ORIGINAL ARTICLE

Early Treatment with Pegylated Interferon Lambda for Covid-19

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ABSTRACT

BACKGROUND

The efficacy of a single dose of pegylated interferon lambda in preventing clinical events among outpatients with acute symptomatic coronavirus disease 2019 (Covid-19) is unclear.

METHODS

We conducted a randomized, controlled, adaptive platform trial involving predominantly vaccinated adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brazil and Canada. Outpatients who presented with an acute clinical condition consistent with Covid-19 within 7 days after the onset of symptoms received either pegylated interferon lambda (single subcutaneous injection, 180 μg) or placebo (single injection or oral). The primary composite outcome was hospitalization (or transfer to a tertiary hospital) or an emergency department visit (observation for >6 hours) due to Covid-19 within 28 days after randomization.

RESULTS

A total of 933 patients were assigned to receive pegylated interferon lambda (2 were subsequently excluded owing to protocol deviations) and 1018 were assigned to receive placebo. Overall, 83% of the patients had been vaccinated, and during the trial, multiple SARS-CoV-2 variants had emerged. A total of 25 of 931 patients (2.7%) in the interferon group had a primary-outcome event, as compared with 57 of 1018 (5.6%) in the placebo group, a difference of 51% (relative risk, 0.49; 95% Bayesian credible interval, 0.30 to 0.76; posterior probability of superiority to placebo, >99.9%). Results were generally consistent in analyses of secondary outcomes, including time to hospitalization for Covid-19 (hazard ratio, 0.57; 95% Bayesian credible interval, 0.33 to 0.95) and Covid-19–related hospitalization or death (hazard ratio, 0.59; 95% Bayesian credible interval, 0.35 to 0.97). The effects were consistent across dominant variants and independent of vaccination status. Among patients with a high viral load at baseline, those who received pegylated interferon lambda had lower viral loads by day 7 than those who received placebo. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Among predominantly vaccinated outpatients with Covid-19, the incidence of hospitalization or an emergency department visit (observation for >6 hours) was significantly lower among those who received a single dose of pegylated interferon lambda than among those who received placebo. (Funded by FastGrants and others; TOGETHER ClinicalTrials.gov number, NCT04727424.)

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The identification of convenient, widely available, and effective antiviral therapies against coronavirus disease 2019 (Covid-19) for outpatients is of great importance. In infected cells, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces weak expression of naturally produced type III interferons, which are an early line of defense in upper respiratory tract infections.[1] Treatment with an exogenous source of interferon lambda such as pegylated interferon lambda could stimulate antiviral immunity and treat early SARS-CoV-2 infection.[2]

In more than 20 clinical trials, the administration of pegylated interferon lambda to more than 4000 patients for a variety of conditions (including hepatitis B, C, and D, and Covid-19) has provided a well-understood safety and side-effect profile.[3,4] Pegylated interferon lambda has broad-spectrum antiviral activity in numerous cell cultures, animal models, and clinical settings.[3-8] With respect to SARS-CoV-2, pegylated interferon lambda has potent in vitro and in vivo activity.[3,9] The results of two phase 2 studies characterizing the effect of pegylated interferon lambda on SARS-CoV-2 viral load have been published.[10,11] To further evaluate the effect of this agent on clinical outcomes, we used the TOGETHER trial master protocol[12] to conduct a large, phase 3, randomized, placebo-controlled adaptive platform trial involving outpatients with Covid-19 in Brazil and Canada.

Methods

Trial Design and Oversight

The TOGETHER platform trial began recruitment for its first investigational groups in June 2020. This trial has evaluated 12 different therapeutic interventions. Here, we report the evaluation of patients who were randomly assigned to receive either pegylated interferon lambda (the interferon group) or placebo (the placebo group) between June 24, 2021, and February 7, 2022. The protocol was approved by local and national research ethics boards in Brazil and by the Hamilton Integrated Research Ethics Board and Clinical Trials Ontario, with the University Health Network as the board of record in Canada. The full protocol and statistical analysis plan have been published previously[12] and are available with the full text of this article at NEJM.org. The CONSORT (Consolidated Standards of Reporting Trials) extension statement for adaptive design trials guided this trial report.[13] All the patients provided written informed consent.

A Quick Take is available at NEJM.org

The trial was coordinated by Platform Life Sciences, and Cardresearch conducted the trial and collected the data. MMS Holdings, a clinical research organization, created the electronic data capture system. The first and next-to-last authors had full access to all the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The initial draft of the manuscript was written by the first author and the last three authors, and all the authors approved the final version of the manuscript and decided to submit it for publication. The funders had no role in the design and conduct of the trial; the collection, management, analysis, and interpretation of the data; or the preparation and submission of the manuscript for publication. Pegylated interferon lambda was provided at no cost by Eiger BioPharmaceuticals, which was not made aware of any trial results before the completion of the trial.

Patients

On presentation to one of the trial outpatient care clinics, potential participants were screened to identify those meeting eligibility criteria. Inclusion criteria were an age of 18 years or older, presentation to an outpatient care setting with an acute clinical condition consistent with Covid-19 within 7 days after the onset of symptoms, a positive rapid antigen test for SARS-CoV-2, and at least one high-risk criterion for progression of Covid-19. These high-risk criteria included the following: an age of 50 years or older, diabetes mellitus, hypertension leading to the use of medication, cardiovascular disease, lung disease, smoking, obesity (defined as a body-mass index [the weight in kilograms divided by the square of the height in meters] of >30), organ transplantation, chronic kidney disease (stage IV) or receipt of dialysis, immunosuppressive therapy (receipt of ≥10 mg of prednisone or equivalent daily), a diagnosis of cancer within the previous 6 months, and receipt of chemotherapy for cancer. Up to 25% of the participants were permitted to be enrolled with no high-risk criteria as long as they had severe or debilitating symptoms of Covid-19. Further inclusion and exclusion criteria are listed in the trial protocol.[12]

If a patient met these eligibility criteria, trial

personnel obtained written in-person informed consent and performed a rapid antigen test for SARS-CoV-2 (Panbio, Abbott Laboratories). Before randomization, trial personnel obtained data on the patients' demographic characteristics, medical history, coexisting conditions, concomitant medications, and previous exposure to a person with Covid-19, as well as the score on the World Health Organization clinical progression scale.[14]

SETTING

The Supplementary Appendix, available at NEJM.org, lists the cities and investigators of the 12 participating clinical sites in Brazil and the 5 participating clinical sites in Canada. Participants were recruited by local investigators, in partnership with local public health authorities, at emergency departments and Covid-19–specific emergency settings. Recruitment was supplemented by social media outreach. The representativeness of the trial population is described in the Supplementary Appendix.

RANDOMIZATION AND INTERVENTIONS

An independent pharmacist conducted the randomization at a central trial facility, from which the trial sites requested randomization by means of text message. Patients underwent randomization by means of a block randomization procedure for each participating site, with stratification according to age (<50 years or ≥50 years). To maintain blinding, no other team members were present during administration of pegylated interferon lambda or placebo. The trial personnel who were involved in screening or randomization were not involved with any trial-related activities after randomization. The treating physicians, trial staff involved in the conduct of the trial, and patients were unaware of the randomized assignments.

Pegylated interferon lambda (also called lambda PEG-rIL-29) is supplied in mannitol, L-histidine, polysorbate 80, hydrochloric acid, and water for subcutaneous injection as a single-use, prefilled syringe with a rigid needle shield. It is labeled with a dose indicator used to administer 0.45 ml containing 180 μg of pegylated interferon lambda. Because this was a platform trial, most of the control patients received a saline placebo injection or another form of placebo (capsule or tablet) that was identical in appearance to that in a comparable active-treatment group in the trial.

OUTCOME MEASURES

The primary composite outcome was Covid-19–related hospitalization (or transfer from an emergency department to a tertiary hospital) owing to the progression of Covid-19 within 28 days after randomization, or an emergency department visit (defined as observation for >6 hours) within 28 days after randomization. Details of the composite outcome are provided in the Supplementary Appendix. The event-adjudication committee, whose members were unaware of the randomized assignments, judged the reason for hospitalization as being related or not related to the progression of Covid-19. Guidance for the validity of composite outcomes indicates that outcomes should have a similar level of patient importance.[15]

Secondary outcomes included clearance of SARS-CoV-2, the time from randomization to hospitalization for any cause or due to progression of Covid-19, the time from randomization to death from Covid-19, the number of days in the hospital and days with mechanical ventilation, adverse events, and adverse reactions to interferon or placebo. We added an outcome that allowed comparison with previously authorized therapies for Covid-19 as outpatient treatment. This addition was made on the basis of external clinical trials and according to the CONSERVE (CONSORT and SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] Extension for RCTs [Randomized Clinical Trials] Revised in Extenuating Circumstances) 2021 statement reflecting modifications to Covid-19 trials.[16] This composite outcome was Covid-19–related hospitalization or death in patients who had undergone randomization. We assessed all the secondary outcomes through 28 days after randomization.

TRIAL PROCEDURES

Trial personnel obtained outcome data by means of in-person, telephone, or WhatsApp (a smartphone app for video-teleconferencing) contact on days 1, 2, 3, 4, 5, 7, 10, 14, and 28. All the trial procedures are listed in the protocol. Adverse events were recorded at the time they occurred. All serious and nonserious adverse events were reported to trial personnel according to

local regulatory requirements. Reportable adverse events included serious adverse events and adverse events that were assessed by the investigators as being possibly related to interferon or placebo.

VIROLOGIC ASSESSMENTS

On day 3 and day 7 after randomization, assessments of symptoms and events were performed virtually. Mid-turbinate nasal swabs were obtained from the patients at the sites in Brazil on days 0, 3, and 7 to allow for viral kinetic data; at the sites in Canada, swabs were obtained from the patients daily up to 14 days.

DATA AND SAFETY MONITORING COMMITTEE OVERSIGHT

The data and safety monitoring committee met four times after the enrollment of the first patient to assess the safety and efficacy status of pegylated interferon lambda as compared with placebo with regard to the primary outcome, on the basis of prespecified thresholds in the statistical analysis plan. On February 6, 2022, the data and safety monitoring committee recommended stopping the enrollment of patients into the interferon group because the prespecified threshold for efficacy had been met.

STATISTICAL ANALYSIS

We applied a Bayesian framework to all analyses and report the posterior probabilities of superiority of interferon to placebo with regard to the primary outcome and the safety outcomes. The adaptive design protocol and the master statistical analysis plan (available with the protocol) provide details of the sample-size calculation and statistical analysis (Supplementary Appendix), including reassessment of the sample size. In planning for the trial, we assumed a minimum clinical utility of 37.5% of interferon (relative risk difference vs. placebo) in order for the trial to have 80% power, at a two-sided type I error of 0.05, for a pairwise comparison with placebo, assuming that 15% of the patients in the placebo group would have a primary-outcome event. This calculation resulted in a planned minimum recruitment of 681 participants in each group.

Interim analyses were planned to occur after approximately 25%, 50%, and 75% of the maximum number of patient outcomes had been observed, as well as at the trial completion. The posterior efficacy threshold was set at 97.6% and the futility thresholds at 20%, 40%, and 60%. If the intervention group showed a posterior probability of efficacy by crossing a boundary, the data and safety monitoring board could consider recommending stopping the trial. These superiority and futility thresholds were determined on the basis of 200,000 simulation runs in which different values of the relative risk difference were considered (0, 20, and 37.5 percentage points).

The characteristics of the patients at baseline are reported as counts and percentages or, for continuous variables, as medians with interquartile ranges. Posterior probability for the efficacy of pegylated interferon lambda with regard to the primary outcome was calculated with the use of a Bayesian Cox proportional-hazards model. The modified intention-to-treat population included all the patients who had received interferon or placebo for at least 24 hours before a primary-outcome event (i.e., if events occurred before 24 hours after randomization, the patient was not counted in this analysis). The matched-placebo population included only the patients who had received injectable placebo. Exploratory subgroup effects were assessed in accordance with the prespecified statistical analysis plan. We assessed time-to-event outcomes using a Bayesian Cox proportional-hazards model, binary outcomes using logistic regression, and continuous outcomes using linear regression. We determined subgroups a priori, as in previous drug evaluations in our trial. We applied the Instrument to Assess the Credibility of Effect Modification Analyses (ICEMAN) tool for subgroup credibility.[17] A frequentist approach to the analysis is also described in Table S10 in the Supplementary Appendix.

Statistical analyses were conducted by personnel at RainCity Analytics. Analyses were performed with the use of R software, version 4.1.0. Details regarding the Bayesian analysis are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

A total of 13,396 potential participants were screened for inclusion in the trial. Of these patients, 2617 were recruited, of whom 933 were randomly assigned to receive pegylated interferon

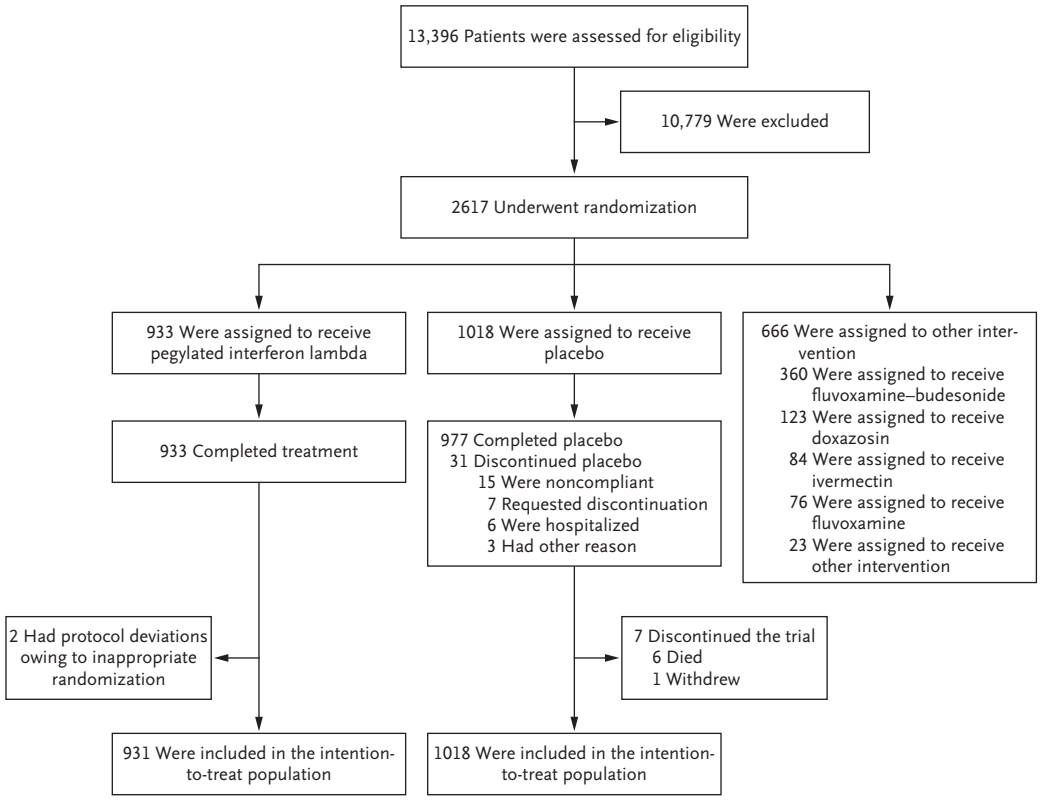


Figure 1. Randomization and Follow-up of the Patients.
Only the results in the interferon group as compared with the placebo group are reported in this article.

lambda and 1018 to receive concurrent placebo (Fig. 1); observations from 2 of the 933 patients in the interferon group were excluded from the analysis owing to protocol deviations. Only the results in the interferon group as compared with the placebo group are reported in this article. The remaining 666 patients were randomly assigned to other intervention groups. Of the 1018 patients assigned to receive placebo, 825 received a single subcutaneous injection and 193 received oral placebo. The median age of the patients was 43 years (range, 18 to 92), and 1113 (57.1%) were women. Most of the patients identified as being of mixed race (1853 [95.1%]), with 58 patients (3.0%) identifying as White and 28 (1.4%) as Black. With respect to covariates, the data in Table 1 suggest that the groups were well balanced. The mean (±SD) number of days with Covid-19 symptoms before randomization was 3.3±1.6.

PRIMARY OUTCOME

In the intention-to-treat population, a primary-outcome event occurred in 25 of 931 patients (2.7%) in the interferon group, as compared with 57 of 1018 patients (5.6%) in the placebo group (relative risk, 0.49; 95% Bayesian credible interval, 0.30 to 0.76; posterior probability of superiority to placebo, >99.9%) (Table 2), a difference that represented a 51% decrease. Figure 2A shows the absolute reduction in the risk of a primary-outcome event in the two groups. Similar results were observed in the modified intention-to-treat population (23 of 929 patients in the interferon group, as compared with 55 of 1018 patients in the placebo group, had a primary-outcome event; relative risk, 0.47; 95% Bayesian credible interval, 0.29 to 0.73) and in the matched-placebo analysis that included only the 825 patients who received a saline placebo injection (25 of 931 patients in the interferon group,

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Pegylated Interferon Lambda (N=931)	Placebo (N=1018)	Total (N=1949)
Median age (range) — yr	43 (18–92)	43 (18–88)	43 (18–92)
Sex — no. (%)			
Female	531 (57.0)	582 (57.2)	1113 (57.1)
Male	400 (43.0)	436 (42.8)	836 (42.9)
Country — no. (%)			
Brazil	916 (98.4)	1003 (98.5)	1919 (98.5)
Canada	15 (1.6)	15 (1.5)	30 (1.5)
Race or ethnic group — no. (%)†			
Mixed race	876 (94.1)	977 (96.0)	1853 (95.1)
White	31 (3.3)	27 (2.7)	58 (3.0)
Black	18 (1.9)	10 (1.0)	28 (1.4)
Pacific Islander	1 (0.1)	0	1 (0.1)
Other	2 (0.2)	2 (0.2)	4 (0.2)
Time since onset of symptoms — no. (%)			
0–3 days	567 (60.9)	591 (58.1)	1158 (59.4)
4–7 days	364 (39.1)	426 (41.8)	790 (40.5)
Missing data	0	1 (0.1)	1 (0.1)
Risk factors for severe illness from Covid-19 — no. (%)‡			
Age ≥50 yr	349 (37.5)	403 (39.6)	752 (38.6)
Obesity	321 (34.5)	398 (39.1)	719 (36.9)
Hypertension	261 (28.0)	320 (31.4)	581 (29.8)
Chronic cardiac disease	18 (1.9)	29 (2.8)	47 (2.4)
Asthma diagnosed by physician	91 (9.8)	101 (9.9)	192 (9.9)
Chronic pulmonary disease	21 (2.3)	26 (2.6)	47 (2.4)
Type 2 diabetes mellitus	88 (9.5)	93 (9.1)	181 (9.3)
Cancer	13 (1.4)	12 (1.2)	25 (1.3)
Multiple coexisting conditions	517 (55.5)	607 (59.6)	1124 (57.7)
Doses of Covid-19 vaccine >14 days before randomization — no./total no. (%)			
None	142/931 (15.3)	177/1018 (17.4)	319/1949 (16.4)
1 dose	223/911 (24.5)	258/996 (25.9)	481/1907 (25.2)
2 doses	458/911 (50.3)	483/996 (48.5)	941/1907 (49.3)
3 doses	88/911 (9.7)	78/996 (7.8)	166/1907 (8.7)
Missing data	20/931 (2.1)	22/1018 (2.2)	42/1949 (2.2)
SARS-CoV-2 variant — no./total no. (%)			
Alpha	6/602 (1.0)	3/600 (0.5)	9/1125 (0.8)
Delta	266/602 (44.2)	261/554 (47.1)	527/1158 (45.5)
Gamma	88/602 (14.6)	57/570 (10.1)	145/1160 (12.5)
Omicron, BA.1	241/602 (40.0)	233/553 (42.1)	474/1156 (41.0)
Zeta	1/602 (0.2)	1/500 (0.2)	2/1000 (0.2)
Missing data	329/931 (35.3)	463/1018 (45.5)	792/1949 (40.6)
SARS-CoV-2 status — no./total no. (%)			
Positive	812/931 (87.2)	719/1018 (70.6)	1531/11949 (78.6)
Negative	34/931 (3.7)	13/1018 (1.3)	47/1949 (2.4)
Missing data	85/931 (9.1)	286/1018 (28.1)	371/1949 (19.0)

* Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Race or ethnic group was reported by the patient.
‡ The list of risk factors was not inclusive of all risk factors used for trial eligibility.

Table 2. Primary and Secondary Outcomes.*

Outcome	Pegylated Interferon Lambda (N=931)	Placebo (N=1018)	Estimated Treatment Effect (95% Bayesian Credible Interval)†	Posterior Probability of Superiority to Placebo
				percent
Primary outcome				
Hospitalization or emergency department visit >6 hr for Covid-19 — no. (%)	25 (2.7)	57 (5.6)	0.49 (0.30 to 0.76)	>99.9
Secondary outcomes				
Time from randomization to hospitalization or emergency department visit >6 hr for Covid-19	—	—	0.47 (0.29 to 0.73)‡	>99.9
Hospitalization for Covid-19 — no. (%)	21 (2.3)	40 (3.9)	0.58 (0.34 to 0.96)	
Time from randomization to hospitalization for Covid-19	—	—	0.57 (0.33 to 0.95)‡	
Death or hospitalization due to Covid-19 — no. (%)	22 (2.4)	40 (3.9)	0.61 (0.36 to 0.99)	
Time from randomization to death or hospitalization due to Covid-19	—	—	0.59 (0.35 to 0.97)‡	
Death due to Covid-19 — no. (%)	1 (0.1)	4 (0.4)	0.39 (0.05 to 1.95)	
Time from randomization to death from Covid-19	—	—	0.22 (0.01 to 1.64)‡	
Hospitalization or emergency department visit of any duration for Covid-19 — no. (%)	99 (10.6)	140 (13.8)	0.78 (0.61 to 0.99)	
No. of days with mechanical ventilation	10.2±7.4	13.6±11.9	−4.47 (−6.89 to 3.09)§	
Adverse event during treatment period — no. (%)	141 (15.1)	172 (16.9)	0.90 (0.73 to 1.10)	85.2
Grade 1	26 (2.8)	38 (3.7)	0.75 (0.46 to 1.22)	87.6
Grade 2	87 (9.3)	93 (9.1)	1.02 (0.78 to 1.35)	43.6
Grade 3	20 (2.1)	42 (4.1)	0.53 (0.31 to 0.88)	99.3
Grade 4	9 (1.0)	8 (0.8)	1.22 (0.49 to 3.06)	33.5
Grade 5	4 (0.4)	6 (0.6)	0.76 (0.22 to 2.43)	67.6
Serious adverse event during treatment period — no. (%)	32 (3.4)	49 (4.8)	0.72 (0.46 to 1.10)	93.4
Possibly treatment-related adverse event during treatment period — no. (%)¶	7 (0.8)	11 (1.1)	0.72 (0.28 to 1.76)	76.3

* Plus–minus values are means ±SD. Dashes indicate that the median was not reached.
† The estimated treatment effect is presented as a relative risk unless otherwise stated.
‡ The estimated treatment effect is a hazard ratio. A Cox proportional-hazards model was used, so a median was not required to estimate the treatment effect.
§ Shown is the mean difference from a linear regression.
¶ The investigators made the determination regarding whether adverse events were related to pegylated interferon lambda or placebo.

as compared with 43 of 825 patients in the placebo group; relative risk, 0.52; 95% Bayesian credible interval, 0.32 to 0.84) (Table S4).

Most of the primary-outcome events in the intention-to-treat population were hospitalizations (61 of 82 events [74%]). Primary-outcome events in the trial occurred a median of 5 days (interquartile range, 3 to 7) after randomization. When the analysis was restricted to patients who had received interferon or placebo within 3 days after the onset of symptoms, the treatment effect increased (11 of 567 patients in the inter-

feron group, as compared with 28 of 590 patients in the placebo group; relative risk, 0.42; 95% Bayesian credible interval, 0.21 to 0.80). Data for the components of the primary outcome are shown in Table S1.

SECONDARY OUTCOMES

Table 2 presents findings of the secondary outcome analyses. We found that the direction of the treatment effect of pegylated interferon lambda was consistent across all outcomes. The risk of Covid-19–related hospitalization or death from any cause was 47% lower in the interferon group than in the placebo group (hazard ratio, 0.53; 95% Bayesian credible interval, 0.31 to 0.91). A low number of deaths occurred (one Covid-19–related death in the interferon group and four Covid-19–related deaths in the placebo group; hazard ratio, 0.39; 95% Bayesian credible interval, 0.05 to 1.95). Details are provided in Table S6. The time to hospitalization for Covid-19 was shorter in the interferon group than in the placebo group (hazard ratio, 0.57; 95% Bayesian credible interval, 0.33 to 0.95). The median time to recovery, as reported by the patients, was 10 days in both groups (hazard ratio for extended illness, 1.06; 95% Bayesian credible interval, 0.96 to 1.18).

When the analysis was restricted to patients who had received interferon or placebo within 3 days after the onset of symptoms, larger treatment effects were observed with respect to the secondary outcomes. The incidence of Covid-19–related hospitalization was 65% lower in the interferon group than in the placebo group (relative risk, 0.38; 95% Bayesian credible interval, 0.17 to 0.79), and the risk of death from Covid-19 was 81% lower in the interferon group than in the placebo group (none of the 567 patients in the interferon group, as compared with 3 of 590 patients in the placebo group; relative risk, 0.19; 95% Bayesian credible interval, 0.01 to 1.57) (Table S2). In the modified intention-to-treat analysis, among unvaccinated patients who had received interferon within 3 days after the onset of symptoms, the risk reduction was 89% (hazard ratio, 0.11; 95% Bayesian credible interval, 0.01 to 0.83). No deaths occurred among patients who had received early treatment in the interferon group. There was no substantial between-group difference in the number of adverse events (Table 2).

SUBGROUP ANALYSES

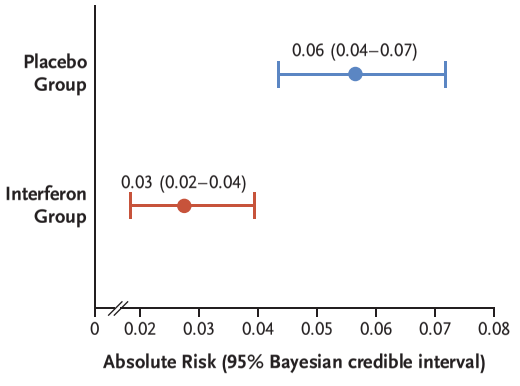
In prespecified subgroup analyses, we found consistent evidence of treatment benefits with pegylated interferon lambda as compared with placebo in subgroups defined according to patient age, sex, days since symptom onset, or vaccination status (Fig. 2B). An analysis of dominant SARS-CoV-2 variants of concern showed treatment benefits across variants (Fig. 2C). Estimates across the subgroups were generally consistent with the overall treatment effect. Figure S4 shows the results of a subgroup analysis involving patients who received early treatment (≤3 days).

VIROLOGIC RESULTS

Among the patients with a high baseline viral load (defined in a previous phase 2 trial[10] as the 15% of patients with the highest baseline load, all >192 million copies per milliliter), we observed a treatment effect at day 7 (beta, −1.01; 95% Bayesian credible interval, −1.65 to −0.36). Patients in the interferon group had a greater reduction in viral load by day 7 than those in the placebo group (median $\log_{10}$ decline, 8.29 in the interferon group as compared with 5.16 in the placebo group). Among patients with a high viral load at baseline, a greater percentage of patients in the interferon group than in the placebo group had a level that was below the limit of quantitation (defined as ≥1000 copies per milliliter) at day 7 (50.5% of the patients in the interferon group as compared with 32.9% of those in the placebo group; odds ratio, 2.13; 95% Bayesian credible interval, 1.14 to 4.00). Among patients with a low viral load at baseline, we did not observe a treatment effect with respect to viral load (beta, 0.22; 95% Bayesian credible interval, −0.09 to 0.52).

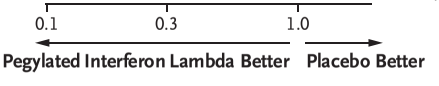
The results were consistent when we included additional variables to account for variance. Figure 2D shows the change over time across all patients, and Figure 2E shows the change in viral load among patients with a high viral load at baseline. Among hospitalized patients, at day 7, the median decrease in the viral load from baseline was 7.19 $\log_{10}$ copies per milliliter in the interferon group, as compared with 3.16 $\log_{10}$ copies per milliliter in the placebo group. The nested sample of viral kinetics from day 0 through 14 is provided in Figures S1 through S3.

A



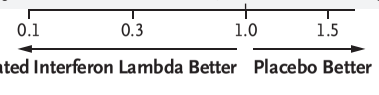
B

Subgroup	Pegylated Interferon Lambda	Placebo	Relative Risk (95% Bayesian credible interval)
	no. of patients with event/total no.		
Intention-to-treat population	25/931	57/1018	0.49 (0.30–0.76)
Age			
≥50 yr	18/350	38/404	0.56 (0.32–0.93)
<50 yr	7/581	19/614	0.41 (0.17–0.91)
Sex			
Male	16/400	32/436	0.55 (0.30–0.96)
Female	9/531	25/582	0.41 (0.19–0.83)
Onset of symptoms			
≤3 days	11/567	28/590	0.42 (0.21–0.80)
>3 days	14/364	29/428	0.58 (0.31–1.05)
Vaccination status			
Unvaccinated	6/143	18/177	0.44 (0.18–0.98)
Vaccinated	19/786	38/835	0.54 (0.31–0.91)
Obesity			
Yes	10/323	29/403	0.45 (0.22–0.86)
No	15/608	28/615	0.55 (0.30–1.00)

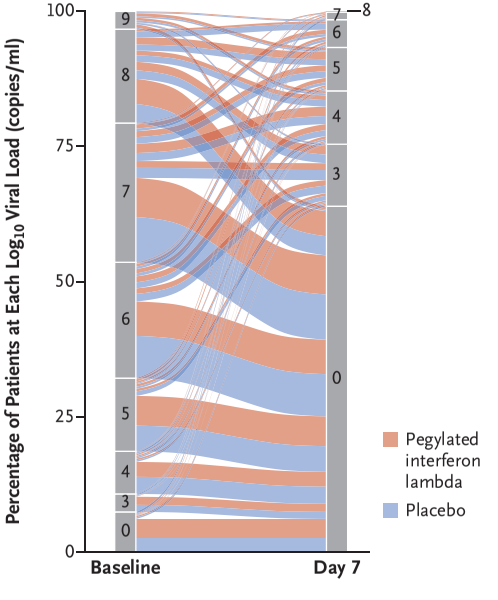


C

Subgroup	Pegylated Interferon Lambda	Placebo	Relative Risk (95% Bayesian credible interval)
	no. of patients with event/total no.		
Intention-to-treat population	25/931	57/1018	0.49 (0.30–0.76)
Dominant SARS-CoV-2 variant			
Omicron	2/439	18/513	0.17 (0.04–0.50)
Delta	12/360	23/365	0.54 (0.27–1.04)
Alpha or gamma	11/132	16/140	0.74 (0.36–1.50)



D



E

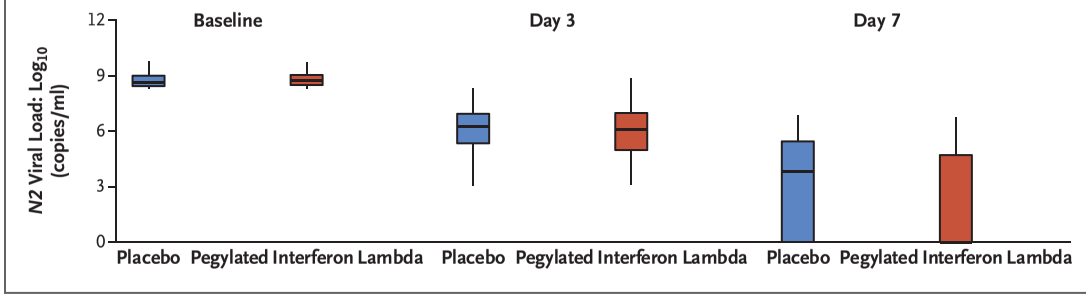


Figure 2 (facing page). Subgroup Analyses.

Panel A shows the absolute reduction (with the 95% Bayesian credible interval) in the risk of hospitalization (or transfer from an emergency department to a tertiary hospital) owing to symptomatic coronavirus disease 2019 (Covid-19) or an emergency department visit due to Covid-19 (defined as observation for >6 hours) within 28 days after randomization (the primary composite outcome) among patients receiving peginterferon lambda and those receiving placebo (intention-to-treat population). SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2. I bars indicate the 95% credible interval. Panel B shows treatment effects according to subgroup. Panel C shows treatment effects according to SARS-CoV-2 dominant variant of concern. Arrows indicate that the 95% Bayesian credible interval extends outside the graphed range. In Panels A, B, and C, horizontal bars indicate the 95% credible interval. Panel D shows an alluvial plot of the change in viral load at day 7, as compared with baseline. The $\log_{10}$ viral loads are denoted by the numbers in the gray columns. Values are rounded to the nearest integer for plotting. Most patients had a reduction in viral load, and a small percentage had an increase by day 7. Panel E shows the change in viral load in patients with a high viral load at baseline. All data are presented in box-and-whisker plots. The whiskers indicate the range, the top and bottom of the boxes indicate the interquartile range, and the horizontal line within each box indicates the median. *N2* denotes the *N2* gene of SARS-CoV-2.

DISCUSSION

This phase 3 trial, which was conducted in a predominantly vaccinated population infected with various SARS-CoV-2 variants of concern, showed the efficacy of a single subcutaneous dose of pegylated interferon lambda administered within 7 days after the onset of symptoms (mean, 3 days). This regimen resulted in a greater than 50% reduction in the risk of a primary-outcome event. Our trial findings were consistent across the SARS-CoV-2 variants of concern and across multiple subgroups according to vaccination status.

In order to place the findings in the context of available oral therapies for outpatient treatments, we examined the effect of pegylated interferon lambda on the composite outcome of Covid-19–related hospitalization or death. Our trial showed a 41% reduction in time to death or hospitalization due to Covid-19 (hazard ratio, 0.59; 95% Bayesian credible interval, 0.35 to 0.97). Among patients who had begun to receive interferon within 3 days after symptom onset, this reduction increased to 65% (relative risk, 0.42; 95% Bayesian credible interval, 0.21 to 0.80).

During the conduct of this trial, two periods of disruption in the supply chain for drugs occurred. This was a multigroup trial, so we included only a concomitant control group in our analysis.[18] Since the completion of our trial, a polymorphism in the innate antiviral response gene *OAS1* has been associated with clearance of SARS-CoV-2, and a common haplotype could be used to identify patients with an increased likelihood of response.[19] Evaluation of the prevalence of this haplotype is warranted.

In this trial involving largely vaccinated outpatients who presented with acute symptomatic Covid-19, the incidence of hospitalization or an emergency department visit due to Covid-19 was significantly lower among patients who received a single dose of pegylated interferon lambda than among those who received placebo. These results, which were observed regardless of viral variant, offer the possibility that a single-dose regimen can play a role in the response to Covid-19.

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APPENDIX

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REFERENCES

1. Andreakos E, Salagianni M, Galani IE, Koltsida O. Interferon-λs: front-line guardians of immunity and homeostasis in the respiratory tract. Front Immunol 2017;8:1232.
2. Prokunina-Olsson L, Alphonse N, Dickenson RE, et al. COVID-19 and emerging viral infections: the case for interferon lambda. J Exp Med 2020;217(5):e20200653.
3. Chan HLY, Ahn SH, Chang T-T, et al. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: a randomized phase 2b study (LIRA-B). J Hepatol 2016;64:1011-9.
4. Muir AJ, Arora S, Everson G, et al. A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. J Hepatol 2014;61:1238-46.
5. Baños-Lara MDR, Harvey L, Mendoza A, et al. Impact and regulation of lambda interferon response in human metapneumovirus infection. J Virol 2015;89:730-42.
6. Nice TJ, Baldridge MT, McCune BT, et al. Interferon-λ cures persistent murine norovirus infection in the absence of adaptive immunity. Science 2015;347:269-73.
7. Davidson S, McCabe TM, Crotta S, et al. IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of IFNα treatment. EMBO Mol Med 2016;8:1099-112.
8. Hakim MS, Chen S, Ding S, et al. Basal interferon signaling and therapeutic use of interferons in controlling rotavirus infection in human intestinal cells and organoids. Sci Rep 2018;8:8341.
9. Dinnon KH III, Leist SR, Schäfer A, et al. A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. Nature 2020;586:560-6.
10. Feld JJ, Kandel C, Biondi MJ, et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respir Med 2021;9:498-510.
11. Jagannathan P, Andrews JR, Bonilla H, et al. Peginterferon lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. Nat Commun 2021;12:1967.
12. Reis G, Silva E, Silva D, et al. A multicenter, adaptive, randomized, platform trial to evaluate the effect of repurposed medicines in outpatients with early coronavirus disease 2019 (COVID-19) and high-risk for complications: the TOGETHER master trial protocol. Gates Open Research 2021;5:117.
13. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
14. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192-e197.
15. Montori VM, Permanyer-Miralda G, Ferreira-González I, et al. Validity of composite end points in clinical trials. BMJ 2005;330:594-6.
16. Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. JAMA 2021;326(3):257-65.
17. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ 2020;192:E901-E906.
18. Dodd LE, Freidlin B, Korn EL. Platform trials — beware the noncomparable control group. N Engl J Med 2021;384:1572-3.
19. Banday AR, Stanifer ML, Florez-Vargas O, et al. Genetic regulation of OAS1 nonsense-mediated decay underlies association with COVID-19 hospitalization in patients of European and African ancestries. Nat Genet 2022;54:1103-16.