Effect of Early Treatment with Peginterferon Lambda among Patients with COVID-19: The *TOGETHER* Randomized Platform Clinical Trial

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July 29, 2022

Disclosures
JSG: Romark Laboratories, Genentech, Merck, Roche, StemCells Inc., Eiger Group International Inc., Eiger BioPharmaceuticals, Inc., Riboscience, LLC, I-Cubed Therapeutics, LLC
EM: None

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Phase 3 Study with Peginterferon Lambda

OVERVIEW

- First major study in a predominantly vaccinated patient population
- 51% (CrI 24-70%, Pr >99.9%) risk reduction in COVID-19-related hospitalizations or ER retention > 6hr (primary endpoint)
- 89% hazard reduction in COVID-19-related-hospitalization or all-cause death amongst unvaccinated patients receiving early treatment (HR 0.11, 95% CrI 0.01-0.75, Pr 99.2%)
- Efficacy across viral variants, including Omicron
- Comparable reduction of SARS-CoV-2 viral loads as demonstrated in Phase 2
- Treatment emergent adverse events similar to placebo
- Single injection; 100% compliance
- Potential combination with Paxlovid, offering strategy to supress protease inhibitor resistance

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OUTLINE

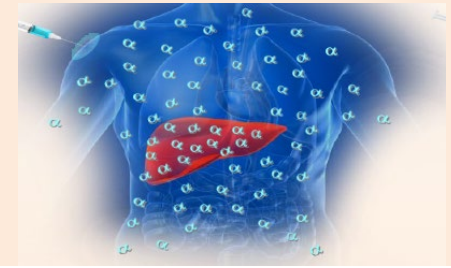
- Background on Peginterferon Lambda
- Topline Phase 2 *ILIAD* data of Peginterferon Lambda in COVID-19 outpatients
- Topline Phase 3 *TOGETHER* study design and results
- Conclusions

Peginterferon Lambda – a broad-spectrum antiviral

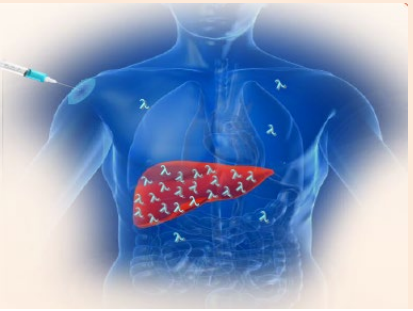
IN DEVELOPMENT AT EIGER FOR THE TREATMENT OF CHRONIC HDV INFECTION

- Pegylated recombinant IL-29 Type III interferon (“Lambda”)
- Binds to Type III receptors as compared to Type I receptors (eg, Alfa)
  - Highly expressed on epithelial cells within the lungs, intestine, and liver
  - Limited expression on hematopoietic, muscle, and CNS cells
- Both Type I and Type III interferons signal through similar Jak-STAT pathway
- Peginterferon lambda extensively investigated in 19 Phase 1, 2 and 3 clinical trials
  - > 3,000 patients have been treated in HCV / HBV / HDV studies
- Convenient subcutaneous dosing (once weekly)

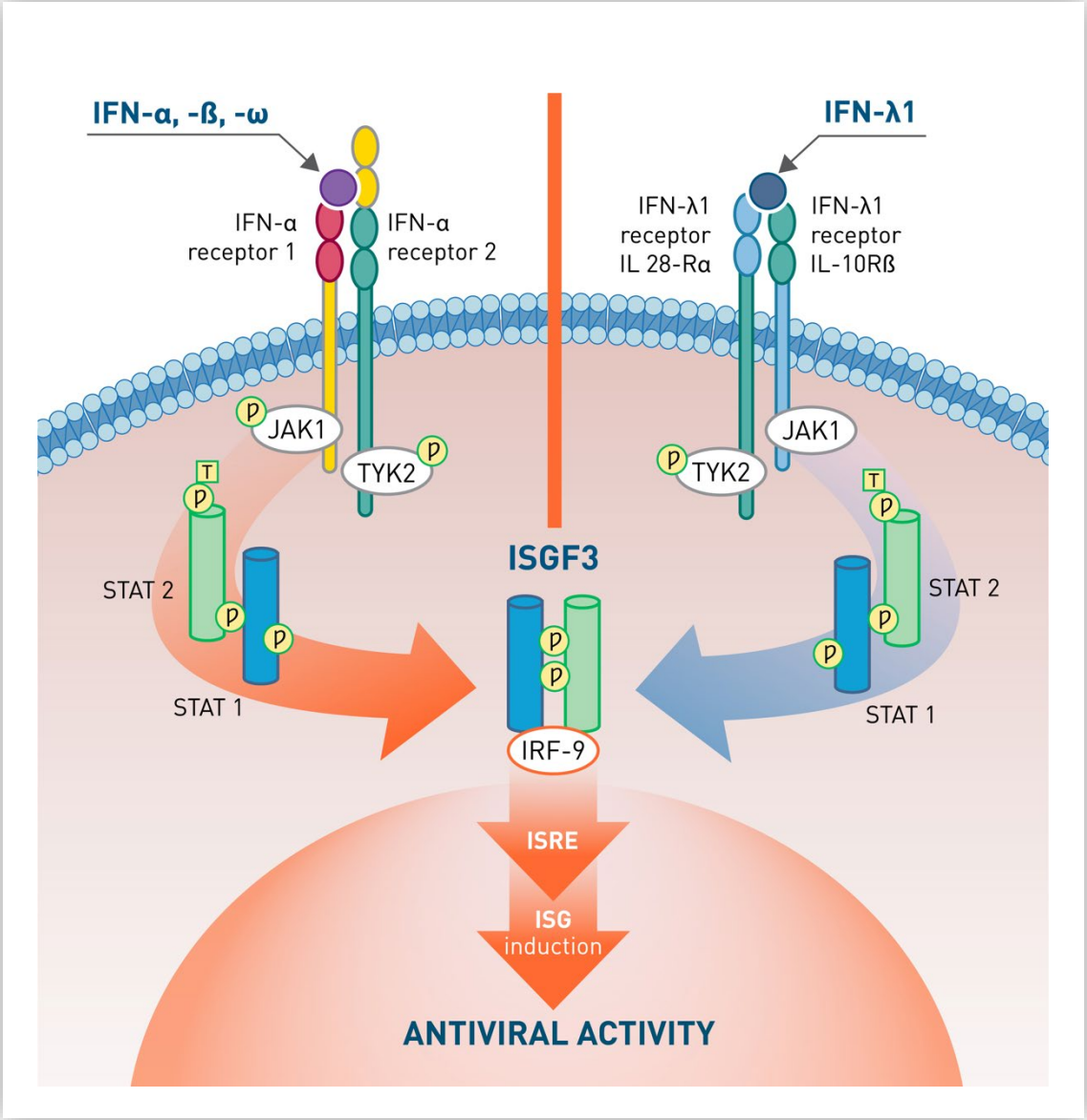
Alfa Receptor Expression



Lambda Receptor Expression



Lambda and Alfa Induce Similar Antiviral Responses



PEG-IFN lambda vs. PEG-IFN alfa for HCV*(EMERGE)

*all with ribavirin, treatment-naïve genotypes 1 and 4

Pts:	48 weeks	cEVR 12	SVR 24
98	PEG-IFN lambda 1a 120 ug sc qw	55%	46%
102	PEG-IFN lambda 1a 180 ug sc qw	56%	37%
104	PEG-IFN lambda 1a 240 ug sc qw	57%	39%
103	PEG-IFN alfa 2a 180 ug sc qw	37%	37%

Muir et al., Journal of Hepatology 2014, 1238–1246

Peginterferon Lambda vs Peginterferon Alfa Tolerability

PHASE 2 *EMERGE* STUDY IN HCV

	Genotypes 1,4 (48 weeks' treatment)			
	Lambda			Alfa
	120 µg (N = 98)	180 µg (N = 102)	240 µg* (N = 104)	180 µg (N = 103)
Total number of AEs, n	706	663	787	1006
Headache	26 (26.5)	28 (27.5)	29 (27.9)	43 (41.7)
Myalgia	10 (10.2)	6 (5.9)	13 (12.5)	34 (33.0)
Arthralgia	14 (14.3)	6 (5.9)	10 (9.6)	21 (20.4)
Pyrexia	12 (12.2)	8 (7.8)	5 (4.8)	34 (33.0)
Insomnia	31 (31.6)	18 (17.6)	23 (22.1)	26 (25.2)
Chills	4 (4.1)	4 (3.9)	2 (1.9)	22 (21.4)
Irritability	15 (15.3)	16 (15.7)	18 (17.3)	13 (12.6)
Pruritus	19 (19.4)	18 (17.6)	29 (27.9)	30 (29.1)
Rash	13 (13.3)	15 (14.7)	12 (11.5)	25 (24.3)
Laboratory abnormalities, n/N (%)				
ALT and/or AST high				
Grade 3	2/98 (2.0)	3/101 (3.0)	19/102 (18.6)	7/103 (6.8)
Grade 4	0	0	3/102 (2.9)	1/103 (1.0)
Total bilirubin high				
Grade 3	2/98 (2.0)	5/101 (5.0)	8/102 (7.8)	4/103 (3.9)
Grade 4	0	2/101 (2.0)	2/102 (2.0)	1/103 (1.0)
Haemoglobin low				
Grade 3	11/97 (11.3)	6/101 (5.9)	7/102 (6.9)	32/103 (31.1)
Neutrophils low				
Grade 3	0	1/101 (1.0)	1/102 (1.0)	20/103 (19.4)
Grade 4	0	0	0	1/103 (1.0)
Platelets low				
Grade 2	0	2/101 (2.0)	0	18/103 (17.5)
Grade 3	0	0	0	2/103 (1.9)

Muir et al., *J Hepatology* **2014**, 1238–1246

Peginterferon Lambda Has Broad-Spectrum Antiviral Activity

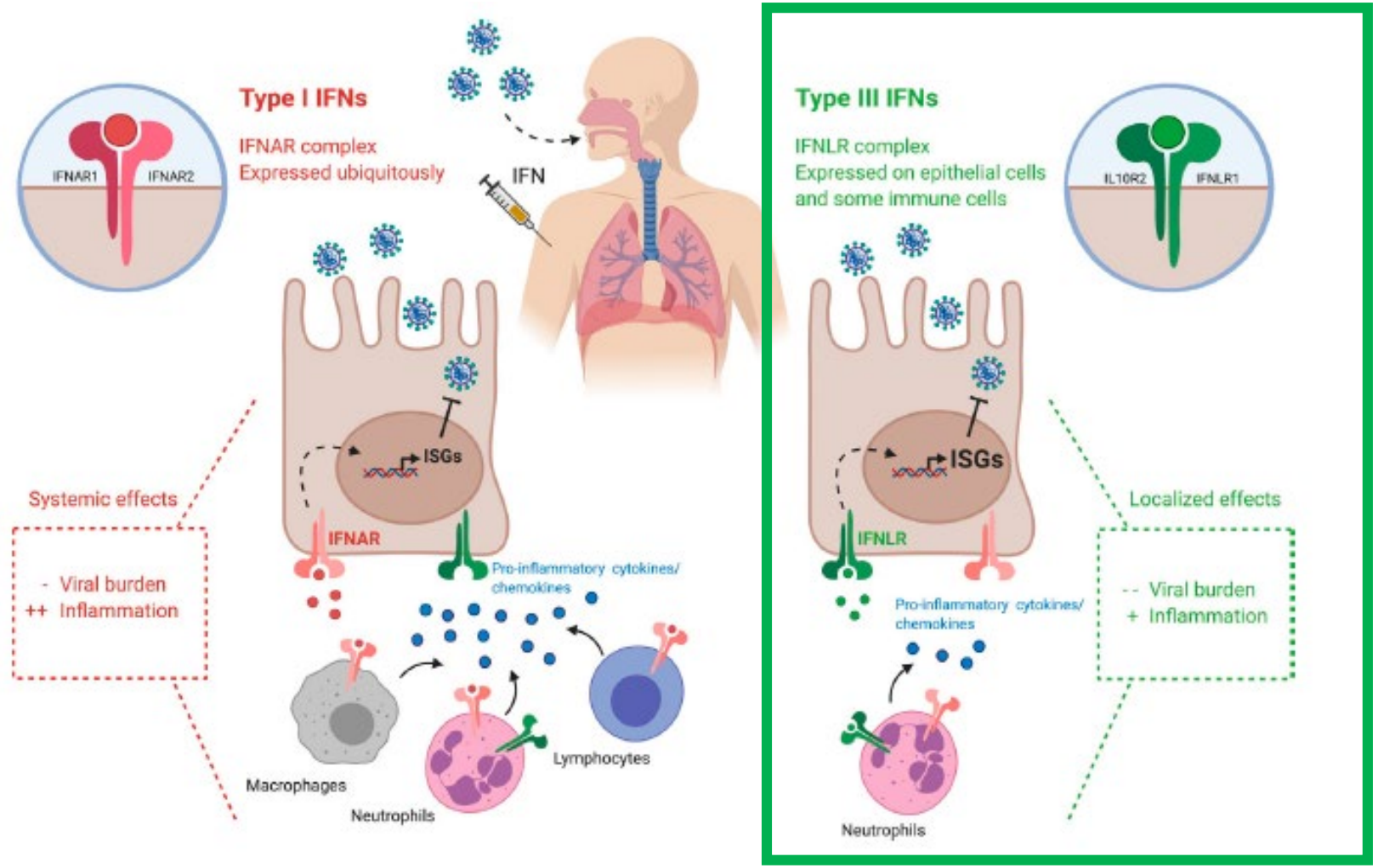
MAJOR COMPONENT OF INNATE IMMUNE DEFNESE TO VIRUSES, BACTERIA, FUNGI

	POTENT ANTIVIRAL EFFECTS	
	Lambda in Animal Models	Lambda in Human Studies
HBV, HCV, HDV	✓	✓
SARS-CoV-2	✓	✓
Influenza, Human Metapneumovirus	✓	*TBD*
Rotavirus, Norovirus, Reovirus	✓	*TBD*

Read et al 2019

Potential Benefits of Type III Interferons Against COVID-19

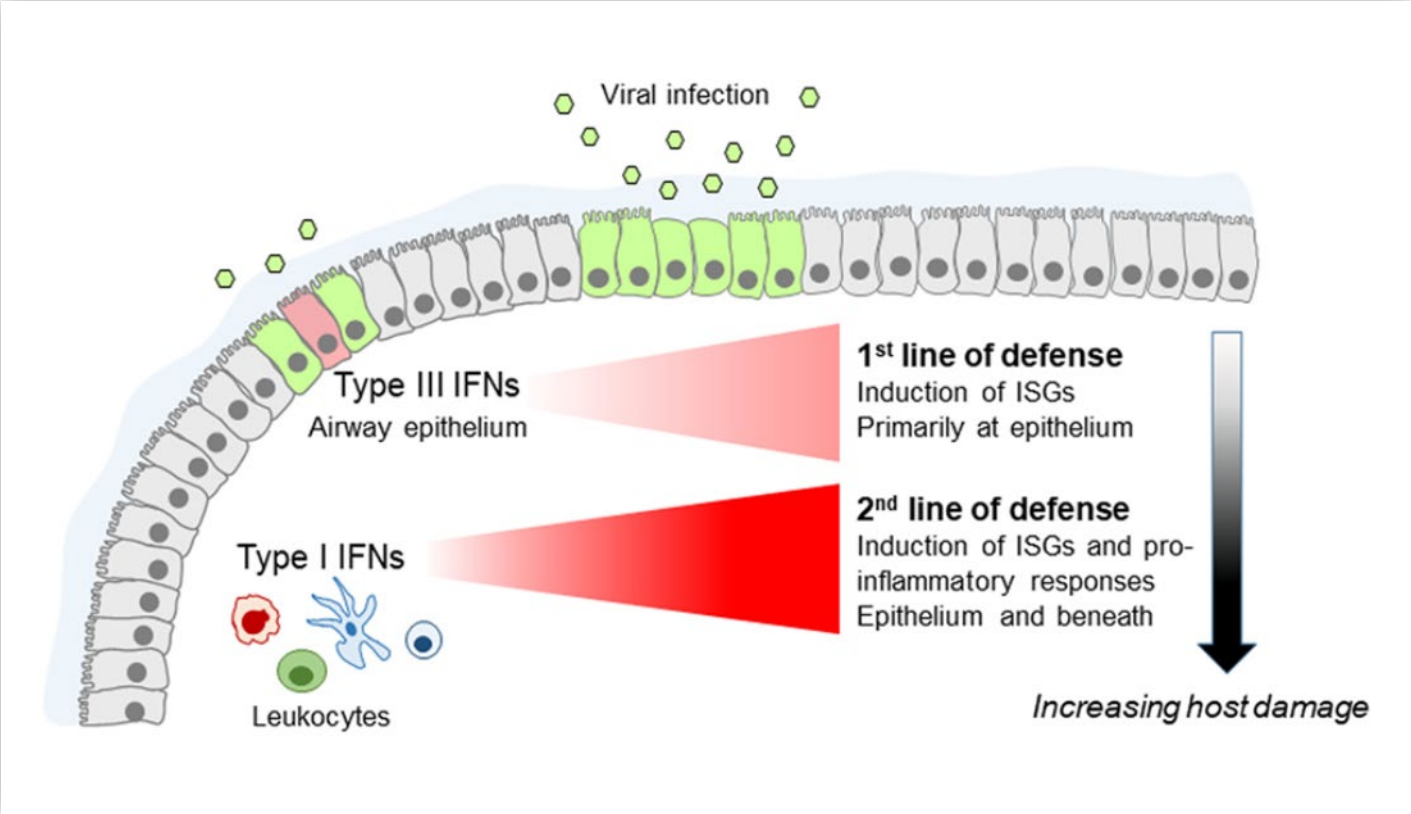
TYPE III IFNS HAVE LESS PRO-INFLAMMATORY PROPERTIES THAN TYPE I IFNS



Prokunina-Olsson et al 2020, JEM

Type III IFNS: First Line of Defense Upon Infection of Airways

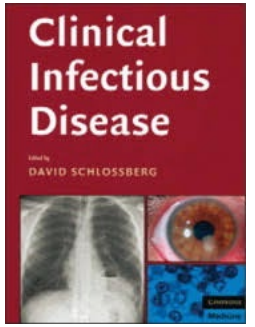
LAMBDA IFN PRODUCED FIRST TO LIMIT VIRUS SPREAD AT EPITHELIAL BARRIER WITHOUT TRIGGERING INFLAMMATION



- If infection escapes Type III IFN control, Type I IFNs are induced that provide second line of defense
- Alfa IFN enhances antiviral response beyond the respiratory epithelium
- Alfa IFN activates pro-inflammatory responses and causes immunopathology (cytokine storm)

Andreakos et al 2017

Weak Induction of Interferon Expression by SARS-CoV-2 Supports Clinical Trials of Interferon Lambda to Treat Early COVID-19



Thomas R. O'Brien[1], David L. Thomas[2], Sarah S. Jackson[1], Ludmila Prokunina-Olsson[3], Raymond P. Donnelly[4], Rune Hartmann[5]

[1]National Institutes of Health, USA; [2]Johns Hopkins University, School of Medicine, USA; [3]National Cancer Institute, USA; [4]Food and Drug Administration, USA; [5]University of Aarus, Denmark.

> *"SARS-CoV-2 induces very weak expression of interferons in infected cells. Absence of IFN production likely hampers the early innate immune response to SARS-CoV-2 infection and suggests that use of exogenous IFN to stimulate antiviral immunity might be successful for treating SARS-CoV-2 infection…While IFN-l has less pro-inflammatory properties than type I IFN, pegylated-IFN-l1 has not been tested in patients with respiratory infections and ideally, should be first studied in patients with early SARS-CoV-2 infection or as prophylaxis."*

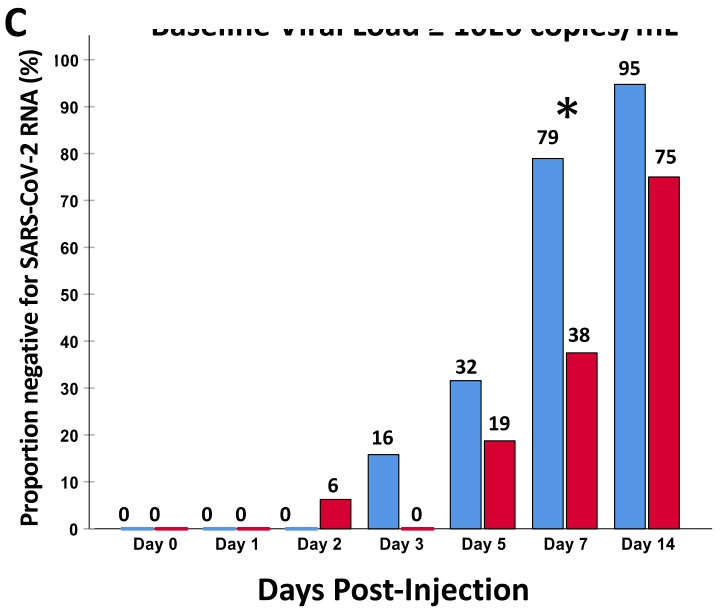
Clin. Infec. Dis. April 2020

Phase 2 *ILIAD* Study – Proof of Concept

A

B

C



rom COVID symptoms

Feld et al, Lancet Resp Med 2021

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clinical trials

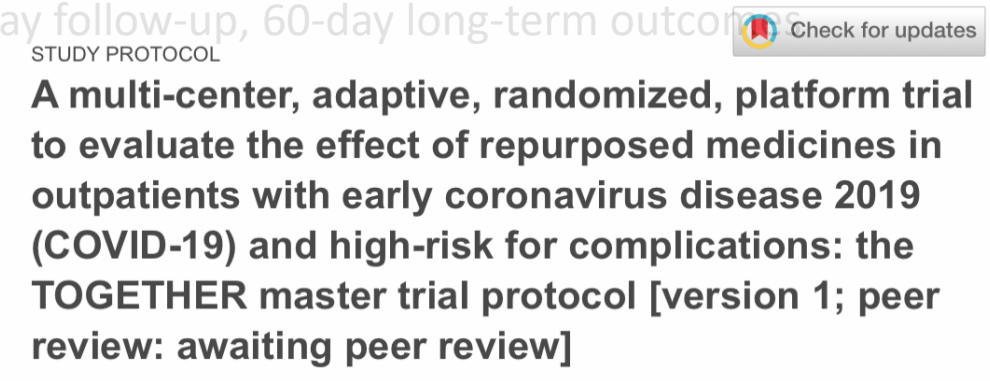
SCT
SOCIETY FOR CLINICAL TRIALS

DAVID SACKETT TRIAL OF THE YEAR

The NEW ENGLAND JOURNAL of MEDICINE

TRIAL OVERVIEW

- Randomized adaptive platform trial to investigate the efficacy of repurposed treatments for COVID-19 disease among high-risk adult outpatients
- Received ethics board approval in Brazil (CEP/CONEP#: 41174620.0.1001.5120), and Canada (HiREB#: 13390; UHN21-5018)
- Data and Safety Monitoring Committee provides independent oversight
- The trial was initiated on June 2, 2020
- Enrollment into the Peginterferon Lambda arm began on June 24th, 2021
- 28-day follow-up, 60-day long-term outcomes



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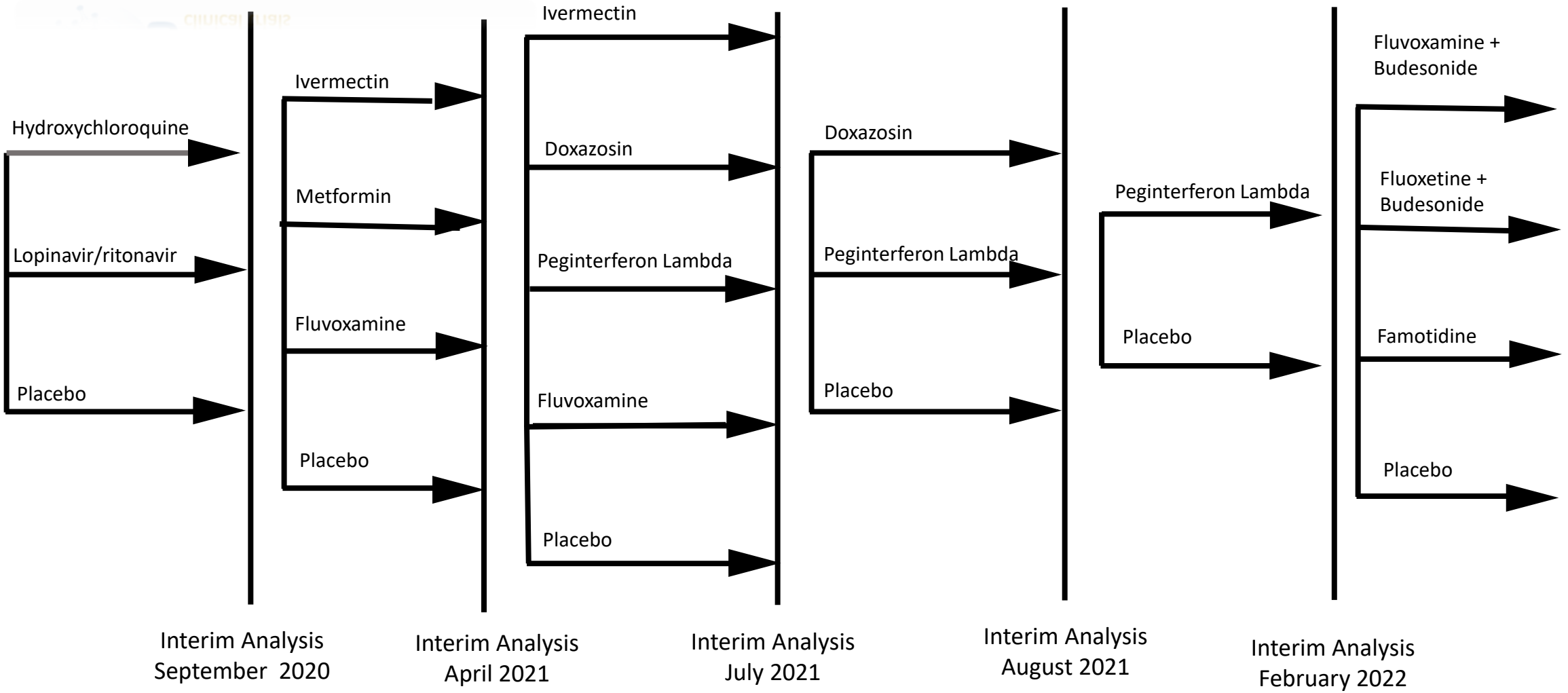


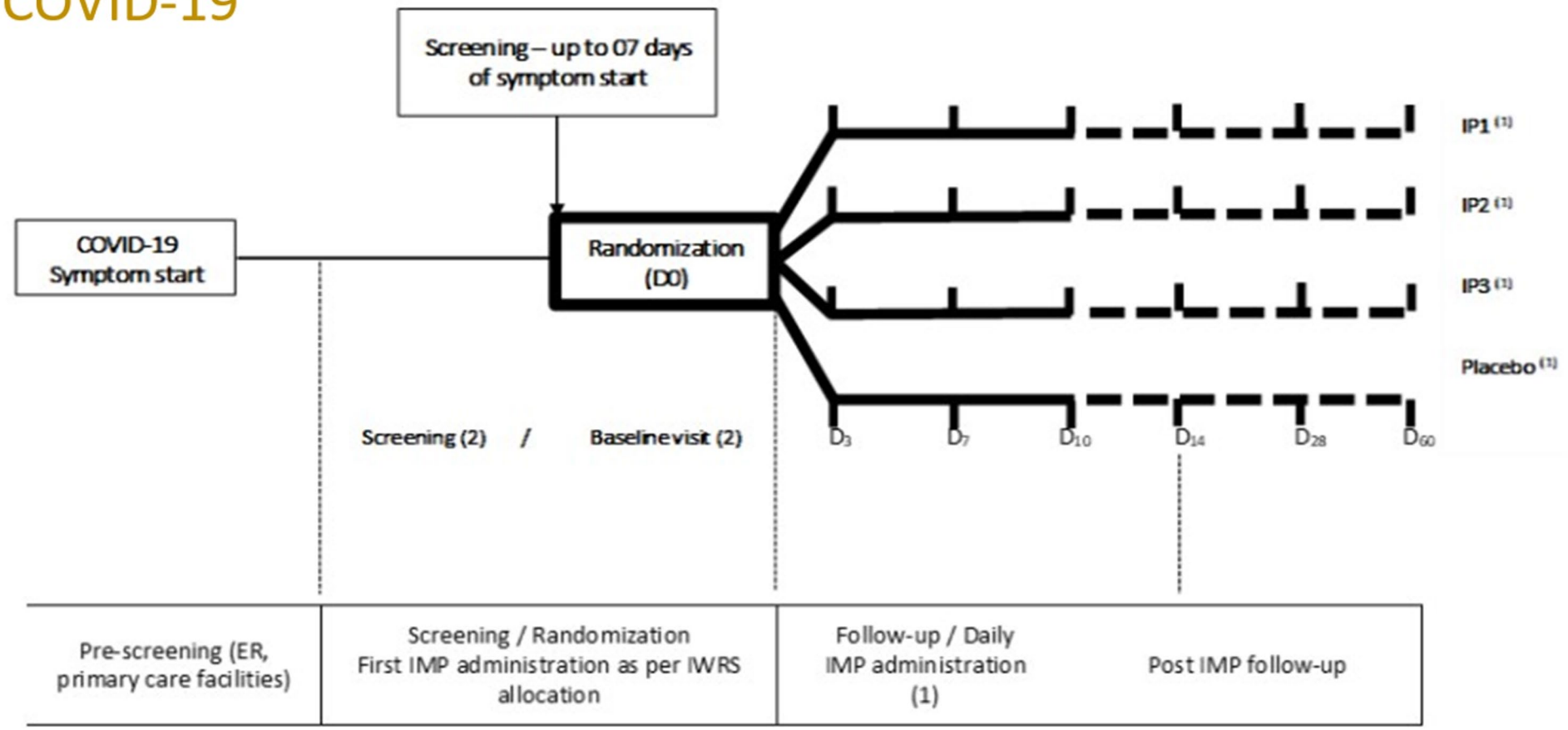
In collaboration with our global partners

17

- Inclusion criteria
  - > 18 years with a known risk factor for disease progression
  - Presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date
  - Positive rapid test for SARS-CoV-2 antigen

- Exclusion criteria
  - Acute respiratory condition compatible with COVID-19 treated in the primary care and requiring hospitalization

DATA COLLECTION



- Participants were contacted on Days 1, 2, 3, 4, 5, 7, 10, 14, and 28 via telephone and social media applications
- Participants were contacted at Day 60 to assess long-term outcomes
- All SAEs were documented and reported as per local regulatory requirements
- Data were entered into the trial's EDC system (IBM Clinical Development)

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OUTCOMES

Primary Outcomes:

- COVID-19 emergency setting visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours)
- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.
- COVID-19 hospitalization or death

Secondary Outcomes:

- WHO clinical worsening scale
- PROMIS global health scale
- Mortality defined and all-cause
- Cause-specific hospitalization
- Viral clearance and viral load
- Respiratory symptoms
- Adverse events
- Adverse drug reactions
- Adherence with medication

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STATISTICAL PRINCIPLES

- Run in a Bayesian framework
- Stopping rules inform the DSMB
- Stopping for superiority based on *a priori* probability of superiority >97.6% on primary endpoint
- Adaptive design permits changes
- Events reported as both binary and time-to-events


Ibirité
em Ação
Corona Não.

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SECOND LARGEST TREATMENT EVALUATION IN OUTPATIENT COVID-19

- Multi-center, investigator-sponsored, randomized, placebo-controlled Phase 3 study in Brazil (12 sites) and Canada (5 sites)
- Single injection of peginterferon lambda vs. placebo
- Randomized within 7 days of symptom onset and positive SARS-CoV-2 test
- Enrolled >1,900 high-risk, non-hospitalized, 84% vaccinated patients from Jul 2021 – Feb 2022
- High-risk criteria defined by patients having at least one of the following criteria, including but not limited to: > age 50, diabetes, hypertension, CV disease, lung disease, kidney disease, obesity, etc.
- Primary endpoint is reduction of COVID-19–related hospitalizations or emergency hospital visits (>6h) through Day 28
- Key secondary endpoint is reduction of COVID-19–related hospitalizations or deaths through Day 28

Baseline Characteristic	# of Patients (%)		
	Peginterferon lambda (n = 931)	Placebo (n = 1018)	Overall (N = 1947)
Median age (range)	43 (18 – 92)	43 (18 – 88)	43 (18 – 92)
Sex			
Female	531 (57.0)	582 (57.2)	1113 (57.1)
Male	400 (43.0)	436 (42.8)	836 (42.9)
Race or ethnic group			
Mixed Race[†]	876 (94.1)	977 (96.0)	1853 (95.1)
White	31 (3.3)	27 (2.7)	58 (3.0)
Black or African American	18 (1.9)	10 (1.0)	28 (1.4)
Pacific Islander	1 (0.1)	0 (0)	1 (0.1)
Other	2 (0.2)	2 (0.2)	4 (0.2)
Risk factors for severe illness from COVID-19			
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 (physician diagnosed)	91 (9.8)	101 (9.9)	192 (9.9)
Chronic pulmonary disease	21 (2.3)	26 (2.6)	47 (2.4)
Type 2 diabetes	88 (9.5)	93 (9.1)	181 (9.3)
Cancer	13 (1.4)	12 (1.2)	25 (1.3)
Multiple comorbidities	517 (55.5)	607 (59.6)	1124 (57.7)

Baseline Characteristic	# of Patients (%)		
	Peginterferon lambda (n = 931)	Placebo (n = 1018)	Overall (N = 1947)
Vaccination doses before randomization			
No	142 (15.3)	177 (17.5)	319 (16.5)
1 dose	223 (24.5)	258 (25.9)	481 (25.3)
2 doses	458 (50.3)	483 (48.6)	941 (49.3)
3 doses	88 (9.7)	78 (7.8)	166 (8.6)
Missing	20	22	42
COVID-19 variant			
Alpha	6 (1.0)	3 (0.5)	9 (0.8)
Delta	266 (44.2)	261 (47.1)	527 (45.5)
Gamma	88 (14.6)	57 (10.1)	145 (12.5)
Omicron	241 (40.0)	233 (42.1)	474 (41.0)
Zeta	1 (0.2)	1 (0.2)	2 (0.2)
Missing	329	463	792
Days since onset of symptoms			
0-3 days	567 (60.9)	591 (58.1)	1158 (59.4)
4-7 days	364 (39.1)	426 (41.9)	790 (40.6)
Missing	0	1	1

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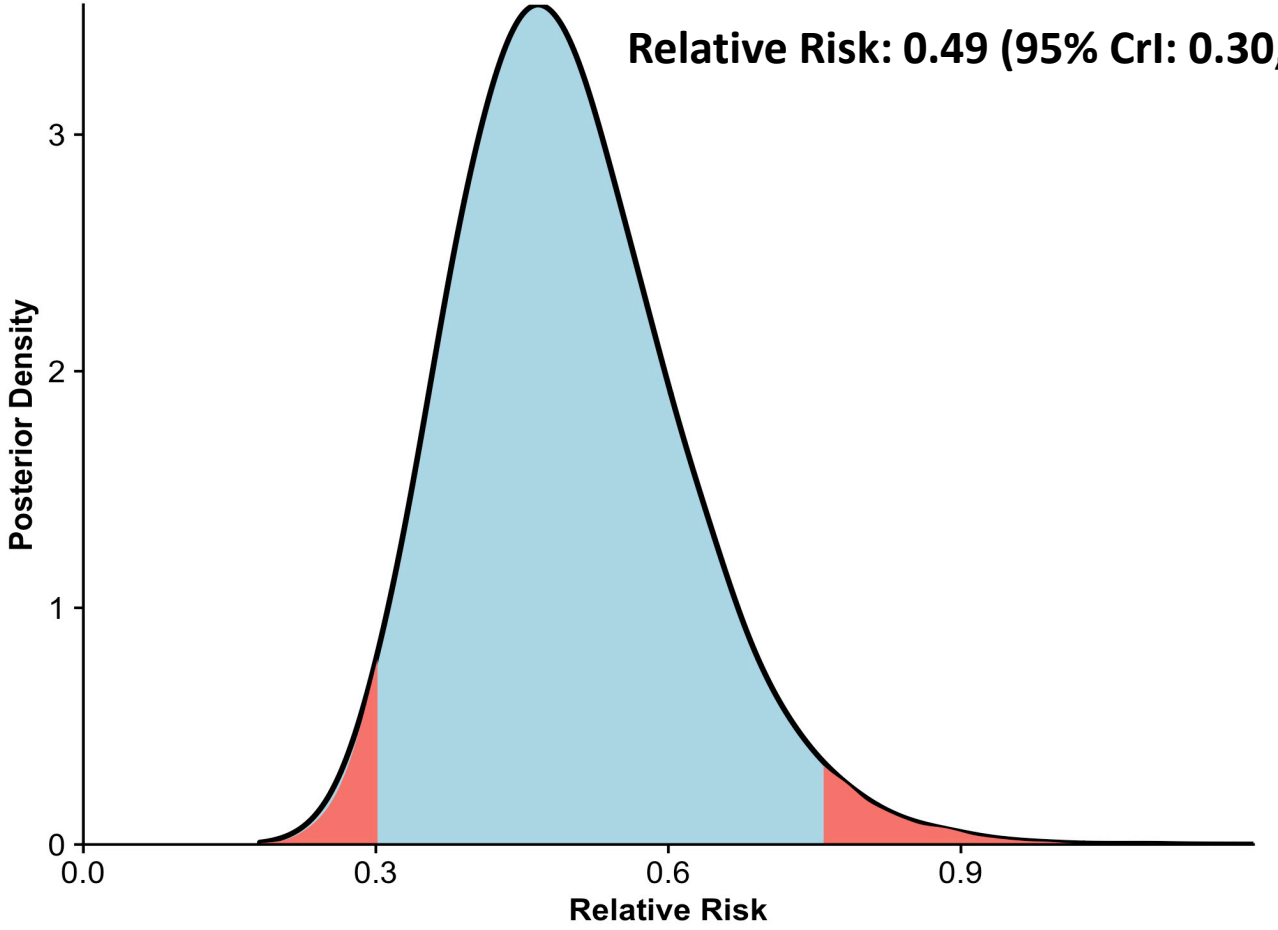
HIGHLY SIGNIFICANT ON PRIMARY ENDPOINT

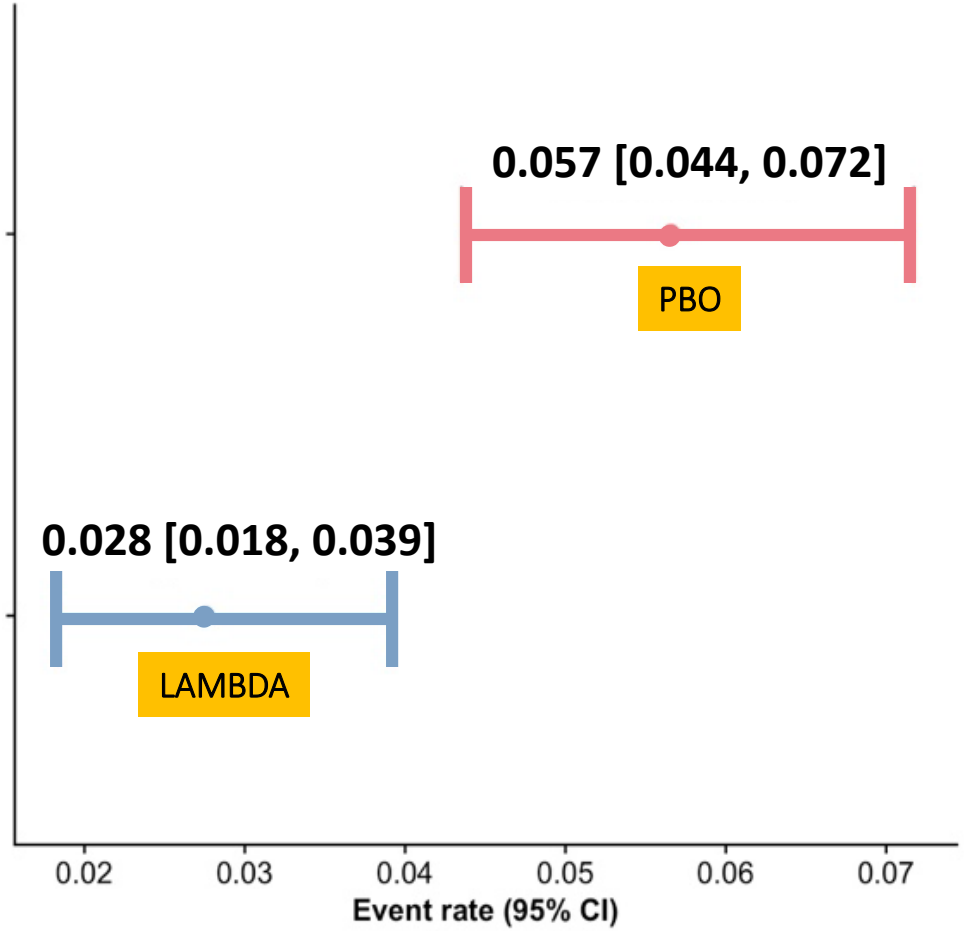
Risk	# Days of Symptoms Before Treatment	Risk Reduction (95% BCI)	Probability of Superiority*
COVID-19-Related Hospitalization or ER retention	≤ 7 days	51% (24 - 70%)	>99.9%
	≤ 3 days	57% (19 - 79%)	99.6%

*Prespecified Threshold of Superiority = 97.6%

Peginterferon Lambda Highly Superior Compared to Placebo

***99.91% PROBABILITY OF SUPERIORITY*, SURPASSING PRESPECIFIED SUPERIORITY THRESHOLD OF 97.6%**





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PRIMARY ENDPOINT DRIVEN BY HOSPITALIZATIONS : 74% OF EVENTS WERE HOSPITALIZATIONS

Risk	# Days of Symptoms Before Treatment	Risk Reduction (95% BCI)	Probability of Superiority*
Hospitalization due to COVID-19	≤ 7 days	43% (5-67%)	98.3%
	≤ 3 days	65% (25-85%)	99.6%
Hospitalization due to COVID-19 or Death due to COVID-19	≤ 7 days	41% (3 –65%)	98.1%
	≤ 3 days	65% (25–85%)	99.6%

No deaths in the peginterferon lambda arm in early treated patients

Comparable Populations

Unvaccinated populations

Primary outcome

COVID hospitalization or death

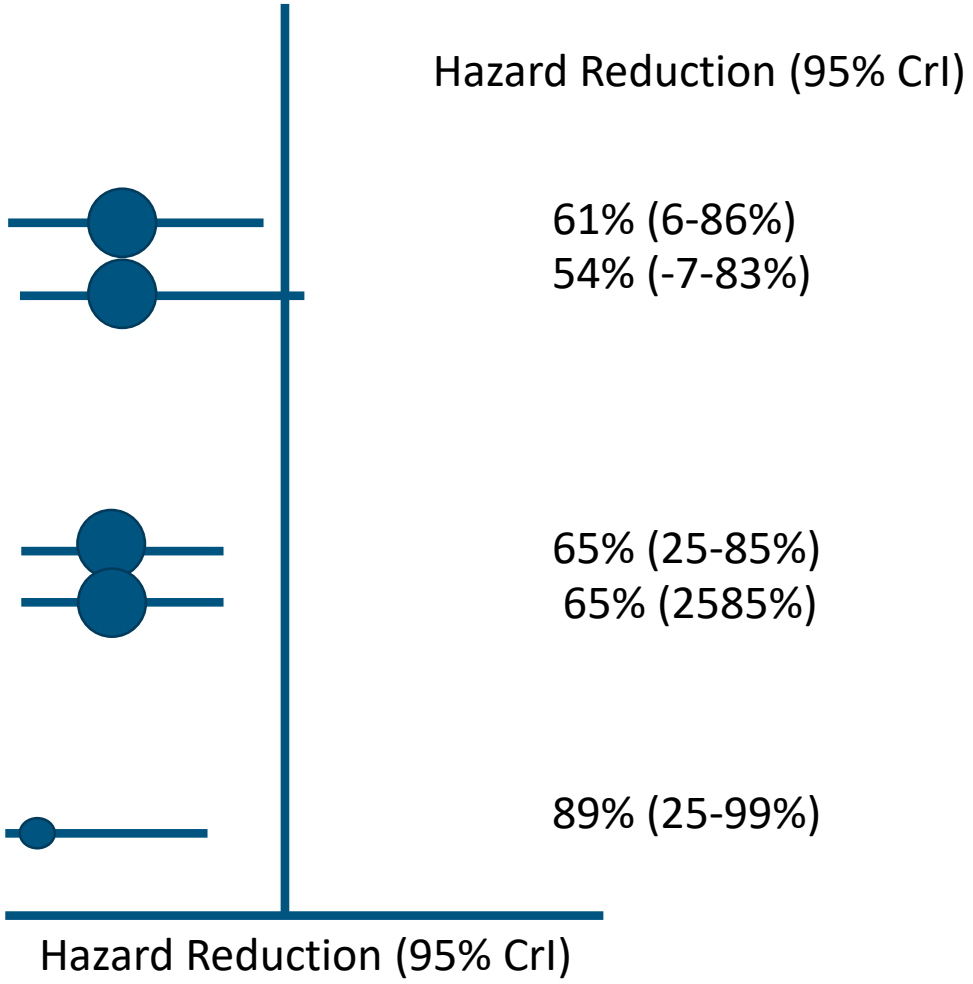
Early treated (≤3 days)

Primary outcome

COVID hospitalization or death

Unvaccinated and early treatment

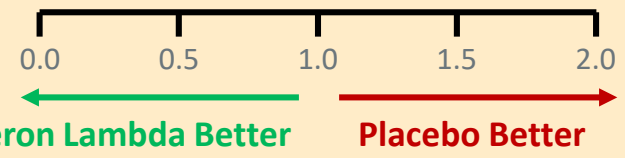
COVID hospitalization or death



Clear Peginterferon Lambda Treatment Effect by Subgroup

COVID-19-RELATED HOSPITALIZATIONS OR ER RETENTION (TREATED WITHIN 7 DAYS OF SYMPTOMS)

	Peginterferon Lambda	Placebo	Risk Reduction (RR, 95% CrI)
ITT	25/931	57/1018	51% (0.49, 0.30 to 0.76)
Age			
≥50	18/350	38/404	44% (0.56, 0.32 to 0.93)
<50	7/581	19/614	59% (0.41, 0.17 to 0.91)
Sex			
Male	16/400	32/436	45% (0.55, 0.30 to 0.96)
Female	9/531	25/582	59% (0.41, 0.19 to 0.83)
Symptom onset			
≤ 3 days	11/567	28/590	58% (0.42, 0.21 to 0.80)
> 3 days	14/364	29/428	42% (0.58, 0.31 to 1.05)
Vaccination status			
Unvaccinated	6/143	18/177	56% (0.44, 0.18 to 0.98)
Vaccinated	19/786	38/835	46% (0.54, 0.31 to 0.91)
Obesity			
Yes	10/323	29/403	55% (0.45, 0.22 to 0.86)
No	15/608	28/615	45% (0.55, 0.30 to 1.00)



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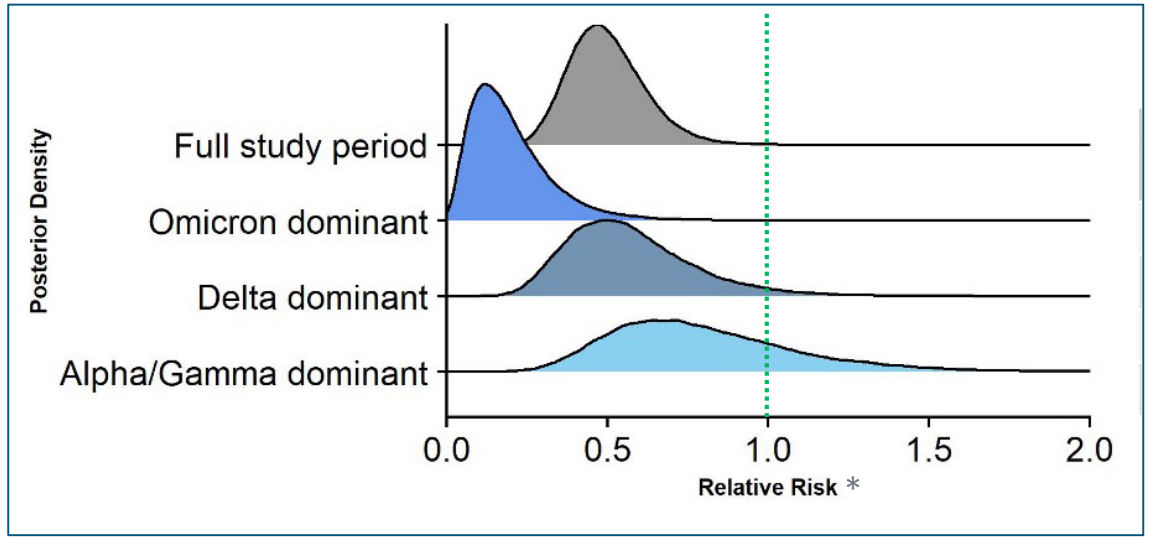
PRELIMINARY ANALYSIS DEMONSTRATES LAMBDA IS ACTIVE AGAINST MULTIPLE VARIANTS

Time Period	Dominant Variant	Lambda N (# events)	Placebo N (# events)
Jun 21 to Feb 22	Full Study	916 (25)	1001 (57)
Dec 21 to Feb 22	Omicron	425 (2)	500 (18)
Aug 21 to Dec 21	Delta	358 (12)	363 (23)
Jun 21 to Aug 21	Gamma	128 (11)	138 (16)



- Preliminary analysis of treatment response against dominant variants: Gamma, Delta, and Omicron
- Jun 2021 to Aug 2021 (Gamma predominant)
  - 25% risk reduction during this earliest period
- Aug 2021 to Dec 2021 (Delta predominant)
  - 46% risk reduction
- Dec 2021 to Feb 2022 (Omicron predominant)
  - Highest risk reduction of 83%

*Risk reduction of COVID-19 related hospitalizations or ER visits

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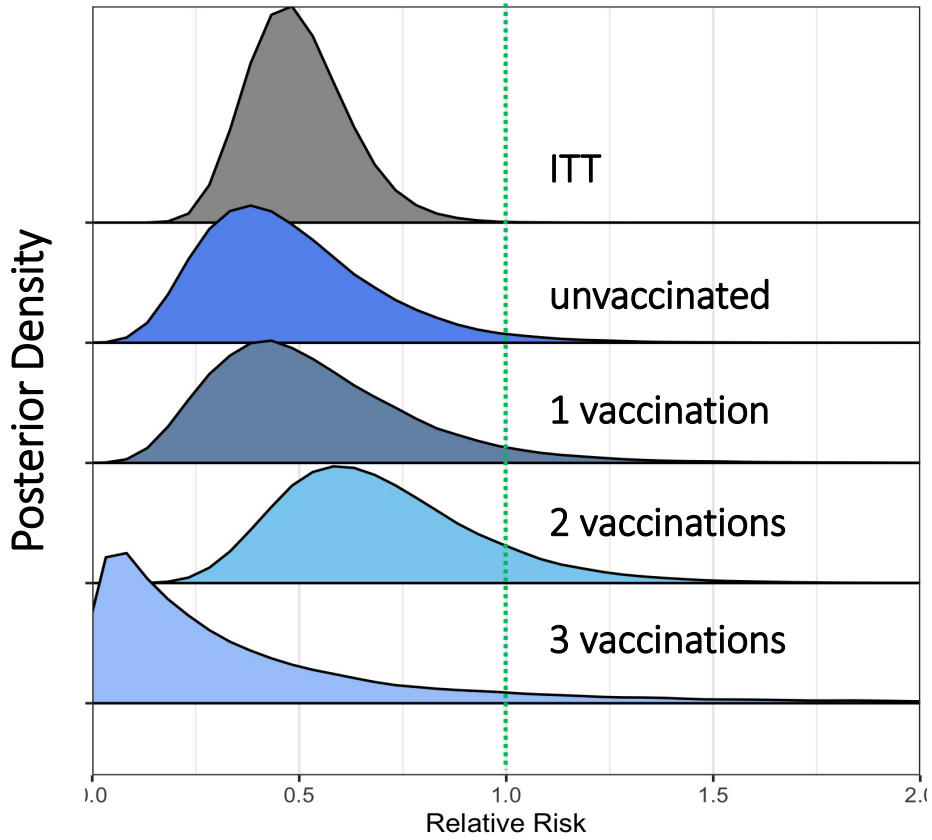
PEGINTERFERON LAMBDA IS ACTIVE ACROSS MULTIPLE VACCINE STATUS

# Doses	Lambda n (# events)	Placebo n (# events)
unvaccinated	142 (6)	177 (18)
1 dose	223 (6)	258 (15)
2 dose	458 (13)	483 (21)
3 dose	88 (0)	78 (2)

Majority of vaccinated patients received Pfizer or AZ vaccines



*Risk reduction of COVID-19 related hospitalizations or ER retentions

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Outcome	Measure	Peginterferon Lambda* (N=931)	Placebo* (N=1018)	Estimated Treatment Effect
Hospitalization or ER retention > 6h for COVID-19	RR (95% CrI)	25 (2.7%)	57 (5.6%)	0.49 (0.30, 0.76)
Days to hospitalization or ER > 6h for COVID-19	HR (95% CrI)	--	--	0.47 (0.29, 0.73)
Hospitalization for COVID-19	RR (95% CrI)	21 (2.3%)	40 (3.9%)	0.58 (0.34, 0.96)
Days to hospitalization for COVID-19	HR (95% CrI)	--	--	0.57 (0.33, 0.95)
Death or hospitalization due to COVID-19	RR (95% CrI)	22 (2.4%)	40 (3.9%)	0.61 (0.36, 0.99)
Days to death or hospitalization due to COVID-19	HR (95% CrI)	--	--	0.59 (0.35, 0.97)
Death due to COVID-19	RR (95% CrI)	1 (0.1%)	4 (0.4%)	0.39 (0.05, 1.95)
Days to death for COVID-19	HR (95% CI)	--	--	0.22 (0.01, 1.64)
Hospitalization or ER (any duration) for COVID-19	RR (95% CrI)	99 (10.6%)	140 (13.8%)	0.78 (0.61, 0.99)
Days on mechanical ventilation	MD (95% CrI)	10.2 (7.4)	13.6 (11.9)	-4.47 (-6.89, 3.09)

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TREATMENT EMERGENT ADVERSE EVENTS COMPARABLE TO PLACEBO

	RR	Lambda n (%)	Placebo n (%)	Effect size
TEAE, Grade 1	RR (95% CrI)	27 (2.9%)	37 (3.6%)	0.78 (0.48, 1.26)
TEAE, Grade 2	RR (95% CrI)	86 (9.2%)	99 (9.7%)	0.95 (0.72, 1.25)
TEAE, Grade 3	RR (95% CrI)	21 (2.3%)	35 (3.4%)	0.66 (0.39, 1.11)
TEAE, Grade 4	RR (95% CrI)	8 (0.9%)	8 (0.8%)	1.09 (0.42, 2.86)

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GREATER VIRAL LOAD DECLINE IN PATIENTS WITH HIGH BASELINE VIRAL LOAD

- Viral load reduction similar to Phase 2
- Patients with higher baseline viral loads:
  - Greater median viral load decline at Day 7
    - 8.2 $\log_{10}$ (peginterferon lambda) vs. 5.16 $\log_{10}$ (placebo)
  - Greater proportion of patients BLOQ at Day 7
    - 50.5% (peginterferon lambda) vs. 32.9 % for (placebo)

- Paxlovid (Pfizer M^{pro} protease inhibitor + ritonavir)

  ritonavir→ challenge for rapid dosing in patients with many medications

- Protease inhibitor susceptible to developing resistance
  (?occurring in cases of relapse post treatment)

- Orthogonal MOA compared to Lambda

- Combination of Paxlovid + peginterferon lambda has potential to both:
  - increase efficacy and
  - decrease emergence of resistance to Paxlovid

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POTENTIAL "ONE AND DONE" FOR NEWLY DIAGNOSED COVID-19 OUTPATIENTS

- First major study in mostly vaccinated patients: early treatment resulted in greater treatment effects on all outcomes
- Primary endpoint: 51% (CrI 24-70%, Pr >99.9%)) risk reduction
- Unvaccinated patients receiving early treatment: hazard reduction of 89% in COVID-19-related-hospitalization or death (HR 0.11, 95% CrI 0.01-0.75, Pr 99.2%*)
- 100% compliance with efficacy seen across viral variants, including Omicron
- Treatment emergent adverse events similar to placebo
- Ongoing, active discussions with FDA on potential Emergency Use Application

Demonstrated efficacy in a relevant patient population, regardless of vaccination status or SARS-CoV-2 variant

*Prespecified Threshold of Superiority = 97.6%

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FAST — GRANTS
COVID-19 RESEARCH FUNDING

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PATIENTS —THANK YOU!