%)	0.71 (0.51, 0.98)
Death due to COVID-19	RR (95% CrI)	0 (0%)	3 (0.5%)	0.19 (0.01, 1.57)
Death or hospitalization due to COVID-19	RR (95% CrI)	8 (1.4%)	23 (3.9%)	0.38 (0.17, 0.79)
All cause death or hospitalization due to COVID-19	RR (95% CrI)	9 (1.6%)	23 (3.9%)	0.42 (0.19, 0.86)
All cause ER visit, hospitalization, or death	RR (95% CrI)	69 (12.2%)	86 (14.6%)	0.84 (0.62, 1.12)
All cause ER visit > 6h, hospitalization, or death	RR (95% CrI)	14 (2.5%)	28 (4.7%)	0.53 (0.28, 0.97)
Mechanical ventilation	RR (95% CrI)	2 (0.4%)	4 (0.7%)	0.59 (0.12, 2.49)
Days on mechanical ventilation	MD (95% CrI)			-3.09 (-6.83, 5.73)
Days of hospitalization	MD (95% CrI)			-0.18 (-4.07, 2.82)
Days to hospitalization for COVID-19	HR (95% CrI)			0.35 (0.15, 0.75)
Days to hospitalization or ER visit > 6h for COVID-19	HR (95% CrI)			0.40 (0.20, 0.79)
Days to death for COVID-19	HR (95% CrI)			0.00 (0.00, 0.55)
Days to hospitalization or death for COVID-19	HR (95% CrI)			0.35 (0.15, 0.75)
Days to recovery	HR (95% CrI)			1.01 (0.89, 1.14)

*For categorical outcomes, totals and percentages are shown. For time-to-event outcomes, medians and 95% CIs are shown. CI, confidence interval; CrI, credible confidence interval; HR, hazard ratio; MD, mean difference; RR, risk ratio. These analyses were exploratory and have not been corrected for multiplicity.

Table S3: Primary and secondary outcomes for peginterferon lambda versus placebo (Modified intention to treat population)

	Measure	Peginterferon lambda*	Placebo*	Estimated treatment effect
		(n=929)	(n=1016)	
Hospitalization or ER > 6h for COVID-19	RR (95% CI)	23 (2.5%)	55 (5.4%)	0.47 (0.29, 0.73)
Hospitalization for COVID-19	RR (95% CrI)	19 (2%)	38 (3.7%)	0.56 (0.32, 0.93)
Hospitalization or ER (any duration) for COVID-19	RR (95% CrI)	97 (10.4%)	138 (13.6%)	0.77 (0.60, 0.98)
Death due to COVID-19	RR (95% CrI)	1 (0.1%)	4 (0.4%)	0.39 (0.05, 1.91)
Death or hospitalization due to COVID-19	RR (95% CrI)	20 (2.2%)	38 (3.7%)	0.59 (0.34, 0.98)
All cause death or hospitalization due to COVID-19	RR (95% CrI)	22 (2.4%)	38 (3.7%)	0.64 (0.38, 1.05)
All cause ER visit, hospitalization, or death	RR (95% CrI)	122 (13.1%)	149 (14.7%)	0.90 (0.72, 1.11)
All cause ER visit > 6h, hospitalization, or death	RR (95% CrI)	32 (3.4%)	57 (5.6%)	0.62 (0.41, 0.93)
Mechanical ventilation	RR (95% CrI)	4 (0.4%)	7 (0.7%)	0.67 (0.20, 2.02)
Days on mechanical ventilation	MD (95% CrI)			-4.47 (-6.89, 3.09)
Days of hospitalization	MD (95% CrI)			-1.10 (-4.14, 1.49)
Days to hospitalization for COVID-19	HR (95% CrI)			0.53 (0.30, 0.93)
Days to hospitalization or ER visit > 6h for COVID-19	HR (95% CrI)			0.45 (0.27, 0.72)
Days to death for COVID-19	HR (95% CrI)			0.20 (0.01, 1.83)
Days to hospitalization or death for COVID-19	HR (95% CrI)			0.56 (0.33, 0.95)
Days to recovery	HR (95% CrI)			0.94 (0.85, 1.05)

*For categorical outcomes, totals and percentages are shown. For time-to-event outcomes, medians and 95% CIs are shown. CI, confidence interval; CrI, credible confidence interval; HR, hazard ratio; MD, mean difference; RR, risk ratio.

Table S4: Primary and secondary outcomes for Peginterferon lambda versus placebo (Matched placebo population)

	Measure	Peginterferon lambda*	Placebo*	Estimated treatment effect
		(n=931)	(n=825)	
Hospitalization or ER > 6h for COVID-19	RR (95% CI)	25 (2.7%)	43 (5.2%)	0.52 (0.32, 0.84)
Hospitalization for COVID-19	RR (95% CrI)	21 (2.3%)	29 (3.5%)	0.65 (0.37, 1.11)
Hospitalization or ER (any duration) for COVID-19	RR (95% CrI)	99 (10.6%)	109 (13.2%)	0.81 (0.62, 1.04)
Death due to COVID-19	RR (95% CrI)	1 (0.1%)	3 (0.4%)	0.40 (0.05, 2.23)
Death or hospitalization due to COVID-19	RR (95% CrI)	22 (2.4%)	29 (3.5%)	0.68 (0.39, 1.16)
All cause death or hospitalization due to COVID-19	RR (95% CrI)	24 (2.6%)	29 (3.5%)	0.74 (0.43, 1.24)
All cause ER visit, hospitalization, or death	RR (95% CrI)	124 (13.3%)	117 (14.2%)	0.94 (0.74, 1.19)
All cause ER visit > 6h, hospitalization, or death	RR (95% CrI)	34 (3.7%)	43 (5.2%)	0.70 (0.45, 1.08)
Mechanical ventilation	RR (95% CrI)	4 (0.4%)	5 (0.6%)	0.73 (0.21, 2.48)
Days on mechanical ventilation	MD (95% CrI)			-4.05 (-6.87, 4.27)
Days of hospitalization	MD (95% CrI)			-0.85 (-3.97, 1.98)
Days to hospitalization for COVID-19	HR (95% CrI)			0.63 (0.35, 1.11)
Days to hospitalization or ER visit > 6h for COVID-19	HR (95% CrI)			0.51 (0.31, 0.85)
Days to death for COVID-19	HR (95% CrI)			0.25 (0.01, 2.18)
Days to hospitalization or death for COVID-19	HR (95% CrI)			0.66 (0.38, 1.17)
Days to recovery	HR (95% CrI)			0.95 (0.85, 1.06)

*For categorical outcomes, totals and percentages are shown. For time-to-event outcomes, medians and 95% CIs are shown. CI, confidence interval; CrI, credible confidence interval; HR, hazard ratio; MD, mean difference; RR, risk ratio.

Table S5: Summary of 10 most frequent adverse events

	# Events (% of total events)		
	Peginterferon lambda	Placebo	Overall
COVID-19	67 (39.4)	85 (40.1)	152 (39.8)
COVID-19 pneumonia	24 (14.1)	40 (18.9)	64 (16.8)
Dyspnoea	8 (4.7)	8 (3.8)	16 (4.2)
Influenza like illness	5 (2.9)	7 (3.3)	12 (3.1)
Cough	4 (2.4)	6 (2.8)	10 (2.6)
Fatigue	1 (0.6)	5 (2.4)	6 (1.6)
Headache	4 (2.4)	2 (0.9)	6 (1.6)
Vertigo	2 (1.2)	4 (1.9)	6 (1.6)
Chest pain	1 (0.6)	4 (1.9)	5 (1.3)
Back pain	3 (1.8)	1 (0.5)	4 (1.0)

Percent refers to total adverse events, not total patients.

Table S6: Mortality due to any cause

Randomization date	Treatment	Death date	Pulmonary death	Cardiac death	COVID death	Death due to other reason	Days to death
2021-09-16	Peginterferon lambda	2021-10-02				Status Epilepticus	16
2021-09-20	Peginterferon lambda	2021-09-26		Yes	Yes		6
2021-09-15	Placebo	2021-10-23	Yes		Yes		38
2021-09-28	Placebo	2021-10-22	Yes		Yes		24
2021-06-24	Placebo	2021-07-02	Yes		Yes		8
2021-09-07	Peginterferon lambda	2021-10-15	Yes		Yes		38
2021-09-13	Peginterferon lambda	2021-10-03				Closed Head Trauma, Respiratory failure	20
2021-10-11	Placebo	2021-10-20	Yes		Yes		9
2021-10-05	Placebo	2021-10-19	Yes		Yes		14
2022-01-11	Placebo	2022-02-28			Yes	acute myeloid leukemia	48

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628 **Table S7: Representativeness of Study Participants**

Category	Example
Disease under investigation	COVID-19
Special considerations related to	
Age	Age is one of the key factors, if not the most significant risk factors for severe disease. Infection rates and deaths increase with age, as 62% of infections are in people > 50 years, and 95% of deaths from COVID-19 are for those > 50 years[7,8]
Sex	COVID-19 affects men more than women, with men at higher risk than women to develop severe disease. The fatality rate is also increased in men compared to women. A review shows that men are 50% more men requiring hospitalization than women, and the ICU admission is between 3-4 times higher for men.[9]
Race	COVID-19 affects different races disproportionately, however this is thought to be due to factors such health care access and exposure risk. Most studies investigating these differences were based in the United States. Compared with white Americans, African Americans were 1.5-3 times more likely to be hospitalized, 3.6 times higher risk of mortality, and Hispanics were 3.2 times higher risk of mortality. These differences are thought to be caused by socioeconomic factors.[7]
Pre-existing conditions	Pre-existing conditions is another key risk factor for COVID-19. According to COVID-NET, 89% of hospitalized patients had a pre-existing condition, most commonly hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%) and cardiovascular disease (27.8%).[8]
Other considerations	Most of the data gathered on the different effects of COVID-19 on different groups were gathered from the US, China and Europe, as data was lacking for Brazil. Some of these aspects, especially the differences in race, will not translate directly to Brazil as many of findings were related to socioeconomic differences in the US.
Overall representativeness of the trial	Participants were asked their age, sex, race and pre-existing conditions during the screening visit. The participants in the trial were split between 41.8% male to 58.2% female. The proportion of race was 95.2% mixed rice, 0.9% black/African American, and 2.9% unknown. Our age

	distribution was also evenly split, with 53.8% of participants < 50 years, while 46.2% were ≥ 50 years. The study had a higher representation of females and those < 50 years, which represented the course of the pandemic at that time. The distribution of females and males was split evenly between the peginterferon lambda arm and placebo.

A search of Pubmed was done to determine how COVID-19 affects people of different ages, sex, race and pre-existing conditions.

Table S8: Adverse events by grade, MEDRA type and treatment group

	# Events (%)					
	Peginterferon lambda			Placebo		
	Grade 1 / 2 n = 135	Grade 3 / 4 n = 31	Grade 5 n = 4	Grade 1 / 2 n = 154	Grade 3 / 4 n = 52	Grade 5 n = 6
Cardiac disorders	1 (0.7)	1 (3.2)	1 (25.0)	2 (1.3)	0 (0)	0 (0)
Ear and labyrinth disorders	2 (1.5)	0 (0)	0 (0)	5 (3.2)	0 (0)	0 (0)
Eye disorders	0 (0)	0 (0)	0 (0)	2 (1.3)	0 (0)	0 (0)
Gastrointestinal disorders	8 (5.9)	1 (3.2)	0 (0)	5 (3.2)	0 (0)	0 (0)
General disorders and administration site conditions	9 (6.7)	0 (0)	0 (0)	18 (11.7)	0 (0)	0 (0)
Hepatobiliary disorders	1 (0.7)	2 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)
Immune system disorders	1 (0.7)	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)
Infections and infestations	73 (54.1)	23 (74.2)	1 (25.0)	80 (51.9)	46 (88.5)	6 (100)
Injury, poisoning and procedural complications	0 (0)	0 (0)	1 (25.0)	1 (0.6)	1 (1.9)	0 (0)
Investigations	5 (3.7)	0 (0)	0 (0)	2 (1.3)	0 (0)	0 (0)
Metabolism and nutrition disorders	0 (0)	0 (0)	0 (0)	4 (2.6)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	5 (3.7)	0 (0)	0 (0)	3 (1.9)	0 (0)	0 (0)
Nervous system disorders	8 (5.9)	1 (3.2)	1 (25.0)	5 (3.2)	1 (1.9)	0 (0)
Psychiatric disorders	3 (2.2)	1 (3.2)	0 (0)	3 (1.9)	1 (1.9)	0 (0)
Renal and urinary disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.9)	0 (0)
Respiratory, thoracic and mediastinal disorders	12 (8.9)	1 (3.2)	0 (0)	16 (10.4)	1 (1.9)	0 (0)
Skin and subcutaneous tissue disorders	4 (3.0)	0 (0)	0 (0)	3 (1.9)	0 (0)	0 (0)
Surgical and medical procedures	0 (0)	1 (3.2)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	3 (2.2)	0 (0)	0 (0)	4 (2.6)	1 (1.9)	0 (0)

Number of adverse events categorized by MedDRA SOC term. Includes data from both Brazil and Toronto.

Table S9: Primary outcome results by site

SITENUM	Peginterferon lambda	Placebo
1	2.05%	6.21%
2	2.86%	3.57%
3	0%	2.13%
4	0%	9.52%
5	4.88%	0%
6	1.72%	4.62%
7	5.22%	8%
8	5.05%	6.84%
9	2%	5.84%
10	0%	5.88%
11	2.70%	7.14%
12	0%	0%
13	0%	0%
14	0%	0%

The proportion of patients experiencing the primary outcome at each participating site
Site 14 refers to patients recruited in Canada, the rest of the sites are within Brazil.

646 **Table S10. Frequentist ITT analysis**
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Outcome	Measure	Peginterferon lambda* (N=931)	Placebo* (N=1018)	Estimated treatment effect	Probability of Superiority
Hospitalization or ER visit > 6h for COVID-19	RR (95% CrI)	25 (2.7%)	57 (5.6%)	0.48 (0.30, 0.76)	.002
Days to hospitalization or ER visit > 6h for COVID-19	HR (95% CrI)	--	--	0.47 (0.30, 0.76)	.001
Hospitalization for COVID-19	RR (95% CrI)	21 (2.3%)	40 (3.9%)	0.57 (0.34, 0.97))	
Days to hospitalization for COVID-19	HR (95% CrI)	--	--	0.57 (0.34, 0.97)	
Death or hospitalization due to COVID-19	RR (95% CrI)	22 (2.4%)	40 (3.9%)	0.60 (0.36, 0.99)	
Days to death or hospitalization due to COVID-19	HR (95% CrI)	--	--	0.60 (0.35, 0.99)	
Death due to COVID-19	RR (95% CrI)	1 (0.1%)	4 (0.4%)	0.27 (0.03, 2.44)	
Days to death for COVID-19	HR (95% CI)	--	--	0.27 (0.03, 2.44)	
Hospitalization or ER (any duration) for COVID-19	RR (95% CrI)	99 (10.6%)	140 (13.8%)	0.77 (0.61, 0.98)	
Days on mechanical ventilation	MD (95% CrI)	10.2 (7.4)	13.6 (11.9)	-3.32 (-16.33, 9.69)	

LEGEND:*For categorical outcomes, totals and percentages are presented; for time-to-event outcomes, medians and 95% Bayesian credible intervals are presented; for continuous variables, means and standard deviation are presented. CrI, credible interval; HR: hazard ratio; RR: risk ratio; MD: Mean difference, --: Median not reached; TEAE, Treatment emergent adverse events

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Table S11. Demographics of COVID-19 Cases in the US

	Subgroups	Percentage of COVID cases	Percentage of the US population
Race/Ethnicity†	Asian, non-hispanic	4.3%	5.76%
	Black, non-hispanic	12.4%	12.54%
	Hispanic/Latino	24.6%	18.45%
	White, Non-hispanic	53.4%	60.11%
Age, years	0-17	17.4%	22.3%
	18-39	37.6%	29.9%
	40-64	32.7%	31.5%
	65-84	10.7%	14.5%
	85+	1.7%	2%
Sex	Male	46.4%	49.25%
	Female	53.6%	50.75%

*Numbers retrieved from the CDC on September 12, 2022; †: based on 65% of total cases

Source: https://covid.cdc.gov/covid-data-tracker/#demographics

673 **Listing 1: Deaths, serious treatment emergent adverse events and other significant events**
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Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-04 / 2021-08-08	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Cardiac disorders/Atrioventricular block second degree/Type II second degree atrioventricular block	2022-02-03 / 2022-02-16	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-15 / 2021-07-19	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-20 / 2021-07-23	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-23 / 2021-07-27	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-22 / 2021-07-29	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-28 / 2021-08-31	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19/COVID-19	2021-09-10 / 2021-09-10	Grade 3 / Not Related	Recovered / Resolved / Dose Not Changed	Yes	No/No/No/Yes/No
Peginterferon lambda	Surgical and medical procedures/Meniscus operation/Meniscus operation	2021-11-11 / 2021-11-12	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19/COVID-19	2021-08-02 / 2021-08-02	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/No/No

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-18 / 2021-09-22	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-24 / 2021-07-30	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-04 / 2021-08-07	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-27 / 2021-10-31	Grade 3 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-11-10 / 2021-11-16	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Psychiatric disorders/Somatic symptom disorder/Somatoform disorder	2021-12-17 / 2021-12-18	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Peginterferon lambda	Nervous system disorders/Syncope/Syncope	2022-01-03 / 2022-01-03	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Peginterferon lambda	Respiratory, thoracic and mediastinal disorders/Cough/Cough	2021-11-25 / 2021-11-26	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Hepatobiliary disorders/Biliary colic/Biliary colic	2022-01-27 / 2022-01-29	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19/COVID-19	2021-10-31 / 2021-10-31	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Hepatobiliary disorders/Cholecystitis acute/Acute cholecystitis	2022-03-03 / 2022-03-04	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Gastrointestinal disorders/Lumbar hernia/Lumbar hernia	2022-01-31 / 2022-01-31	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-18 / 2021-09-25	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-11-19 / 2021-11-27	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-11-22 / 2021-12-01	Grade 4 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-04 / 2021-09-05	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-13 / 2021-10-08	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-29 / 2021-08-08	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-01-26 / 2022-02-14	Grade 4 / Not Related	Recovering / Resolving / Not Applicable	Yes	No/No/No/Yes/Yes
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-11-08 / 2021-11-18	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/Yes/No
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-02-09 / 2022-02-17	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/Yes
Peginterferon lambda	Nervous system disorders/Epilepsy/Epilepsy	2021-10-01 / 2021-10-02	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/Yes/Yes
Peginterferon lambda	Cardiac disorders/Myocardial infarction/Myocardial infarction	2021-09-26 / 2021-09-26	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/No/Yes
Peginterferon lambda	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-11 / NA	Grade 5 / Not Related	Fatal / Drug Interrupted	Yes	No/No/No/Yes/No
Peginterferon lambda	Injury, poisoning and procedural complications/Craniocerebral injury/Closed head injury	2021-09-10 / 2021-10-03	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/No/Yes

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-28 / 2021-10-01	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-01 / 2021-07-01	Grade 3 / Not Related	Recovered / Resolved / Dose Not Changed	Yes	No/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-07 / 2021-07-13	Grade 3 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2021-09-26 / 2021-09-26	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-21 / 2021-07-26	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-27 / 2021-10-01	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-19 / 2021-07-24	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-20 / 2021-07-30	Grade 3 / Not Related	Recovering / Resolving / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-22 / 2021-07-23	Grade 3 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-05 / 2021-08-11	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2021-09-13 / 2021-09-13	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	Infections and infestations/COVID-19/COVID-19	2021-09-23 / 2021-09-23	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-17 / 2021-08-20	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2021-09-08 / 2021-09-08	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-30 / 2021-10-06	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2021-09-29 / 2021-09-29	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-06 / NA	Grade 3 / Not Related	Recovering / Resolving / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Psychiatric disorders/Suicide attempt/Suicide attempt	2021-10-06 / 2021-10-07	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2022-01-25 / 2022-01-25	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-08 / 2021-07-13	Grade 3 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2021-07-22 / 2021-07-22	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-30 / 2021-08-03	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-04 / 2021-08-11	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-06 / 2021-09-09	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2022-01-10 / 2022-01-10	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Placebo	Renal and urinary disorders/Renal colic/Renal colic	2022-01-29 / 2022-01-29	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-02-14 / 2022-02-20	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-12-28 / 2022-01-02	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-01-29 / 2022-01-29	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Infections and infestations/COVID-19/COVID-19	2021-10-02 / 2021-10-02	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-08-15 / 2021-08-19	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Respiratory, thoracic and mediastinal disorders/Pulmonary embolism/Pulmonary embolism	2021-09-16 / 2021-10-01	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/No/Yes
Placebo	Infections and infestations/COVID-19/COVID-19	2021-09-15 / 2021-09-16	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/No/No
Placebo	Vascular disorders/Hypertensive crisis/Hypertensive crisis	2022-01-19 / 2022-01-19	Grade 3 / Not Related	Recovered / Resolved / Dose Not Changed	No	NA/NA/NA/NA/NA

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-01-25 / 2022-01-30	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2022-01-23 / 2022-01-23	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Nervous system disorders/Headache/Headache	2022-02-10 / 2022-02-10	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/Yes/No/No/No
Placebo	Injury, poisoning and procedural complications/Accident at work/Accident at work	2021-12-17 / 2021-12-24	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2022-01-17 / 2022-01-17	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-01-16 / 2022-01-19	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19/COVID-19	2022-02-02 / 2022-02-02	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	Yes/No/No/No/No
Placebo	Infections and infestations/COVID-19/COVID-19	2022-01-19 / 2022-01-19	Grade 3 / Not Related	Recovered / Resolved / Dose Not Changed	No	NA/NA/NA/NA/NA
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-01-21 / 2022-01-22	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-02-08 / 2022-02-11	Grade 3 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-18 / 2021-10-01	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-06-29 / 2021-07-11	Grade 4 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	Yes/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-03 / 2021-08-17	Grade 4 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-21 / 2021-09-29	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-11 / 2021-10-20	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-07-01 / 2021-07-12	Grade 4 / Not Related	Recovered / Resolved / Drug Interrupted	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-31 / 2021-11-28	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-08 / 2021-10-16	Grade 4 / Not Related	Recovered / Resolved / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-09-20 / 2021-10-23	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/Yes/Yes
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-02 / 2021-10-22	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/No/Yes/No
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-06-29 / 2021-07-02	Grade 5 / Not Related	Fatal / Drug Interrupted	Yes	No/No/Yes/Yes/Yes
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-13 / 2021-10-20	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/Yes/Yes
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2021-10-06 / 2021-10-19	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/Yes/Yes
Placebo	Infections and infestations/COVID-19 pneumonia/COVID-19 pneumonia	2022-01-15 / 2022-02-09	Grade 5 / Not Related	Fatal / Not Applicable	Yes	No/No/Yes/Yes/Yes

678 **Listing 2: Treatment emergent adverse events unlikely related, possibly related, or related to intervention**

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Peginterferon lambda	General disorders and administration site conditions/Malaise/Sickness	2021-09-22 / 2021-09-22	Grade 1 / Unlikely Related	Recovering / Resolving / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Gastrointestinal disorders/Diarrhoea/Diarrhea	2022-01-31 / 2022-01-31	Grade 1 / Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Nervous system disorders/Migraine/Migraine	2022-01-18 / 2022-01-18	Grade 1 / Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Immune system disorders/Hypersensitivity/Allergic reaction	2022-01-15 / 2022-01-16	Grade 1 / Related	Recovering / Resolving / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Investigations/Alanine aminotransferase increased/ALT increased	2021-12-29 / NA	Grade 1 / Possibly Related	Unknown / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Investigations/Aspartate aminotransferase increased/AST increased	2021-12-29 / 2022-01-05	Grade 1 / Possibly Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Skin and subcutaneous tissue disorders/Urticaria/Urticaria	2021-08-22 / 2021-08-24	Grade 2 / Possibly Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Skin and subcutaneous tissue disorders/Urticaria/Urticaria	2021-08-14 / 2021-08-14	Grade 2 / Possibly Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Skin and subcutaneous tissue disorders/Pruritus/Itchy skin	2022-01-23 / 2022-01-27	Grade 2 / Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Infections and infestations/COVID-19/COVID-19	2021-11-15 / 2021-11-15	Grade 2 / Unlikely Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Peginterferon lambda	Skin and subcutaneous tissue disorders/Urticaria/Urticaria	2022-01-12 / 2022-01-12	Grade 2 / Possibly Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	General disorders and administration site conditions/Influenza like illness/Flu like symptoms	2022-01-25 / 2022-01-25	Grade 1 / Related	Recovering / Resolving / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Respiratory, thoracic and mediastinal disorders/Cough/Cough	2022-01-21 / 2022-01-21	Grade 1 / Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Ear and labyrinth disorders/Vertigo/Vertigo	2021-07-21 / 2021-07-22	Grade 1 / Possibly Related	Recovered / Resolved / Dose Reduced	No	NA/NA/NA/NA/NA
Placebo	Vascular disorders/Orthostatic hypotension/Orthostatic hypotension	2021-07-19 / 2021-07-21	Grade 1 / Possibly Related	Recovered / Resolved / Drug Interrupted	No	NA/NA/NA/NA/NA
Placebo	Ear and labyrinth disorders/Vertigo/Vertigo	2021-07-26 / 2021-07-27	Grade 1 / Possibly Related	Recovered / Resolved / Dose Reduced	No	NA/NA/NA/NA/NA
Placebo	Ear and labyrinth disorders/Vertigo/Vertigo	2021-07-20 / 2021-07-24	Grade 1 / Possibly Related	Recovered / Resolved / Dose Not Changed	No	NA/NA/NA/NA/NA
Placebo	Ear and labyrinth disorders/Vertigo/Vertigo	2021-07-22 / 2021-07-22	Grade 1 / Possibly Related	Recovered / Resolved / Dose Increased	No	NA/NA/NA/NA/NA
Placebo	Skin and subcutaneous tissue disorders/Dermatitis allergic/Allergic skin reaction	2022-01-28 / 2022-01-30	Grade 1 / Possibly Related	Recovered / Resolved / Dose Not Changed	No	NA/NA/NA/NA/NA
Placebo	Vascular disorders/Orthostatic hypotension/Orthostatic hypotension	2021-08-05 / 2021-08-05	Grade 1 / Possibly Related	Recovered / Resolved / Dose Not Changed	No	NA/NA/NA/NA/NA
Placebo	Vascular disorders/Hypotension/Hypotension	2021-07-20 / 2021-07-20	Grade 2 / Possibly Related	Recovering / Resolving / Drug Interrupted	No	NA/NA/NA/NA/NA
Placebo	General disorders and administration site conditions/Influenza like illness/Flu-like symptoms	2021-07-18 / 2021-07-21	Grade 2 / Unlikely Related	Recovering / Resolving / Not Applicable	No	NA/NA/NA/NA/NA

Treatment	System Organ Class / Preferred term / Verbatim Term	Start Date / End Date	Severity / Relationship to IP	Outcome / Study Drug Action Taken	Serious?	IME/CA/DE/HO/LT ?
Placebo	Gastrointestinal disorders/Vomiting/Vomiting	2021-09-27 / 2021-09-28	Grade 2 / Unlikely Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Metabolism and nutrition disorders/Dehydration/Dehydration	2021-09-27 / 2021-09-28	Grade 2 / Unlikely Related	Recovered / Resolved / Not Applicable	No	NA/NA/NA/NA/NA
Placebo	Vascular disorders/Hypotension/Hypotension	2021-08-29 / 2021-09-01	Grade 2 / Related	Recovered / Resolved / Dose Reduced	No	NA/NA/NA/NA/NA
Placebo	Infections and infestations/COVID-19/COVID-19	2022-02-05 / 2022-02-06	Grade 2 / Unlikely Related	Recovered / Resolved / Dose Not Changed	No	NA/NA/NA/NA/NA

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN)

in randomized controlled trials Version 1.0

Quick instructions

Synonyms for effect modification include subgroup effect, interaction, and moderation

The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier

Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility

Completely unclear goes under probably reduced credibility

It is helpful to provide a supporting comment or quotation under each question

Whether an effect modification is patient-important is not part of the credibility assessment

The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): NCT04727424

If available, protocol reference(s): NCT04727424

State a single outcome and, if applicable, time-point of interest (e.g., mortality at 1 year follow-up): primary outcome, 28 days

State a single effect measure of interest (e.g., relative or absolute risk difference): Risk ratio

State a single potential effect modifier of interest (e.g., age or comorbidity): days since symptom onset, or vaccination status

Was the potential effect modifier measured before or at randomization? [**X**] yes, continue [ ] no, stop here, refer to manual for further instructions

Credibility assessment

1: Was the direction of the effect modification correctly hypothesized a priori?

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[**X**] Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	*Vague hypothesis or hypothesized direction unclear*	*No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification*	*Prior protocol available and includes correct specification of direction of effect modification, e.g., based on a biologic rationale*

Comment:

2: Was the effect modification supported by prior evidence?

[ ] Inconsistent with prior evidence	[ ] Little or no support or unclear	[x] Some support	[] Strong support
Prior evidence suggested a different direction of effect modification	*No prior evidence or consistent with weak or very indirect prior evidence (e.g., animal study at high risk of bias) or unclear*	*Consistent with more limited or indirect prior evidence (e.g., large observational study, non-significant effect modification in prior RCT, or different population)*	*Consistent with strong prior evidence directly applicable to the clinical scenario (e.g., significant effect modification in related RCT)*

Comment:

3: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers) find strongest

[x] Chance a very likely explanation	[ ] Chance a likely explanation or unclear	[ ] Chance may not explain	[ ] Chance an unlikely explanation
Interaction p-value >0.05	*Interaction p-value ≤0.05 and >0.01, or no test of interaction reported and not computable*	*Interaction p-value ≤0.01 and >0.005*	*Interaction p-value ≤0.005*

Comment:

4: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[ ] Definitely no	[ ] Probably no or unclear	[**X**] Probably yes	[ ] Definitely yes

Explicitly exploratory analysis or large number of effect modifiers tested (e.g., greater than 10) and multiplicity not considered in analysis	*No mention of number or 4-10 effect modifiers tested and number not considered in analysis*	*No protocol available but unequivocal statement of 3 or fewer effect modifiers tested*	*Protocol available and 3 or fewer effect modifiers tested or number considered in analysis*

Comment:

5: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [X] not applicable: not continuous

[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Analysis based on exploratory cut point (e.g., picking cut point associated with highest interaction p-value)	*Analysis based on cut point(s) of unclear origin*	*Analysis based on pre-specified cut points, e.g., suggested by prior RCT*	*Analysis based on the full continuum, e.g., assuming a linear or logarithmic relationship*

Comment:

6 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 2.6)

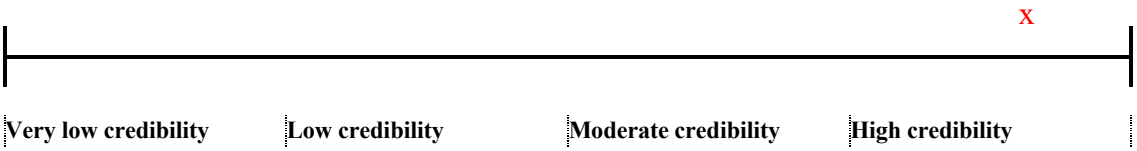
[ ] Yes, probably decrease [ ] Yes, probably increase

Comment:

7: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:
All responses definitely or probably reduced credibility or unclear → very low
Two or more responses definitely reduced credibility → maximum usually low even if all other responses satisfy credibility criteria
One response definitely reduced credibility → maximum usually moderate even if all other responses satisfy credibility criteria
Two responses probably reduced credibility → maximum usually moderate even if all other responses satisfy credibility criteria
No response options definitely or probably reduced credibility → high very likely

Place a mark on the continuous line (or type "x" in electronic version)



Very likely no effect modification
Use overall effect for each subgroup
Likely no effect modification
Use overall effect for each subgroup but note remaining uncertainty
Likely effect modification
Use separate effects for each subgroup but note remaining uncertainty
Very likely effect modification
Use separate effects for each subgroup

Comment:

The trial did not hypothesize any subgroup effects and no effect modification was found.

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