Baricitinib (OLUMIANT®)

A Review of Pertinent Drug Information for SARS-CoV-2

Arun Mattappallil, PharmD

Clinical Pharmacist Specialist – Infectious Diseases

University Hospital, Newark, NJ

mattapar@uhnj.org

@namastay6ftawy

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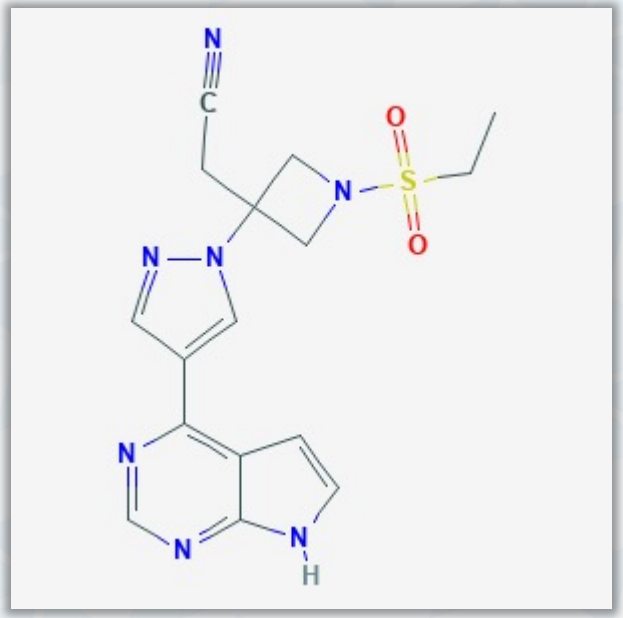
Data as of July 15, 2021

Indications for Use



- **United States FDA Approval / Health Canada Approval / Australian Approval**
  - **Rheumatoid arthritis (Moderate to Severe)**
    - **In patients with an inadequate response or intolerance to 1 or more tumor necrosis factor antagonist therapies**
- **European Medicines Agency (EMA) Approval**
  - **Rheumatoid Arthritis (Moderate to Severe)**
  - **Atopic Dermatitis (Moderate to Severe)**

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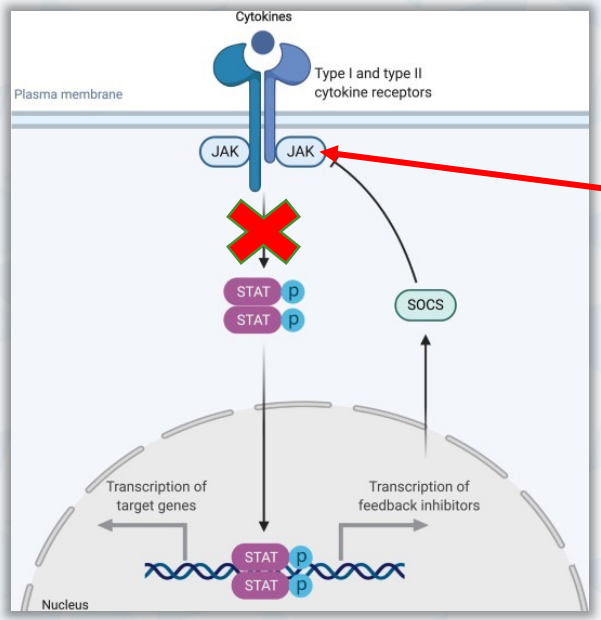
National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 44205240, Baricitinib. https://pubchem.ncbi.nlm.nih.gov/compound/Baricitinib
Olumiant [FDA approved package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.
European Medicines Agency: Olumiant Product Information - EMEA/H/C/004085; 2020.

Mechanism of Action (Approved Indications)



- Within the intracellular signaling pathway, JAKs (Janus-associated kinase) phosphorylate and activate STATs (signal transducers and activators of transcription), which modulate gene expression within the cell
- Baricitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs (reversible)
  - Anti-inflammatory property
- Within in vitro assays, baricitinib has greater inhibitory potency at JAK1, JAK2, and TYK2, relative to JAK3
  - JAK family consists of four members: JAK1, JAK2, and TYK2, JAK3

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Luo W, et al. Trends Pharmacol Sci. 2020. https://doi.org/10.1016/j.tips.2020.06.007
Olumiant [FDA approved package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.

Dosing (Approved Indications, > 18 years)

- Rheumatoid arthritis (Moderate to Severe)
  - EMA
    - 4mg/daily → Consider reducing to 2mg/daily when disease activity is controlled
  - FDA/Canada
    - 2mg/daily
- Atopic Dermatitis (Moderate to Severe)
  - 4mg/daily → Consider reducing to 2mg/daily when disease activity is controlled

FDA & EMA: With or without

FDA: Avoid use with eGFR <60 mL/min/1.73 m2

EMA: ↓ Dose when CrCl 30-60 mL/min

FDA: Avoid with Organic Anion Transporter 3 (OAT3) inhibitors (e.g. probenecid, gemfibrozil)

EMA: ↓ Dose with Strong OAT3 inhibitors

FDA: No recommendations

EMA: ↓ Dose ≥ 75 years of age

FDA: Avoid use of live vaccines

EMA: Avoid use with live vaccines (during, or immediately prior to start)

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Olumiant [FDA approved package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.
European Medicines Agency: Olumiant Product Information - EMEA/H/C/004085; 2020.

Safety in Specific Populations

FDA: “The limited **human data** on use of baricitinib in pregnant women are **not sufficient to inform** a drug-associated risk for major birth defects or miscarriage.”
EMA: “Baricitinib is **contraindicated** during pregnancy. Women of childbearing potential have to use effective contraception during and for at least 1 week after treatment.”

FDA: “Because of the potential for serious adverse reactions in nursing infants, advise an baricitinib-treated woman not to breastfeed.”
EMA: “A risk to newborns/infants cannot be excluded and baricitinib should not be used during breast-feeding.”

FDA & EMA: “The safety and effectiveness of baricitinib in pediatric patients have not been established.”

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European Medicines Agency: Olumiant Product Information - EMEA/H/C/004085; 2020.

Adverse Events (Approved Indications)

System/Organ Disorders	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Infections	Upper respiratory tract infections	Herpes zoster[b] Herpes simplex Gastroenteritis Urinary tract infections Pneumonia[d]	
Blood and lymphatic system		Thrombocytosis > 600 x 10^9 cells/L[a, d]	Neutropenia < 1 x 10^9 cells/L[a]
Metabolism and Nutrition	Hypercholesterolemia[a]		Hypertriglyceridemia[a]
CNS		Headache	
Gastrointestinal		Nausea[d] Abdominal pain	Diverticulitis
Hepatobiliary		ALT increased ≥ 3 x ULN[a, d]	AST increased ≥ 3 x ULN[a]
Skin and subcutaneous tissue		Rash Acne[c]	
Immune			Swelling of the face, Urticaria
Respiratory, thoracic, mediastinal, vascular			Pulmonary embolism Deep Vein Thrombosis
Other		Creatine phosphokinase increased > 5 x ULN[a, c]	Weight increased

a Includes changes detected during laboratory monitoring.
b Frequency for herpes zoster is based on rheumatoid arthritis clinical trials.
c Frequency for acne and creatine phosphokinase increased > 5 x ULN is based on the pooled rheumatoid arthritis and atopic dermatitis clinical trials. In patients treated with baricitinib in the rheumatoid arthritis clinical trials, the frequency of those events was uncommon.
d Frequency for pneumonia, thrombocytosis > 600 x 109 cells/L, nausea, and ALT ≥3 x ULN is based on the pooled rheumatoid arthritis and atopic dermatitis clinical trials. In patients treated with baricitinib in the atopic dermatitis clinical trials, the frequency of those events was uncommon.

****FDA "Black Box" Warnings****

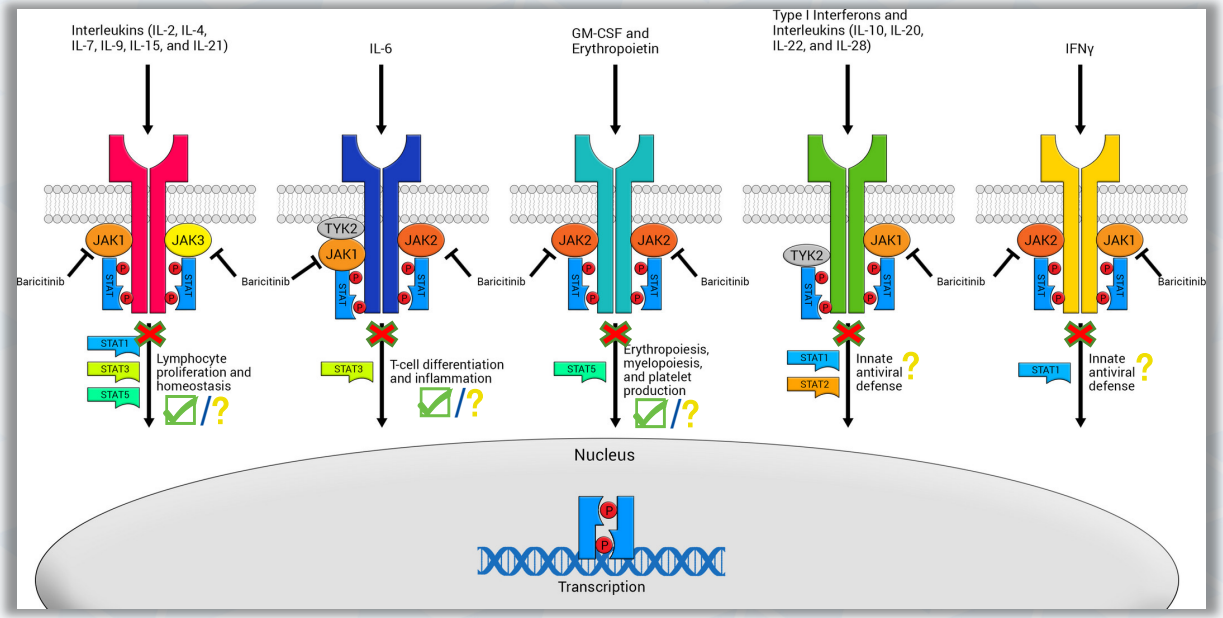
SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

Serum creatinine
Absolute lymphocyte count
Absolute neutrophil count
Hemoglobin
Platelets
ALT
AST
Bilirubin
CPK
LDL/HDL (if prolonged use)
Signs and symptoms of infection
Signs and symptoms of thromboembolic event

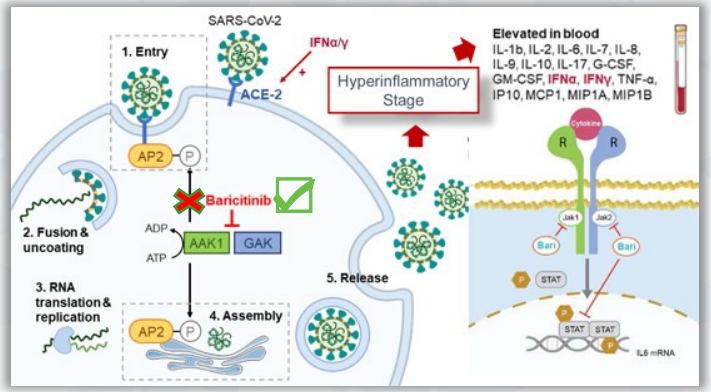
Olumiant [FDA approved package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.
European Medicines Agency: Olumiant Product Information - EMEA/H/C/004085; 2020.
Jorgensen SCJ, et al. Pharmacotherapy. 2020. https://doi.org/10.1002/phar.2438

Proposed Mechanism of Actions in SARS-Cov-2-Infected Cell

Anti-Inflammatory Properties



Anti-Viral Properties



Prevents viral entry into cells by:

- Inhibition of AP2-associated protein kinase 1 (AAK1) & interaction with cyclin G-associated kinase (GAK) which both promote endocytosis of the virus

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Jorgensen SCJ, et al. Pharmacotherapy. 2020. https://doi.org/10.1002/phar.2439
Stebbing J et al. EMBO Mol Med. 2020. https://doi.org/10.15252/emmm.202012697

Clinical Trials Evaluating Baricitinib Use in COVID-19

NCT Number	Title	Start Date	Status	Interventions	Number Enrolled	Study Designs	Locations
NCT04358614	Baricitinib Therapy in COVID-19	16-Mar-20	Completed	Drug: Baricitinib	12	Allocation: Non-Randomized|Intervention Model: Crossover Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy
NCT04381936	Randomised Evaluation of COVID-19 Therapy (RECOVERY)	19-Mar-20	Recruiting	Drug: Lopinavir-Ritonavir|Drug: Corticosteroid|Drug: Hydroxychloroquine|Drug: Azithromycin|Biological: Convalescent plasma|Drug: Tocilizumab|Biological: Immunoglobulin|Drug: Synthetic neutralizing antibodies|Drug: Aspirin|Drug: Colchicine|Drug: Baricitinib|Drug: Anakinra	40000	Allocation: Randomized|Intervention Model: Factorial Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	U.K.
NCT04321993	Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	17-Apr-20	Recruiting	Drug: Baricitinib	800	Allocation: Non-Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Canada
NCT04362943	Clinical-epidemiological Characterization of COVID-19 Disease in Hospitalized Older Adults	20-Apr-20	Recruiting	Drug: Baricitinib or Anakinra	576	Observational Model: Other|Time Perspective: Retrospective	Spain
NCT04373044	Baricitinib, Placebo and Antiviral Therapy for the Treatment of Patients With Moderate and Severe COVID-19	1-May-20	Recruiting	Drug: Baricitinib|Drug: Hydroxychloroquine|Drug: Placebo Administration	144	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Treatment	U.S.A

More information available at: clinicaltrials.gov

Clinical Trials Evaluating Baricitinib Use in COVID-19

NCT Number	Title	Start Date	Status	Interventions	Number Enrolled	Study Designs	Locations
NCT04393051	Baricitinib Compared to Standard Therapy in Patients With COVID-19	20-May-20	Not yet recruiting	Drug: Baricitinib Oral Tablet	126	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy
NCT04421027	A Study of Baricitinib (LY3009104) in Participants With COVID-19 (COV-BARRIER)	12-Jun-20	Active, not recruiting	Drug: Baricitinib|Drug: Placebo	1400	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Treatment	Global
NCT04693026	Efficacy of Ramdicivir and Baricitinib for the Treatment of Severe COVID 19 Patients	10-Sep-20	Recruiting	Drug: Remdesivir|Drug: Baricitinib|Drug: Tocilizumab	150	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Bangladesh
NCT04640168	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	24-Nov-20	Active, not recruiting	Drug: Baricitinib|Drug: Dexamethasone|Other: Placebo|Drug: Remdesivir	1500	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Treatment	Global
NCT04346147	Clinical Trial to Evaluate Efficacy of 3 Types of Treatment in Patients With Pneumonia by COVID-19	7-May-20	Recruiting	Drug: Imatinib tablets|Drug: Baricitinib Oral Tablet|Other: Supportive treatment	165	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Spain
NCT04390464	mulTi-Arm Therapeutic Study in Pre-ICu Patients Admitted With Covid-19 - Repurposed Drugs (TACTIC-R)	8-May-20	Recruiting	Drug: Ravulizumab|Drug: Baricitinib|Other: Standard of care	1167	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	U.K.

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Clinical Trials Evaluating Baricitinib Use in COVID-19

NCT Number	Title	Start Date	Status	Interventions	Number Enrolled	Study Designs	Locations
NCT04401579	Adaptive COVID-19 Treatment Trial 2 (ACTT-2)	8-May-20	Completed	Other: Placebo|Drug: Remdesivir|Drug: Baricitinib	1034	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Double (Participant, Investigator)|Primary Purpose: Treatment	Global
NCT04399798	Baricitinib for coRona Virus pnEumonia (COVID-19): a THerapeutic Trial	15-May-20	Not yet recruiting	Drug: Baricitinib	13	Allocation: N/A|Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy
NCT04320277	Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study.	16-May-20	Not yet recruiting	Drug: Baricitinib	200	Allocation: Non-Randomized|Intervention Model: Crossover Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy
NCT04832880	Factorial Randomized Trial of Remdesivir and Baricitinib Plus Dexamethasone for COVID-19 (the AMMURAVID Trial)	6-April-21	Not yet recruiting	Drug: Baricitinib|Drug: Remdesivir| Drug: Dexamethasone	4000	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Italy
NCT04890626	Clinical Trial to Evaluate the Efficacy of Different Treatments in Patients With COVID-19	4-April-20	Recruiting	Drug: Emtricitabine/Tenofovir Disoproxil Fumarate|Drug: Baricitinib + Dexamethasone| Drug: Dexamethasone	2193	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	Spain
NCT04891133	EU SolidAct: An Adaptive Pandemic and Emerging Infection Platform Trial	May-21	Recruiting	Drug: Baricitinib|Drug: Placebo	1900	Allocation: Randomized|Intervention Model: Parallel Assignment|Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)|Primary Purpose: Treatment	Europe

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More information available at: clinicaltrials.gov

Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Trial Characteristic	ACTT - 2
Intervention	baricitinib 4-mg o.d vs. placebo for up to 14 days (everyone gets remdesivir (≤10 days))
Sponsor	NIAID/DMID (USA)
Sites, Countries	67 sites, 8 countries
Recruitment Dates	8 May 2020 –1 July 2020
Randomized	1:1
Blinding	Double blinded for baricitinib
Stratification	By site, disease severity
Severe COVID-19 Definition	Invasive or non-invasive mechanical ventilation, use of high-flow supplemental oxygen devices
Sample Size, Primary Analysis	The study was designed to achieve 85% power for detecting a recovery rate ratio of 1.25 with a two-sided type-I error rate of 5%. Enrollment to ensure at least 723 recoveries.

Adapted from [Tweet] of @franciscomarty_

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Kalil AC, et al. N Engl J Med. 2020. https://doi.org/10.1056/nejmoa2031994
Marty, Francisco. Twitter, Twitter, 21 Dec. 2020, twitter.com/FranciscoMarty_/status/1341074338414551042

Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Inclusion Criteria (Selected Summary):

Admitted to a hospital with symptoms suggestive of COVID-19

Adult > / = 18 years of age at time of enrollment

Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:

- PCR positive in sample collected < 72 hours prior to randomization

OR

- PCR positive in sample collected >/= 72 hours prior to randomization, documented inability to obtain a repeat sample AND progressive disease suggestive of ongoing SARS-CoV-2 infection

Illness of any duration, and at least one of the following:

- Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
- SpO2 < / = 94% on room air, OR
- Requiring supplemental oxygen, OR
- Requiring mechanical ventilation or ECMO

Ordinal Scale (OS) (Used in patient enrollment & outcomes):

Recovered	1	Not hospitalized, no limitations on activities
	2	Not hospitalized, limitation on activities and/or requiring home oxygen
	3	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
Enrolled	4	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care
	5	Hospitalized, requiring supplemental oxygen
	6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
	7	Hospitalized, on mechanical ventilation or ECMO
	8	Death

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Kalil AC, et al. N Engl J Med. 2020. https://doi.org/10.1056/nejmoa2031994

Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Exclusion Criteria (Selected Summary)

- ALT or AST > 5 times the upper limit of normal
- eGFR < 30 ml/min or patient is receiving hemodialysis or hemofiltration at time of screening
- Neutropenia (ANC <1000 cells/microliter)
- Lymphopenia (absolute lymphocyte count <200 cells/microliter)

- Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who are at increased risk for serious infections or other safety concerns given the study products
- Have a history of VTE (DVT/PE) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE)
- Pregnancy or breast feeding
- Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours

- Received ≥3 doses of remdesivir outside of the study under the EUA for COVID-19
- Received convalescent plasma or IVIg for COVID-19
- Received small molecule tyrosine kinase inhibitors (e.g. baricitinib), in the 1 week prior to screening
- Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening
- Received monoclonal antibodies targeting B-cell (e.g., rituximab) in the 3 months prior to screening
- Received other immunosuppressants in the 4 weeks prior to screening and in the judgement of the investigator, the risk of immunosuppression with baricitinib is larger than the risk of COVID-19
- Received ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days in the 4 weeks prior to screening
- Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study.
- Use of probenecid that cannot be discontinued at study enrollment
- Allergy to any study medication

- Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that could constitute a risk when taking investigational product
- Have diagnosis of current active TB or known latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only)

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Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Primary Outcome

Time to recovery [Day 1 through Day 29]

- Day of recovery is defined as the first day on which the subject satisfies one of the first three categories from the OS

Key Secondary Outcome

- Clinical status at day 15, based on the eight-category OS

Secondary Safety Outcomes

- Grade 3 and 4 adverse events and serious adverse events that occurred through day 29
- Discontinuation or temporary suspension of trial-product administration for any reason
- Changes in assessed laboratory values over time

Additional Secondary Outcomes (Selected)

- Improvement by one category on OS
- Improvement by two categories on OS
- Discharge or National Early Warning Score ≤2 for 24 hr
- Number of days of receipt of supplemental oxygen, noninvasive ventilation or high-flow oxygen, and invasive ventilation or extracorporeal membrane oxygenation (ECMO)
- Incidence and duration of new use of oxygen, new use of noninvasive ventilation or high-flow oxygen, and new use of invasive ventilation or ECMO
- Duration of hospitalization
- Death or progression to noninvasive or invasive mechanical ventilation
- Death or progression to invasive mechanical ventilation

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Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Demographic and Clinical Characteristics of the Patients at Baseline (Selected)	All Patients (N=1033)	Baricitinib+RDV (N=515)	Placebo+RDV (N=518)
Mean — yr	55.4±15.7	55.0±15.4	55.8±16.0
≥65 yr — no. (%)	305 (29.5)	147 (28.5)	158 (30.5)
Female — no. (%)	381 (36.9)	196 (38.1)	185 (35.7)
Asian — no. (%)	101 (9.8)	49 (9.5)	52 (10.0)
Black — no. (%)	156 (15.1)	77 (15.0)	79 (15.3)
White — no. (%)	496 (48.0)	251 (48.7)	245 (47.3)
Hispanic or Latino — no. (%)	531 (51.4)	263 (51.1)	268 (51.7)
Body-mass index	32.2±8.3	32.2±8.2	32.3±8.4
Median time (IQR) from symptom onset to randomization — days	8 (5–10)	8 (5–10)	8 (5–11)
North America — no. (%)	953 (92.3)	476 (92.4)	477 (92.1)

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Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Demographic and Clinical Characteristics of the Patients at Baseline (Selected)	All Patients (N=1033)	Baricitinib+RDV (N=515)	Placebo+RDV (N=518)
Disease severity — no. (%)			
Moderate	706 (68.3)	358 (69.5)	348 (67.2)
Severe	327 (31.7)	157 (30.5)	170 (32.8)
Coexisting conditions — no./total no. (%)			
None	155/994 (15.6)	64/496 (12.9)	91/498 (18.3)
One	270/994 (27.2)	148/496 (29.8)	122/498 (24.5)
Two or more	569/994 (57.2)	284/496 (57.3)	285/498 (57.2)
Score on OS — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13.7)	70 (13.6)	72 (13.9)
5. Hospitalized, requiring supplemental oxygen	564 (54.6)	288 (55.9)	276 (53.3)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	216 (20.9)	103 (20.0)	113 (21.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	111 (10.7)	54 (10.5)	57 (11.0)

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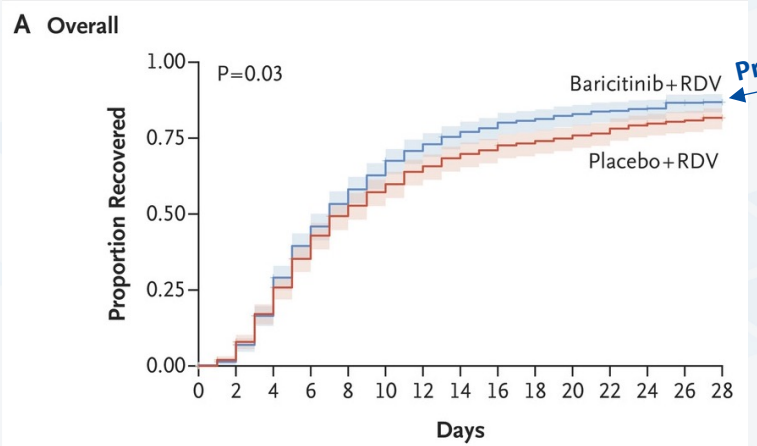
Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Overall



No. at Risk														
Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44

Primary Outcome

Outcome	Overall	
	Baricitinib (N=515)	Placebo (N=518)
Recovery		
No. of recoveries	433	406
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)	
No. of deaths by day 14	8	15
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	0.65 (0.39–1.09)	
No. of deaths by day 28	24	37
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)
Ordinal score at day 15 (±2 days) — no. (%)§ Key Secondary Outcome		
1	177 (34.4)	165 (31.9)
2	177 (34.4)	163 (31.5)
3	8 (1.6)	3 (0.6)
4	31 (6.0)	18 (3.5)
5	43 (8.3)	50 (9.7)
6	20 (3.9)	19 (3.7)
7	48 (9.3)	83 (16.0)
8	11 (2.1)	17 (3.3)
Odds ratio (95% CI)	1.3 (1.0–1.6)	

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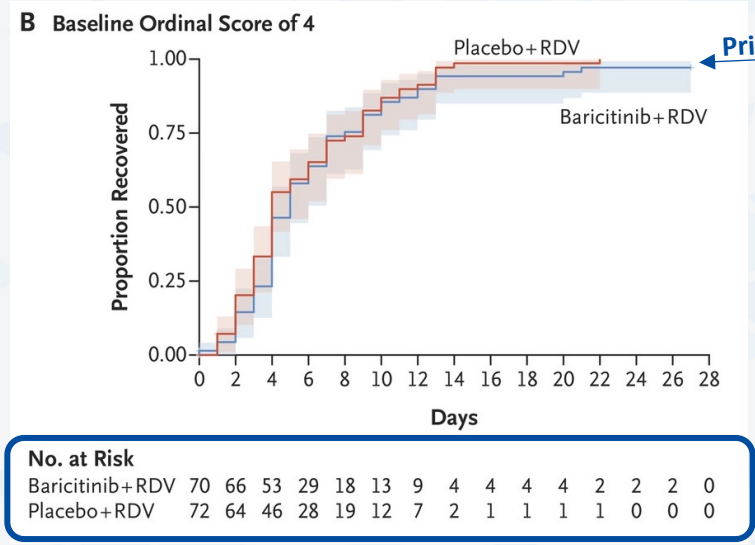
Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care



Primary Outcome

Outcome	4	
	Baricitinib (N=70)	Placebo (N=72)
Recovery		
No. of recoveries	67	69
Median time to recovery (95% CI) — days	5 (4–6)	4 (4–6)
Rate ratio (95% CI)†	0.88 (0.63–1.23)	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through day 14	NE	
No. of deaths by day 14	0	0
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	0 (NE–NE)	0 (NE–NE)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	NE	
No. of deaths by day 28	0	0
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	0 (NE–NE)	0 (NE–NE)
Ordinal score at day 15 (±2 days) — no. (%)§ Key Secondary Outcome		
1	33 (47.1)	44 (61.1)
2	25 (35.7)	20 (27.8)
3	5 (7.1)	2 (2.8)
4	7 (10.0)	6 (8.3)
5	0	0
6	0	0
7	0	0
8	0	0
Odds ratio (95% CI)	0.6 (0.3–1.1)	

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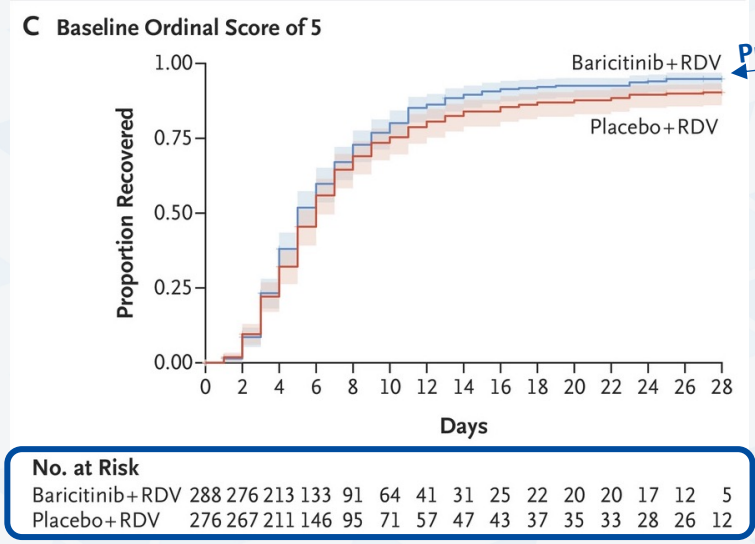
Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Hospitalized, requiring supplemental oxygen



Primary Outcome

Outcome	Baricitinib (N=288)	Placebo (N=276)
Recovery		
No. of recoveries	262	243
Median time to recovery (95% CI) — days	5 (5–6)	6 (5–6)
Rate ratio (95% CI)†	1.17 (0.98–1.39)	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through day 14	0.73 (0.16–3.26)	
No. of deaths by day 14	3	4
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.1 (0.4–3.4)	1.5 (0.6–3.9)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	0.40 (0.14–1.14)	
No. of deaths by day 28	5	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	1.9 (0.8–4.4)	4.7 (2.7–8.1)
Ordinal score at day 15 (±2 days) — no. (%)§ Key Secondary Outcome		
1	114 (39.6)	101 (36.6)
2	120 (41.7)	115 (41.7)
3	2 (0.7)	1 (0.4)
4	14 (4.9)	7 (2.5)
5	18 (6.2)	27 (9.8)
6	9 (3.1)	1 (0.4)
7	8 (2.8)	19 (6.9)
8	3 (1.0)	5 (1.8)
Odds ratio (95% CI)	1.2 (0.9–1.6)	

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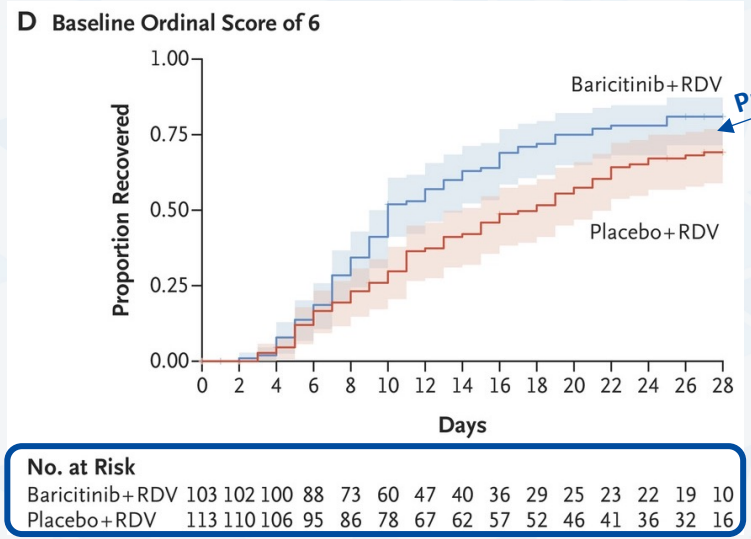
Kalil AC, et al. N Engl J Med. 2020.
https://doi.org/10.1056/nejmoa2031994

Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Hospitalized, on non-invasive ventilation or high flow oxygen devices



Primary Outcome

Outcome	6	
	Baricitinib (N=103)	Placebo (N=113)
Recovery		
No. of recoveries	82	73
Median time to recovery (95% CI) — days	10 (9–13)	18 (13–21)
Rate ratio (95% CI)†	1.51 (1.10–2.08)	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through day 14	0.21 (0.02–1.80)	
No. of deaths by day 14	1	5
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.0 (0.1–6.7)	4.6 (2.0–10.8)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	0.55 (0.22–1.38)	
No. of deaths by day 28	7	13
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	7.5 (3.6–15.2)	12.9 (7.7–21.3)
Ordinal score at day 15 (±2 days) — no. (%)§ Key Secondary Outcome		
1	27 (26.2)	17 (15.0)
2	30 (29.1)	24 (21.2)
3	0	0
4	7 (6.8)	3 (2.7)
5	15 (14.6)	20 (17.7)
6	7 (6.8)	16 (14.2)
7	15 (14.6)	28 (24.8)
8	2 (1.9)	5 (4.4)
Odds ratio (95% CI)	2.2 (1.4–3.6)	

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Kalil AC, et al. N Engl J Med. 2020.
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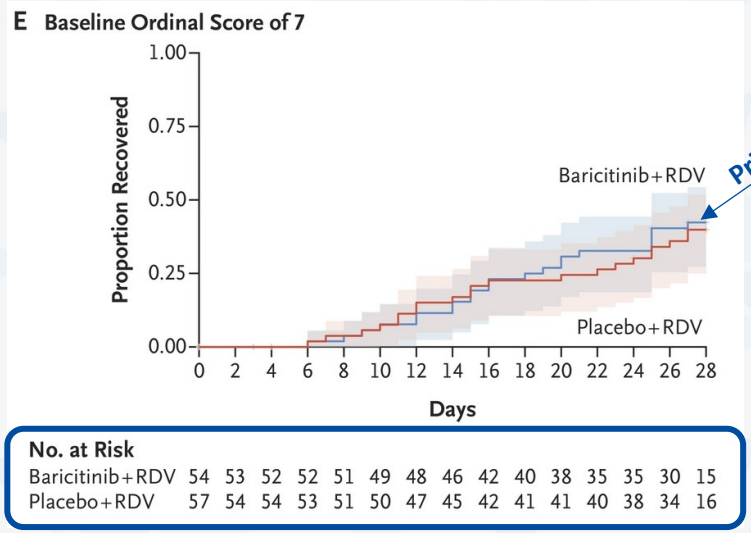
Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Hospitalized, on mechanical ventilation or ECMO



Primary Outcome

Outcome	7	
	Baricitinib (N=54)	Placebo (N=57)
Recovery		
No. of recoveries	22	21
Median time to recovery (95% CI) — days	NE (25–NE)	NE (26–NE)
Rate ratio (95% CI)†	1.08 (0.59–1.97)	
Mortality over first 14 days‡		
Hazard ratio (95% CI) for data through da 14	0.69 (0.19–2.44)	
No. of deaths by day 14	4	6
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	7.6 (2.9–19.1)	11.3 (5.3–23.5)
Mortality over entire trial period‡		
Hazard ratio (95% CI)	1.00 (0.45–2.22)	
No. of deaths by day 28	12	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	23.1 (13.8–37.1)	22.6 (13.5–36.4
Ordinal score at day 15 (±2 days) — no. (%)§		
1	3 (5.6)	3 (5.3)
2	2 (3.7)	4 (7.0)
3	1 (1.9)	0
4	3 (5.6)	2 (3.5)
5	10 (18.5)	3 (5.3)
6	4 (7.4)	2 (3.5)
7	25 (46.3)	36 (63.2)
8	6 (11.1)	7 (12.3)
Odds ratio (95% CI)	1.7 (0.8–3.4)	

Key Secondary Outcome

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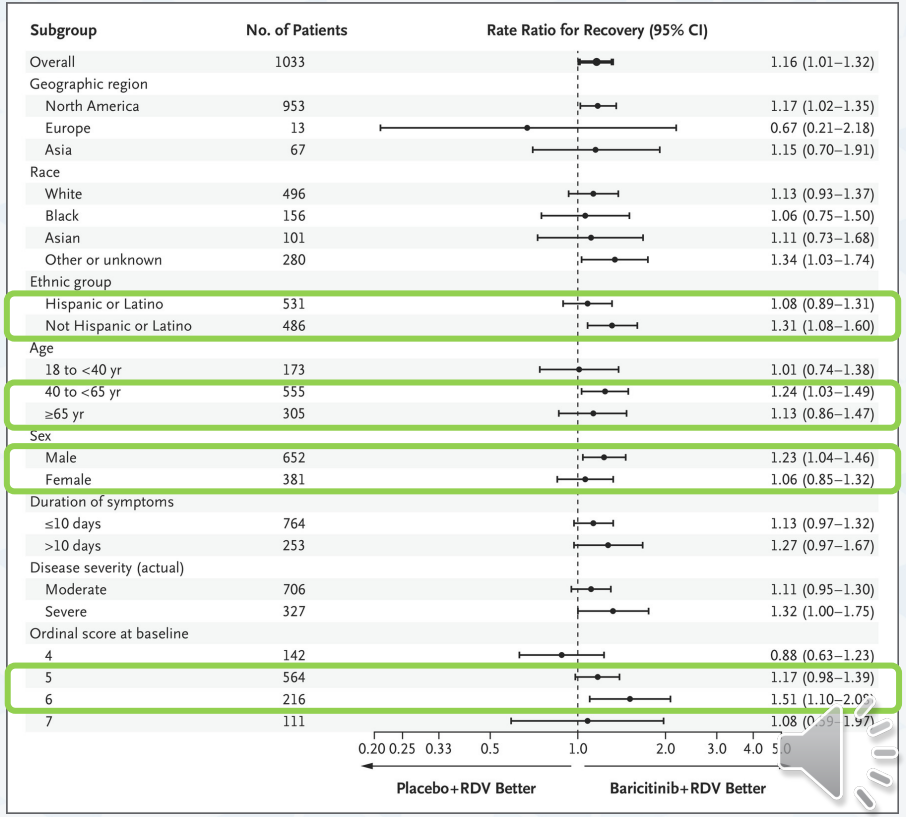
Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Time to Recovery According to Subgroup

Focused Highlights

- Age 40 to < 65 y/o vs. ≥ 65 y/o
- Female versus Male
- Ethnic group
- OS at baseline



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Adaptive COVID-19 Treatment Trial 2 (ACTT-2)

Secondary Safety Outcomes

Grade 3 or 4 adverse events

Adverse Events (Selected)	Baricitinib + RDV (N = 508) No.(%)	Placebo + RDV (N = 509) No.(%)
Any	207 (40.7)	238 (46.8)
Anemia	25 (4.9)	33 (6.5)
Lymphopenia	11 (2.2)	24 (4.7)
Glomerular filtration rate decreased	49 (9.6)	42 (8.3)
Hemoglobin decreased	30 (5.9)	30 (5.9)
Lymphocyte count decreased	24 (4.7)	35 (6.9)
Hyperglycemia	25 (4.9)	40 (7.9)
Acute kidney injury	20 (3.9)	36 (7.1)

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Take Home Points: ACTT-2 Trial

Purpose: to evaluate whether baricitinib would improve outcomes among patients hospitalized for COVID-19

METHODS

Double-blind, randomized placebo controlled trial

Remdesivir+Placebo
Remdesivir+Baricitinib

67 trial sites in 8 countries (primarily U.S.)

Patient Demographics
63.1 % male
48% white

RESULTS

Median time to recovery

All patients
Baricitinib < Control
[7 days < 8 days]

Supplemental O2 not on MV
Baricitinib < Control
[10 days < 18 days]

Clinical status at Day 15
Baricitinib had 30% higher odds of improvement

ADVERSE EFFECTS

Similar between groups

Most common included: hyperglycemia, anemia, lymphopenia and acute kidney injury

LIMITATIONS

Trial was not designed to detect mortality difference

Racial and ethnic groups limitations

CONCLUSION

Remdesivr+Baricitinib improved time to recovery at Day 15

When further stratified, patients designated as OS 6 (high flow O2 & non-invasive ventilation) had the greatest difference in time to recovery

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Adapted from [Tweet] of @IDJClub

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FDA Emergency Use Authorization of Baricitinib

11/19/2020

FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF BARICITINIB

Based on review of the data from the randomized, double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) comparing baricitinib in combination with remdesivir to remdesivir alone, also called ACTT-2 (NCT04401579), data for baricitinib that FDA reviewed for the FDA-approved indication of rheumatoid arthritis (NDA 207924), and data from populations studied for other indications, including pediatric patients, it is reasonable to believe that baricitinib may be effective, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib when used to treat COVID-19 in such patients outweigh the known and potential risks of such product.

For emergency use by healthcare providers for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The recommended dosage of baricitinib under the EUA is:

- Adults and pediatric patients 9 years of age and older: 4 mg once daily
- Pediatric patients 2 years to less than 9 years of age: 2 mg once daily

Dosage adjustments are recommended for laboratory abnormalities, including renal impairment (see **Table 1**).

The optimal duration of treatment is unknown.

The recommended total treatment duration of baricitinib is 14 days or until hospital discharge, whichever comes first.

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More information available at: fda.gov

UPDATE

Preprint: Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial

Posted May 30, 2021

Pending publication release

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Marconi VC, et al. Preprint.
https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1

Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomized, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial

Trial Characteristic	COV-BARRIER
Intervention	baricitinib* 4-mg o.d vs. placebo for up to 14 days (everyone gets Standard of Care**)
Sponsor	Eli Lilly and Company
Sites, Countries	101 sites, 12 countries
Recruitment Dates	June 2020 - June 2021
Randomized	1:1
Blinding	Double blinded for baricitinib
Stratification	By site, disease severity
Severe COVID-19 Definition	Invasive or non-invasive mechanical ventilation, use of high-flow supplemental oxygen devices
Sample Size, Primary Analysis	Power was calculated for the primary endpoint to succeed in ≥1 of the two primary populations. Study was designed for the possibility of the sample size to be increased using an unblinded sample size re-estimation of the primary endpoint.

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*dose adjusted for renal function
**included corticosteroids (including dexamethasone), antibiotics, antivirals (including remdesivir), antifungals, and antimalarial

Marconi VC, et al. Preprint.
https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1

COV-BARRIER

Inclusion Criteria (Selected Summary):

- Admitted to a hospital with symptoms suggestive of COVID-19
- Adult > / = 18 years of age at time of enrollment
- Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
  - PCR positive in sample collected < 72 hours prior to randomization

  OR
  - PCR positive in sample collected >/= 72 hours prior to randomization, documented inability to obtain a repeat sample AND progressive disease suggestive of ongoing SARS-CoV-2 infection
- Amendment:
  - Require supplemental oxygen at the time of study entry and at randomization

  Original:
  - Have evidence of pneumonia (SpO2 <94 or PaO2/FiO2 [or SpO2/FiO2] ratio <300 mmHg or chest imaging findings consistent with pneumonia), OR
  - Have evidence of active COVID infection (with clinical symptoms including any of the following: fever, vomiting, diarrhea, dry cough, tachypnea defined as respiratory rate >24 breaths/min).
- Have indicators of risk of progression: at least 1 inflammatory markers >ULN (CRP, D-dimer, LDH, ferritin) with at least 1 instance of elevation >ULN within 2 days before study entry.

Ordinal Scale (OS) (Used in patient enrollment & outcomes):

Recovered	1	Not hospitalized, no limitations on activities
	2	Not hospitalized, limitation on activities and/or requiring home oxygen
	3	Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care
Enrolled	4	Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care
	5	Hospitalized, requiring supplemental oxygen
	6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
	7	Hospitalized, on mechanical ventilation or ECMO
	8	Death

Marconi VC, et al. Preprint.
https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1

COV-BARRIER

Exclusion Criteria (Selected Summary)

- ALT or AST > 5 times the upper limit of normal
- eGFR < 30 ml/min
- Neutropenia (ANC <1000 cells/microliter)
- Lymphopenia (absolute lymphocyte count <200 cells/microliter)

- Require invasive mechanical ventilation, including ECMO at study entry
- Unlikely to survive for at least 48 hours after screening (in the opinion of the investigator)
- Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who are at increased risk for serious infections or other safety concerns given the study products
- Have a history of VTE (DVT/PE) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE)
- Pregnancy or breast feeding
- Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours

- Received convalescent plasma or IVIg for COVID-19
- Received broadly neutralizing antibodies for COVID-19
- Received cytotoxic or biologic treatments (such as TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], T-cell or B-cell targeted therapies (rituximab), interferon, or JAK inhibitors for any indication at study entry
  - A washout period is required prior to screening (see supplement)
- Received other immunosuppressants in the 4 weeks prior to screening and in the judgement of the investigator, the risk of immunosuppression with baricitinib is larger than the risk of COVID-19
- Received ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days in the 4 weeks prior to screening
- Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study.
- Use of probenecid that cannot be discontinued at study enrollment
- Allergy to any study medication

- Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that could constitute a risk when taking investigational product
- Have diagnosis of current active TB or known latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only)

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COV-BARRIER

Population Overview

Population	Description	Total number of participants in population	Number of participants in Placebo+SOC	Number of participants in Baricitinib+SOC	Analysis
ITT	All randomized participants	1525	761	764	All primary and key secondary Kaplan-Meier time-to-event analyses.
MI	All ITT participants with non-missing baseline OS scores	1518	756	762	All primary and key secondary analyses involving OS scores except for time-to event analysis
LOCF	All ITT participants with non-missing baseline OS scores and at least one non-missing post-baseline OS score	1512	754	758	All secondary analyses involving OS scores only except time-to-event analysis and analysis using MI
Safety	All ITT participants who receive at least 1 dose of study intervention and who were not lost to follow-up at the first post baseline visit	1502	752	750	All safety analyses unless specified otherwise

ITT=intent-to-treat. MI=multiple imputation. LOCF=last observation carried forward. SOC=standard of care.

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COV-BARRIER

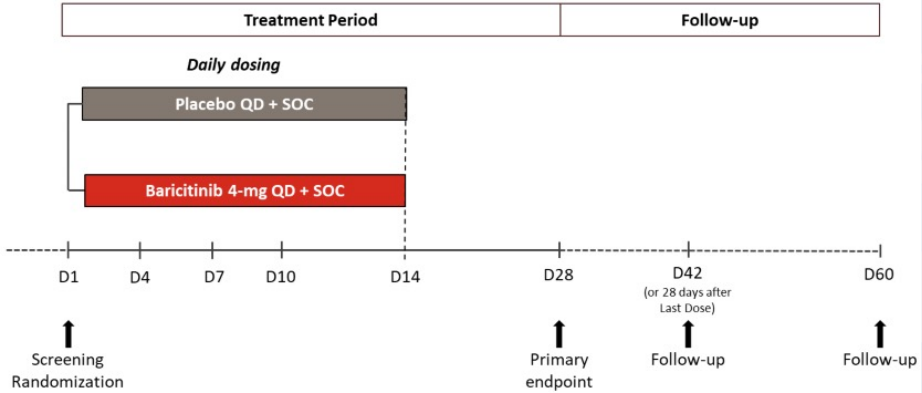
Primary Outcome

Progression to OS category 6-8 by day 28

- Population 1: All patients (intention-to-treat)
- Population 2: Patients required oxygen supplementation and were not receiving systemic corticosteroids for COVID-19

Key Secondary Outcomes

- All-cause mortality at 28 days
- Duration of hospitalization
- Proportion of participants with ≥1- point improvement on the OS or discharge from hospital at days 4, 7, 10, and 14
- Number of ventilator-free days
- Time to recovery (OS 1-3)
- Overall improvement on the OS evaluated at days 4, 7, 10, and 14
- Proportion of participants with a change in oxygen saturation from <94% to ≥94% from baseline to days 4, 7, 10, and 14



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COV-BARRIER

Demographic and Clinical Characteristics of the Patients at Baseline (Selected)	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	All Patients (N=1525)
Mean — yr	57.5±13.8	57.8±14.3	57.6±14.1
≥65 yr — no. (%)	243 (31.9)	256 (33.5)	499 (32.7)
Female — no. (%)	288 (37.8)	274 (35.9)	562 (36.9)
Asian — no. (%)	94 (12.3)	80 (10.5)	174 (11.4)
Black — no. (%)	36 (4.7)	39 (5.1)	75 (4.9)
White — no. (%)	440 (57.8)	480 (62.8)	920 (60.3)
Hispanic or Latino — no. (%)	46 (6)	54 (7.1)	100 (6.6)
Body-mass index	30.6±6.6	30.4±6.4	30.5±6.5
Disease duration of symptoms prior to enrollment ≥7 days	640 (84.1)	625 (81.8)	1265 (83)
Geographic region: North America — no. (%)	158 (20.8)	162 (21.2)	320 (21)

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COV-BARRIER

Demographic and Clinical Characteristics of the Patients at Baseline (Selected)	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	All Patients (N=1525)
Coexisting conditions — no (%)			
Diabetes (Type I and Type II)	233 (30.6)	224 (29.3)	457 (30)
Chronic respiratory disease	36 (4.7)	34 (4.5)	70 (4.6)
Score on OS — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	97 (12.7)	89 (11.6)	186 (12.2)
5. Hospitalized, requiring supplemental oxygen	472 (62)	490 (64.1)	962 (63.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	187 (24.6)	183 (24)	370 (24.3)

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COV-BARRIER

Demographic and Clinical Characteristics of the Patients at Baseline (Selected)	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	All Patients (N=1525)
Median — C-reactive protein	62	67.5	65
Concomitant medications use — no. (%)			
Remdesivir	147 (19.3)	140 (18.3)	287 (18.8)
Systemic corticosteroids	592 (77.8)	612 (80.1)	1204 (79)
Dexamethasone	533 (70)	566 (74.1)	1099 (72.1)

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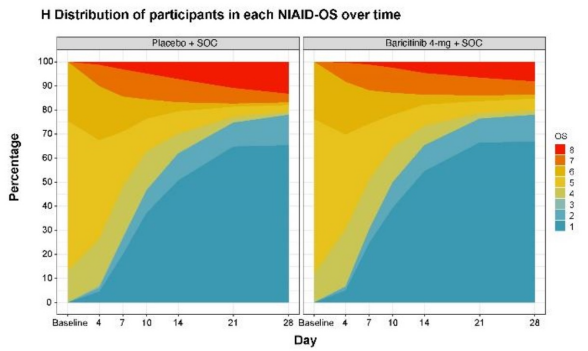
COV-BARRIER

Overall: Primary Outcome

	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	Comparison with placebo (95% CI)*	Nominal p value
Progressed to high-flow oxygen, non-invasive ventilation oxygen, invasive mechanical ventilation/ECMO, or death (OS 6-8) by Day 28				
Population 1	30.5%	27.8%	0.85 (0.67 – 1.08)	0.18
OS 4	9.5%	7%	0.78 (0.27 – 2.22)	0.64
OS 5	28.3%	25.6%	0.87 (0.65 – 1.17)	0.35
OS 6	46.8%	43.8	0.85 (0.56 – 1.30)	0.46
Population 2	27.1%	28.9%	1.12 (0.58 – 2.16)	0.73

*odds ratio

Data are least squares mean (SE), median (95% CI), or n (%)



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COV-BARRIER

Overall: Key Secondary Outcomes

	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	Comparison with placebo (95% CI)	Nominal p value
Proportion of participants with ≥1- point improvement on the OS or discharge from hospital at days 4, 7, 10, and 14				
Day 4	21.1%	25.2%	1.26 (0.98 – 1.61)	0.07
Day 7	45.8%	49.8%	1.18 (0.95 – 1.46)	0.13
Day 10	63.5%	65%	1.07 (0.86 – 1.34%)	0.54
Day 14	72.3%	75.6%	1.21 (0.95 – 1.55%)	0.13

*odds ratio

Data are least squares mean (SE), median (95% CI), or n (%)

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COV-BARRIER

Overall: Key Secondary Outcomes

	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	Comparison with placebo (95% CI)*	Nominal p value
Proportion of participants with a change in oxygen saturation from <94% to ≥94% from baseline to days 4, 7, 10, and 14				
Day 4	119/282 (42.2%)	133/282 (47.2%)	1.20 (0.86 – 1.69)	0.29
Day 7	146/282 (51.8%)	146/282 (51.8%)	0.97 (0.69 – 1.37)	0.88
Day 10	148/282 (52.5%)	160/282 (56.7%)	1.15 (0.81 – 1.63)	0.43
Day 14	166/282 (58.9%)	166/282 (58.9%)	0.95 (0.66 – 1.37)	0.79

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Data are least squares mean (SE), median (95% CI), or n (%)

*odds ratio

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COV-BARRIER

Overall: Key Secondary Outcomes

	Placebo+SOC (N=761)	Baricitinib+SOC (N=764)	Comparison with placebo (95% CI)	Nominal p value
All-cause mortality	100 (13.1%)	62 (8.1%)	0.57 (0.41 – 0.78)*	0.0018
Duration of hospitalization	13.7	12.9	-0.76 (-1.6 – 0)**	0.06
Number of ventilator-free days	23.7	24.5	0.75 (0 – 1.5)**	0.06
Median time to recovery	11 (10 to 12)	10 (9 to 11)	1.11 (0.99 – 1.24)***	0.15

*hazard ratio
**least squares mean difference
***rate ratio

Data are least squares mean (SE), median (95% CI), or n (%)

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COV-BARRIER

All-Cause Mortality According to Subgroup

Focused Highlights

Population 1 & 2

OS 6 (Baseline)

- 17.5% [32/183] vs 29.4% [55/187]; HR 0.52, 95% CI 0.33-0.80; p=0.0065

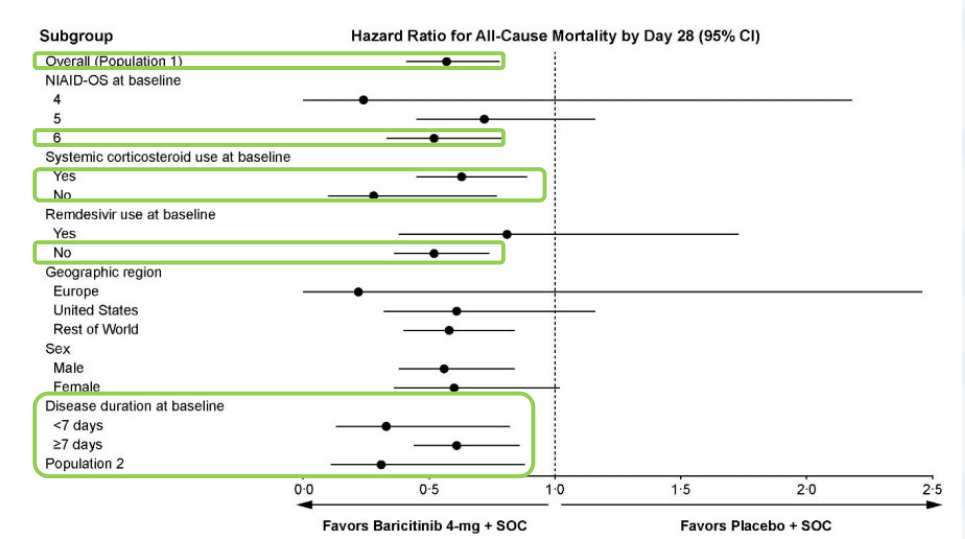
Corticosteroid use (w/ & w/o)

- With
  - 9.3% [57/612] vs 13.9% [82/592]; HR 0.63, 95% CI 0.45-0.89; p=0.0169
- Without
  - 3.3% [5/150] vs 11% [18/164]; HR 0.28, 95% CI 0.10-0.77; p=0·0114

Disease duration

Remdesivir use

- Without
  - 8.0% [50/622] vs 13.8% [84/609]; HR 0.52, 95% CI 0.36-0.74; p=0.0014



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Marconi VC, et al. Preprint. https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1

COV-BARRIER

Safety Outcomes

Adverse Events (Selected)	Placebo+SOC (N=752)	Baricitinib+SOC (N=750)
Treatment-emergent adverse event	334 (44.4%)	334 (44.5%)
Death due to adverse event*	31 (4.1%)	12 (1.6%)
Serious adverse event	135 (18.0%)	110 (14.7%)
Discontinuation from study treatment due to adverse event (including death)	70 (9.3%)	56 (7.5%)

*Included in the overall mortality together with deaths due to disease progression.

Adverse Events (Selected)	Placebo+SOC (N=752)	Baricitinib+SOC (N=750)
Treatment-emergent infection	123 (16.4%)	119 (15.9%)
Serious infections	74 (9.8%)	64 (8.5%)
Opportunistic infections	7 (0.9%)	6 (0.8%)
Venous thromboembolic event**	19 (2.5%)	20 (2.7%)
Major adverse cardiovascular event	9 (1.2%)	8 (1.1%)
Gastrointestinal perforation	0	0

**All patients received prophylaxis for venous thromboembolism unless contraindicated.

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Preprint

Take Home Points: COV-BARRIER

Purpose: to evaluate whether baricitinib would improve outcomes among patients hospitalized for COVID-19

METHODS

Double-blind, randomized placebo-controlled trial

Placebo+SOC
Baricitinib +SOC

101 trial sites in 12 counties (primarily non- U.S.)

Patient Demographics
63.1 % male
61.6% white

RESULTS

Primary outcome:
Progression to OS category 6-8 by day 28

Intent To Treat
Control > Baricitinib
[30.5% > 27.8%]
(p = 0.18)

Key secondary outcome:
All-cause mortality at 28 days

Intent To Treat
Control > Baricitinib
[13.1% > 8.1%], 38.2%↓
(p = 0.0018)

ADVERSE EFFECTS

Similar between groups

LIMITATIONS

Preprint with limited supplementary data available, requires peer review

Primary outcome did not reach statistical significance

Racial and ethnic groups limitations

CONCLUSION

Baricitinib +SOC
may reduce mortality

When further stratified, patients designated as OS 6 (high flow O2 & non-invasive ventilation) had the greatest reported benefit

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Recommendations from U.S Medical Organizations

Infectious Disease Society of America (IDSA)

- Among hospitalized adults with severe COVID-19 having elevated inflammatory markers but not on invasive mechanical ventilation, the IDSA panel suggests baricitinib rather than no baricitinib. **(Conditional recommendation, Moderate certainty of evidence)**
- Among hospitalized patients with severe COVID-19 who cannot receive a corticosteroid (which is standard of care) because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone. **(Conditional recommendation, Low certainty of evidence)**

National Institute of Health (NIH)

- Patients Who Require Supplemental Oxygen but Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation
  - There is insufficient evidence to determine which patients in this group would benefit from adding baricitinib or tocilizumab to dexamethasone treatment.
  - Some Panel members would add baricitinib or tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and increased markers of inflammation but does not yet require high-flow oxygen or noninvasive ventilation.
  - As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.
- Patients Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation
  - For recently hospitalized patients (i.e., those who are within 3 days of hospital admission) who have rapidly increasing oxygen needs, require high-flow oxygen or noninvasive ventilation, and have increased markers of inflammation, add baricitinib **(BIIa)** or tocilizumab **(BIIa)** to standard of care (Dexamethasone alone **(AI)**; or Dexamethasone plus remdesivir **(BIII)**)
  - The Panel recommends against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

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Bhimraj A, at al. Treatment and management of patients with COVID-19. Infectious Diseases Society of America. Available at: http://www.idsociety.org/COVID19guidelines. Accessed [6/22/21]
COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov. Accessed [7/15/21]

Recommendations from Global Medical Organizations

Australian guidelines

- Consider using baricitinib for adults hospitalized with COVID-19 who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation. **(Certainty of the Evidence: Moderate)**
    - In patients hospitalized with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.
    - Evidence from randomized trials versus standard care demonstrates that baricitinib has an acceptable safety profile and probably reduces the incidence of serious adverse events. *Consideration should be given when administering baricitinib to patients already on other immunosuppressant or immunomodulatory drugs.*
- Given the uncertainty regarding the effectiveness of baricitinib in patients who require mechanical ventilation, further evidence is required to inform care in this population.

Health Canada

- No Recommendation

European Medicines Agency (EMA)

- EMA evaluating use of baricitinib in hospitalized COVID-19 patients requiring supplemental oxygen: Opinion to be released July 2021.

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Australian guidelines for the clinical care of people with COVID-19. Australian National COVID-19 Clinical Evidence Taskforce. Available at: https://covid19evidence.net.au/#living-guidelines. Accessed [7/15/21]

EMA starts evaluating use of Olumiant in hospitalised COVID-19 patients requiring supplemental oxygen. European Medicines Agency. Available at: https://www.ema.europa.eu/en/news/ema-starts-evaluating-use-olumiant-hospitalised-covid-19-patients-requiring-supplemental-oxygen. Accessed [7/15/21]

Summary

- In the ACTT-2 Trial, baricitinib plus remdesivir did reduce recovery time and accelerated improvement in clinical status among adult patients with COVID-19, notably among those receiving high-flow oxygen or noninvasive ventilation.
- In the COV-BARRIER Trial, baricitinib plus standard of care did reduce 28-day mortality in adult patients with COVID-19 requiring supplemental oxygen, high-flow oxygen and/or non-invasive ventilation.
- The FDA issued an EUA for baricitinib for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.
  - EUA issued with some guidance.
- The IDSA and NIH suggest similar conditional recommendations for baricitinib use in adults hospitalized with COVID-19 who require high-flow oxygen and/or non-invasive ventilation.
  - Other applications/indications are suggested to be limited to the conditions of a clinical trial.

Baricitinib (OLUMIANT®)

A Review of Pertinent Drug Information for SARS-CoV-2

Arun Mattappallil, PharmD

Clinical Pharmacist Specialist – Infectious Diseases

University Hospital, Newark, NJ

mattapar@uhnj.org

@namastay6ftawy

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Data as of July 15, 2021