Table 4d. Interferons: Selected Clinical Trial Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for interferons. The studies summarized below are the randomized controlled trials that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ACTT-3: Multinational, Double-Blind RCT of Interferon Beta-1a and Remdesivir in Hospitalized Adults With COVID-19[1]		

Key Inclusion Criteria
• Evidence of pneumonia (radiographic infiltrates, SpO_2 ≤94% on room air, or supplemental oxygen)
• No MV required
Key Exclusion Criteria
• AST or ALT >5 times ULN
• Impaired renal function
• Anticipated hospital discharge or transfer within 72 hours
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus IFN beta-1a 44 µg SUBQ every other day for up to 4 doses (n = 487)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus placebo (n = 482)
Primary Endpoint
• Time to recovery by Day 28
Key Secondary Endpoints
• Clinical status at Day 14, as measured by an OS
• Mortality by Day 28
	Participant Characteristics
	• Mean age 59 years; 38% were aged ≥65 years
	• 58% men; 32% Latino, 60% White, 17% Black
	• Mean of 8.6 days of symptoms before enrollment
	• 90% had ≥1 comorbidity; 58% with HTN; 58% with obesity; 37% with DM
	Primary Outcome
	• Median time to recovery for both arms was 5 days (rate ratio 0.99; 95% CI, 0.87–1.13; $P = 0.88$).
	  • In patients on high-flow oxygen or NIV (OS6) at baseline, median time to recovery was >28 days in IFN beta-1a arm and 9 days in placebo arm (rate ratio 0.40; 95% CI, 0.22–0.75; $P = 0.0031$).
	Secondary Outcomes
	• No difference between arms in clinical status at Day 14 (OR 1.01; 95% CI, 0.79–1.28)
	• No difference between IFN beta-1a arm and placebo arm in mortality by Day 28 in:
	  • All patients: 5% vs. 3% (HR 1.33; 95% CI, 0.69–2.55)
	  • Patients who were OS6 at baseline: 21% vs. 12% (HR 1.74; 95% CI, 0.51–5.93)
		Key Limitation
		• OS6 patients were excluded after 270 patients were enrolled because of an increased frequency of AEs in this group.
		Interpretation
		• There was no clinical benefit of IFN beta-1a plus RDV in hospitalized patients compared to RDV alone.
		• The use of IFN beta-1a was associated with worse outcomes among patients who were OS6 at baseline.

Methods	Results	Limitations and Interpretation
WHO Solidarity Trial: Multinational, Open-Label, Adaptive RCT of IV or SUBQ Interferon Beta-1a or Other Repurposed Drugs in Hospitalized Adults With COVID-19[2]		
Key Inclusion Criteria • Diagnosis of COVID-19 • Not expected to be transferred elsewhere within 72 hours **Interventions** • IFN beta-1a 44 µg SUBQ on day of randomization, Day 3, and Day 6 (n = 1,656) • IFN beta-1a 10 µg IV daily for 6 days for patients on high-flow oxygen, ventilation, or ECMO (n = 394) • IFN beta-1a (either SUBQ or IV) and LPV/RTV 400 mg/50 mg twice daily for 14 days (n = 651) • Local SOC (n = 2,050) **Primary Endpoint** • In-hospital mortality **Key Secondary Endpoint** • Initiation of ventilation	**Participant Characteristics** • 35% aged <50 years; 19% aged ≥70 years; 63% men • 70% on supplemental oxygen; 7% on ventilation • Approximately 50% received corticosteroids during the study **Primary Outcome** • In-hospital mortality: 11.9% for combined IFN beta-1a arms vs. 10.5% in SOC arm (rate ratio 1.16; 95% CI, 0.96–1.39). • For IFN beta-1a only (without LPV/RTV) recipients vs. SOC recipients, rate ratio was 1.12 (95% CI, 0.83–1.51). • Among those on ventilation at baseline, age-stratified rate ratio for in-hospital mortality was 1.40 (95% CI, 0.93–2.11). **Secondary Outcome** • 10% initiated ventilation in the combined IFN beta-1a arms and SOC arm.	**Key Limitations** • Open-label study • IFN beta-1a given as IV or SUBQ formulations at different doses **Interpretation** • IFN beta-1a did not reduce in-hospital mortality in hospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
DisCoVeRy Solidarity Trial Add-On: Open-Label, Adaptive RCT of Interferon Beta-1a Plus Lopinavir/Ritonavir, Lopinavir/Ritonavir, or Hydroxychloroquine in Hospitalized Adults With COVID-19 in France[3]		

Key Inclusion Criteria
• Positive SARS-CoV-2 PCR result
• Patients had pulmonary rales or crackles with SpO_2 ≤94% on room air or they required supplemental oxygen
Interventions
• IFN beta-1a 44 ug SUBQ on Days 1, 3, and 6 plus LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• HCQ 400 mg twice on Day 1, then HCQ 400 mg daily for 9 days plus SOC (n = 145)
• SOC alone, which included corticosteroids, anticoagulants, or immunomodulatory agents but not antivirals (n = 148)
Primary Endpoint
• Clinical status at Day 15, as measured by an OS
Key Secondary Endpoints
• Clinical status at Day 29
• Rate of SARS-CoV-2 viral clearance
• Time to SARS-CoV-2 viral clearance by Day 29
• Time to improvement of 2 OS categories by Day 29
• Time to hospital discharge by Day 29
	Participant Characteristics
	• Median age 63 years; 72% men
	• 29% were obese; 26% with chronic cardiac disease; 22% with DM
	• 36% had severe disease
	• Median of 9 days of symptoms before randomization
	• 30% received steroids during the study
	Primary Outcome
	• No difference in clinical status at Day 15 for any intervention compared to SOC:
	  • IFN beta-1a plus LPV/RTV: aOR 0.69 (95% CI, 0.45–1.04; $P = 0.08$)
	  • LPV/RTV: aOR 0.83 (95% CI, 0.55–1.26; $P = 0.39$)
	  • HCQ: aOR 0.93 (95% CI, 0.62–1.41; $P = 0.75$)
	Secondary Outcomes
	• No difference in clinical status at Day 29 between arms
	• No difference in rate and time to SARS-CoV-2 viral clearance between arms
	• Time to improvement of 2 OS categories and hospital discharge by Day 29 longer in LPV/RTV plus IFN beta-1a and LPV/RTV arms than in SOC arm
		Key Limitations
		• Open-label study
		• Most patients had moderate disease
		• No IFN beta-1a arm without LPV/RTV
		• Study stopped early for futility
		Interpretation
		• Compared to SOC alone, the use of IFN-beta-1a plus LPV/RTV did not improve clinical status, rate of viral clearance, or time to viral clearance in hospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Pegylated Interferon Lambda in Nonhospitalized Patients With COVID-19 in Brazil and Canada[4]		

Key Inclusion Criteria
• Positive SARS-CoV-2 antigen test result
• Within 7 days of symptom onset
• ≥1 high-risk factor for disease progression (e.g., age ≥50 years, comorbidities, immunosuppression)
  • Up to 25% of patients could have no high-risk factors
Key Exclusion Criteria
• Need for hospitalization
• SpO_2 ≤93% on room air
Interventions
• Single dose of PEG-IFN lambda 180 µg SUBQ (n = 931)
• Placebo (n = 1,018; 825 received a single SUBQ injection and 193 received PO placebo)
Primary Endpoint
• Composite of ED observation >6 hours or hospitalization for COVID-19 by Day 28
Key Secondary Endpoints
• Composite of COVID-19–related hospitalization or death by Day 28
• SARS-CoV-2 viral clearance at Day 7
• Occurrence of AEs
	Participant Characteristics
	• Median age 43 years; 57.1% women; 95.1% self-identified as mixed race
	• 1,919 (98.5%) from Brazil, 30 (1.5%) from Canada
	• 50% with obesity
	• 59.4% were randomized within 3 days of symptom onset
	• 83% had received COVID-19 vaccine
	Primary Outcome
	• Composite of ED observation >6 hours or hospitalization by Day 28 (ITT): 25 (2.7%) in PEG-IFN lambda arm vs. 57 (5.6%) in placebo arm (relative risk 0.49; 95% Bayesian CrI, 0.30–0.76)
	  • 61 events (74%) were hospitalizations (ITT)
	Secondary Outcomes
	• Composite of COVID-19–related hospitalization or death by Day 28: 22 (2.4%) in PEG-IFN lambda arm vs. 40 (3.9%) in placebo arm (relative risk 0.61; 95% CrI, 0.36–0.99)
	• SARS-CoV-2 viral clearance at Day 7 among the 15% of patients with VL >192 million copies/mL at baseline: 50.5% in PEG-IFN lambda arm vs. 32.9% in placebo arm (OR 2.13; 95% CrI, 1.14–4.00)
	• Occurrence of AEs: 141 (15.1%) in PEG-IFN lambda arm vs. 172 (16.9%) in placebo arm (relative risk 0.90; 95% CrI, 0.73–1.10)
		Key Limitations
		• Health care facility capacity may have influenced the number and duration of ED observations.
		• As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to PEG-IFN lambda.
		Interpretation
		• In outpatients with COVID-19 who were within 7 days of symptom onset, PEG-IFN lambda reduced the need for ED observations >6 hours or hospitalization when compared with placebo.

Methods	Results	Limitations and Interpretation
Single-Blind RCT of Peginterferon Lambda-1a for Treatment of Outpatients With Uncomplicated COVID-19 in the United States[5]		

Key Inclusion Criteria
• Aged 18–65 years
• Asymptomatic or symptomatic
• Positive SARS-CoV-2 RT-PCR result within 72 hours of enrollment
Key Exclusion Criteria
• Current or imminent hospitalization
• Respiratory rate >20 breaths/min
• SpO_2 <94% on room air
• Decompensated liver disease
Interventions
• Single dose of PEG-IFN lambda-1a 180 µg SUBQ (n = 60)
• Placebo (n = 60)
Primary Endpoint
• Time to first negative SARS-CoV-2 RT-PCR result
Key Secondary Endpoints
• Hospitalization by Day 28
• Time to complete symptom resolution
	Participant Characteristics
	• Median age 36 years; 42% women; 63% Latinx, 28% White
	• 7% were asymptomatic
	• Median of 5 days of symptoms before randomization
	Primary Outcome
	• Median time to cessation of viral shedding was 7 days in both arms (aHR 0.81; 95% CI, 0.56–1.19; *P* = 0.29).
	Secondary Outcomes
	• No difference between PEG-IFN lambda-1a and placebo arms in:
	  • Proportion of patients hospitalized by Day 28: 3.3% for each arm
	  • Time to resolution of symptoms: 8 days vs. 9 days (HR 0.94; 95% CI, 0.64–1.39)
	Other Outcomes
	• Patients who received PEG-IFN lambda-1a were more likely to have transaminase elevations than patients who received placebo (25% vs. 8%; *P* = 0.027).
		Key Limitation
		• Small sample size
		Interpretation
		• PEG-IFN lambda-1a provided no virologic or clinical benefit compared to placebo among outpatients with uncomplicated COVID-19.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Peginterferon Lambda in Outpatients With Laboratory-Confirmed COVID-19 in Canada[6]		
Key Inclusion Criteria • Positive SARS-CoV-2 PCR result • Patients were within 7 days of symptom onset, or, if asymptomatic, were within 7 days of first positive SARS-CoV-2 test result **Key Exclusion Criterion** • Immunosuppression or condition that could be worsened by PEG-IFN lambda **Interventions** • Single dose of PEG-IFN lambda 180 µg SUBQ (n = 30) • Placebo (n = 30) **Primary Endpoint** • Proportion of participants with negative nasal mid-turbinate swab for SARS-CoV-2 RNA at Day 7 **Key Secondary Endpoints** • Quantitative change in SARS-CoV-2 RNA over time • Hospitalization by Day 14	**Participant Characteristics** • Median age 46 years; 58% women; 52% White • 19% were asymptomatic • Mean of 4.5 days of symptoms before randomization **Primary Outcome** • 80% in PEG-IFN lambda arm and 63% in placebo arm were negative for SARS-CoV-2 RNA at Day 7 ($P = 0.15$). **Secondary Outcomes** • VL decline by Day 7 was greater in PEG-IFN lambda arm than in placebo arm ($P = 0.0041$). • 1 participant in each arm was admitted to the hospital by Day 14. **Other Outcomes** • 3 participants in each arm had mild elevation of aminotransferase concentrations. Increase was greater in PEG-IFN lambda arm.	**Key Limitation** • Small sample size **Interpretation** • PEG-IFN lambda may accelerate VL decline and clearance in outpatients with COVID-19; however, the clinical significance of this finding is unclear.

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HCQ = hydroxychloroquine; HTN = hypertension; IFN = interferon; ITT = intention-to-treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PEG-IFN = pegylated interferon; PO = oral; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SOC = standard of care; SpO_2 = oxygen saturation; SUBQ = subcutaneous; ULN = upper limit of normal; VL = viral load; WHO = World Health Organization

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