Emergency Use Authorization (EUA) for Baricitinib, FOR THE UNAPPROVED USE OF AN APPROVED PRODUCT
Center for Drug Evaluation and Research (CDER) Review

SEE ATTACHED ADDENDUM

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	92
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Eli Lilly and Company Lilly Corporate Center Indianapolis IN 46285 Attention: Jillian Fuhs, JD, PharmD Advisor, Global Regulatory Affairs-North America (b) (6) jillian_fuhs@lilly.com
Manufacturer, if different from Sponsor	N/A
Submission Date(s)	October 15, 2020
Receipt Date(s)	October 15, 2020
OND Division / Office	Division of Rheumatology and Transplant Medicine/ Office of Immunology and Inflammation
Reviewer Name(s)/Discipline(s)	Stefanie Freeman, MD, Clinical Reviewer Raj Nair, MD, Clinical Team Leader Yunzhao Ren, MD, PhD, Clinical Pharmacology Reviewer Xinyuan Zhang, PhD, Pharmacometrics Reviewer Yuching Yang, PhD, Pharmacometrics Team Leader Ping Ji, PhD, Team Leader Ijeoma Uzoma, PhD, Pharmacology/Toxicology Reviewer Tim Robison, PhD, Pharmacology/Toxicology Team Leader Okpo Eradiri, PhD, Biopharmaceutics Branch Chief Craig Bertha, PhD, CMC Lead Paul Imbriano, PhD, Biostatistics Reviewer Rebecca Rothwell, PhD, Biostatistics Team Leader Gregory Levin, PhD, Biostatistics Deputy Division Director Carolyn Yancey, MD, Medical Officer, DPMH

[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

	Ozlem Belen, MD, MPH, Deputy Director (Acting) Nikolay Nikolov, MD, Director, DRTM
Integrated Review Completion Date	See the electronic stamp date
Proprietary Name	Olumiant
Established Name/Other names used during development	Baricitinib
Dosage Forms/Strengths	Tablet, 2 mg, 1 mg
Therapeutic Class	Janus kinase inhibitor
Intended Use or Need for EUA	Treatment of coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adult and pediatric patients 2 years and older with severe COVID-19 in combination with remdesivir
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	Please refer to the Letter of Authorization for details

I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Pre-EUA Communications to the Sponsor

FDA has completed the review of EUA-092. No further information is requested at this time.

B. EUA Communications

The EUA will be issued for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2

years or older who are receiving remdesivir and also require supplemental oxygen[2], invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Baricitinib should only be administered in a hospital or healthcare setting capable of providing acute care comparable to inpatient hospital care[3].

C. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.

- Based on the scientific evidence available to FDA, it is reasonable to believe that the known and potential benefits of baricitinib, administered in combination with remdesivir, outweigh the known and potential risks of the drug for the treatment of suspected or laboratory confirmed COVID-19 in adults and pediatric patients 2 years and older hospitalized with severe disease and requiring supplemental oxygen, or requiring mechanical ventilation or requiring ECMO.

- There is no adequate, approved and available alternative to baricitinib, when used 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.

  Veklury (remdesivir) is the only drug that is approved by FDA to treat COVID-19 at the time of FDA's review of this EUA request for baricitinib. Remdesivir is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-COV-2. Baricitinib is a Janus kinase (JAK) inhibitor, a class of drugs that block extracellular signals from multiple cytokines that are involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19. The Adaptive COVID-19 Treatment Trial 2 (ACTT-2) provided scientific evidence that the combination of baricitinib plus remdesivir provided a potential clinically meaningful benefit as compared to remdesivir alone in time to recovery, NIAID OS outcome at Day 15, and progression to ventilation or death at Day 29. See section VIII Human Clinical Efficacy below for additional information. FDA also notes that Veklury's FDA-approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring

[2] Supplemental oxygen also includes non-invasive ventilation.
[3] Given the potential for regions to exceed hospital capacity, the Letter of Authorization will clarify that the use of baricitinib under EUA is appropriate in healthcare settings that provide acute care comparable to an inpatient hospital setting.

hospitalization, a narrower population than the use authorized for baricitinib under this EUA.

III. Proposed Use and Dosing of the Product Under the EUA

Proposed Use Under EUA:

- Proposed use(s) under EUA: Use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adult and pediatric patients, 2 years of age or older, requiring supplemental oxygen, invasive mechanical ventilation, or ECMO[4].

Proposed dosing regimen(s) for use under EUA:

- Adult patient and pediatric patients 9 years of age and older: 4-mg once daily dose for up to 14 days or until hospital discharge whichever occurs first. For renally impaired pediatric patients see renal impairment dose adjustments below.
- Pediatric patients 2 years to < 9 years of age: 2-mg once daily dose for up to 14 days duration or hospital discharge, whichever occurs first. For renally impaired pediatric patients see renal impairment dose adjustments below.
- Drug interactions: The recommended dose of baricitinib in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (e.g., probenecid) is 2 mg once daily.
- Pregnant or lactating patients: Baricitinib has not been studied in pregnant or lactating women with COVID-19. The effects on the fetus and the presence or absence of baricitinib in human breast milk are unknown. Dose recommendations in these populations are based on risk/benefit considerations. Embyro-fetal toxicities including skeletal anomalies and reduced fertility were observed in animals that received doses greater than the maximum human exposure.
- Other specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
    - Renal impairment: Baricitinib exposure increases with decreased renal function. Dose adjustment is not required for with eGFR ≥60 mL/min/1.73 m^2. Baricitinib is not recommended for patients on dialysis or those who develop acute kidney injury.
        - Adult patients and pediatric patients 9 years of age and older:

[4] The Sponsor initially proposed monotherapy but based on review of the supporting data and recommendation of the Division, the Sponsor agreed with amending the EUA use for combination therapy of baricitinib with remdesivir.

- The suggested dose for patients with moderate renal impairment (eGFR between 30 and <60 mL/min/1.73 m^2) is 2 mg of baricitinib once daily.
- The suggested dose for patients with severe renal impairment (eGFR between 15 and <30 mL/min/1.73 m^2) is 1 mg of baricitinib once daily.

- Pediatric patients aged 2 years to less than 9 years:
  - eGFR 30 to <60 mL/min/1.73 m^2: 1 mg once daily
  - eGFR <30 mL/min/1.73 m^2: not recommended

- Hepatic impairment: No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Baricitinib has not been studied in patients with severe hepatic impairment. It is not known if dosage adjustment is needed in patients with severe hepatic impairment. Dose recommendations in this population is based on risk/benefit considerations.

- Rationale for dosing regimen: The dosing and duration of treatment are based on the regimen that was evaluated in the randomized, double-blind, placebo-controlled trial conducted by NIAID (NCT04401579). In this study baricitinib was dosed with remdesivir. This trial evaluated adult patients hospitalized with COVID-19. The dosing rationale for pediatric patients 2 years of age or older, is based on the consideration that the disease in adults and pediatric patients is sufficiently similar once patients progress to require supplemental oxygen, or invasive mechanical ventilation of ECMO. The appropriate dosing for pediatric patients is also informed by the accumulated PK and safety information with baricitinib in multiple adult and pediatric populations and physiologically based pharmacokinetic (PBPK) modeling. Age-specific dosing recommendations for pediatric patients are discussed in the section on Human Clinical Pharmacology.

IV. Product Information (Dose Preparation and Administration)

- Drug product tablets are to be taken orally or can be crushed, dispersed in water, and given via gastrostomy, nasogastric, and orogastric tubes (see section XV below).
- Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
- OLUMIANT 2 mg tablets contain a recessed area on each face of the tablet surface and are debossed, film-coated, immediate-release tablets. The 2 mg tablet is light pink, oblong, debossed with “Lilly” on one side and “2” on the other. OLUMIANT 1 mg tablets are very light pink, round, debossed with “Lilly” on one side and “1” on the other. Tablets are supplied in bottles of 30.
- Description of product as packaged (e.g., round pink tablets in blisters, packaged 6 per card, with code “ASD” debossed on one side.)

SEE ATTACHED ADDENDUM

- Keep out of the reach of children.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

- Background information on the condition
    - Coronavirus disease 2019 (COVID-19) can cause severe disease which can result in pneumonia, respiratory failure, multi-organ failure, and death.
    - On March 11, 2020 the WHO declared COVID-19 a pandemic.
    - Globally, according to the World Health Organization (WHO), approximately 38 million confirmed cases of COVID-19 caused by the 2019 novel coronoavirus (SARS-CoV-2) have been reported as of October 13th, 2020, including an estimated 1,083,234 deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), approximately 7,213,419 cases of COVID-19 have been reported with 206,402 deaths as of October 1, 2020.
- Per the CDC COVID-19 data tracker (October 14, 2020) available demographic information demonstrates all age groups are affected by hospitalizations, ICU admissions and deaths with the highest percentage of deaths occurring in older individuals. Following infection with COVID-19 some patients develop severe disease that can progress to pulmonary failure, ARDS, and death. The understanding of the underlying immunopathology and natural history of the disease is rapidly evolving. It is thought that in some cases the immune response results in a hyperinflammatory state that may contribute to organ injury.
- Therapeutic alternatives for the disease/condition
    - On October 22, 2020, remdesivir was approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization.
    - On October 22, 2020, FDA authorized the emergency use of the investigational anti-viral drug remdesivir pursuant to Section 564 of the Act, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.
    - On August 23, 2020, FDA authorized the emergency use of convalescent plasma pursuant to Section 564 of the Act for the treatment of hospitalized patients with COVID-19.
    - The RECOVERY trial showed evidence that dexamethasone may have potential benefit on incidence of death for COVID-19 patients who receive invasive mechanical ventilation or for COVID-19 patients who receive oxygen without invasive mechanical ventilation.

- Description of the proposed EUA product's potential to address an unmet need in treating (or preventing, if applicable) the disease or condition caused by the threat agent, including any available information about any ongoing, relevant clinical trials.

    - No products have demonstrated an improvement of disease in combination with remdesivir. There remains an unmet need for the treatment of COVID-19 infection. Baricitinib in the ACTT-2 study shows promise in combination with remdesivir and is being studied in an ongoing clinical trial on background standard of care.

    - Lilly is requesting an EUA for an approved drug in rheumatoid arthritis, baricitinib 2 mg, for an unapproved use and dose, 4 mg daily (2x 2 mg tablets) for the treatment of COVID-19 in hospitalized adult and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.

    - Lilly has provided data from the ACTT-2 study sponsored by NIAID, a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of 4-mg daily baricitinib + remdesivir versus placebo + remdesivir in hospitalized patients with COVID-19. An additional study, KHAA, a randomized, double-blind, placebo-controlled, parallel-group, phase 3 study evaluating the safety and efficacy of 4-mg daily baricitinib versus placebo in hospitalized patients with COVID-19, is ongoing.

VI. Related Regulatory Submission(s)

- Related Master Files are summarized in Table 1.

Table 1. Related Master Files

DMF #	Type	Holder	Item Referenced
(b) (4)	III	(b) (4)	
	IV		
	III		
	III		
	III		
	III		

- Related NDA
    - NDA 207924
        - Baricitinib (Olumiant) approved for the treatment of adult patients with moderately-to-severely active rheumatoid arthritis (RA) who have had an inadequate response to 1 or more TNF antagonist therapies (2 mg tablets, dosed once daily, approved for oral use)
        - Initial approval 2018
        - Sponsor - Eli Lilly and Company
- Related INDs
    - IND 102204
        - Phase 1-3 clinical trials; Primary baricitinib IND to support baricitib NDA for treatment of RA (NDA 207924), additional clinical studies to evaluate treatment in systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA) and an expanded access, compassionate use program for rare Type-1 interferonopathies
        - Dose, duration, and route: 2 and 4 mg oral tablets, dosed daily
        - Completed nonclinical program to support NDA
        - Sponsor-Eli Lilly and Company
    - IND 112543
        - Evaluate baricitinib as a treatment for atopic dermatitis (AD) and alopecia areata (AA); phase 3 clinical trials
        - Dose, duration, and route: 1 mg, 2 mg, and 4 mg oral baricitinib dosed daily
        - Cross-Reference to IND 102204
        - Sponsor- Eli Lilly and Company
    - IND 147771
        - Randomized clinical trial: Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hopitalized Adults
        - Dose, duration, route (adults): 4 mg oral baricitinib dosed for 14 days with remdesivir 200 mg IV loading dose on Day 1, followed by 100 mg IV daily on Days 2-10.
        - Cross-Reference to IND 102204
        - Sponsor- NIAID
    - IND 149279
        - Ongoing, Study 14V-MC-KHAA, A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of Baricitinib in Patients with COVID-19 Infection,
        - Dose, duration, and route (adults): 4 mg oral baricitinib dosed daily for up to 14 days
        - Cross-Reference to IND 102204 and NDA 207942
        - Sponsor- Eli Lilly and Company
- Related Pre-INDs
    - Pre-IND 152933
        - For the treatment of COVID-19 infection in hospitalized adults and pediatrics requiring supplemental oxygen, mechanical ventilation,

invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Cross-reference to IND 147771

- Sponsor: Eli Lilly and Co.

VII. Summary of Clinical Data

Key design features of baricitinib COVID-19 clinical development program are summarized in Table 2.

Table 2. Clinical Trials in COVID-19

Study Identifier, Protocol Number	IND	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s) Dosing Regimens; Dosage Forms; Routes of Administration, Duration	Study Status
Key study supporting the EUA request						
Protocol No. 20-0006 (ACTT-2) NCT04401579	147,771	Efficacy, Safety	1033 Baricitinib + remdesivir (n=515) Placebo + remdesivir (n=518)	Randomized, double-blind, placebo-controlled, parallel group clinical trial in hospitalized COVID-19 patients	Baricitinib 4 mg oral (two 2 mg tablets), dosed 14 days or placebo All patients received Remdesivir (10 days): Remdesivir 200 mg IV Day 1: Followed by 100 mg IV QD Days 2-10	Completed*
Study supporting the baricitinib COVID-19 clinical development program (this study is ongoing as of the time of this review and no data are available to support the EUA request)						
Study 14V-MC-KHAA NCT04421027	149,279	Efficacy, Safety	Planned 1000 to 1400	Randomized, double-blind, placebo-controlled, parallel group clinical trial in hospitalized COVID-19 patients	Baricitinib, 4 mg oral (two 2 mg tablets) dosed for 14 days on standard of care background treatment	Ongoing

IND=investigational new drug, *ACTT master protocol remains active

The primary efficacy support for the EUA application is from the ACTT-2 clinical trial sponsored by NIAID. This is a randomized, double-blind, placebo-controlled study comparing baricitinib dosed with background remdesivir to placebo with remdesivir. Study 14V-MC-KHAA, a second randomized, double-blind, placebo-controlled trial, is currently ongoing. No clinical efficacy data is currently available from this study, however, study 14V-MC-KHAA is anticipated to provide additional data regarding the use of baricitinib, particularly without background remdesivir and with the allowance of background steroids, in hospitalized patients with COVID-19.

The Sponsor has provided additional literature reports from observational studies, case reports, and retrospective cohort studies to support the use of baricitinib on background standard of care. In these published reports baricitinib was used in a total of 232 patients with a variety of different background treatments and of the 232 patients, 209 were receiving background antiviral medication. Given the small sample sizes and limited endpoint information for these studies and because none of the studies were conducted as randomized, controlled clinical trials, these studies cannot reliably support efficacy or safety of baricitinib. As such, these trials do not provide substantial additional information to support this EUA. The studies provided are summarized in Appendix 2.

VIII. Human Clinical Efficacy

NIAID-Sponsored ACTT-2 Trial (NCT04401579)

Study Design and Primary Endpoint Analysis Plan

This phase 3, double-blind trial randomized a total of 1033 hospitalized patients with laboratory-confirmed SARS-CoV-2 infection in a 1:1 ratio to receive either baricitinib plus remdesivir or placebo plus remdesivir. Baricitinib or placebo were administered daily for either a 14-day total course or the duration of hospitalization as two 2mg oral tablets or crushed for use in a nasogastric (NG) tube. Remdesivir was administered as a 200 mg intravenous (IV) loading dose on Day 1 followed by a 100 mg once-daily IV maintenance dose for a 10-day total course or the duration of hospitalization. Any doses of remdesivir administered under an EUA (or similar mechanism) prior to enrollment were counted towards the total course with a maximum treatment duration of 10 days. Patients were followed for a maximum of 29 days after randomization.

Patients in this trial were classified as having either moderate or severe COVID-19 at baseline. Using the the NIAID 8-point ordinal scale (OS) shown below, subjects at baseline were in categories 4, 5, 6, or 7. Severe disease was defined as hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. Randomization was stratified by baseline classification of moderate versus severe disease status and study site.

8-Point NIAID Ordinal Scale (OS):

8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;
2. Not hospitalized, limitation on activities and/or requiring home oxygen;
1. Not hospitalized, no limitations on activities

The primary efficacy endpoint was time to recovery through Day 29. Recovery was defined by being in category 1, 2, or 3 on the NIAID OS. Patients who died before recovering were censored at the final follow-up visit (Day 29) in the analysis, treating them the same as patients who did not recover by Day 29. Any subjects that were lost to follow-up or terminated early prior to an observed recovery were censored at the day of their last observed assessment. A stratified log-rank test was used as the primary analysis for time-to-recovery. In addition, the median time to event and 95% confidence interval was summarized by treatment arm and estimates of the hazard ratios were produced from Cox regression models. Subgroup analyses based on baseline disease status were also performed. Efficacy results are displayed for the intent-to-treat (ITT) population, which includes all randomized patients. Results for the As Treated population, which includes all randomized patients who received either baricitinib or placebo, were similar. A statistical analysis plan (SAP) written by NIAID and an SAP addendum written by Eli Lilly were provided for this study. Of note, the SAP specified that the ITT population would be used for the primary analysis; however, the As Treated population was the primary analysis population in the SAP addendum.

The study was powered based on an assumed hazard ratio of 1.25 for baricitinib plus remdesivir versus placebo plus remdesivir for the primary endpoint (a hazard ratio > 1 indicates faster recovery in the baricitinib plus remdesivir group). It was estimated that total of 723 recoveries were needed to achieve 85% power with a true hazard ratio of 1.25. The study planned to continue to accrue patients until approximately 723 recoveries had been achieved. It was estimated that with 70% of participants recovering, the total sample size would need to be 1032. The study enrolled 1033 patients and had a total of 839 observed recovery events.

A planned interim efficacy analysis allowing early stopping for both futility and efficacy was to be conducted after approximately 33% of total information had been reached. The actual interim analysis was performed after 286 out of the initially planned 723 recovery events were observed (information fraction of 0.396) and included 528 patients. The Lan-DeMets alpha spending function with approximate O'Brien-Fleming boundaries was used to maintain an overall two-sided type-I error rate of 0.05 for the primary endpoint, resulting in testing at an alpha level of approximately 0.0007 for the interim analysis and 0.0498 for the final analysis. A futility analysis was also performed where early stopping for futility would be considered if conditional power were less than 20%. The study proceeded without stopping based on the interim analysis results.

Primary Endpoint Results

Efficacy results for the primary analysis of time to recovery in all randomized patients (ITT population) are presented in Table 3 below. A hazard ratio > 1 indicates an improvement in time to recovery for the baricitinib plus remdesivir arm compared to the placebo plus remdesivir arm. The hazard ratio of 1.15, its 95% confidence interval, and the p-value indicate a modest but statistically significant effect. The estimated 25th percentile for time to recovery is the same for both arms, and the estimated median time to recovery is only

1 day less for the baricitinib plus remdesivir arm (7 days vs 8 days). However, the estimated 75th percentile for time to recovery is 7 days less for the baricitinib plus remdesivir arm (13 vs 20). The Kaplan-Meier plot for time to recovery (Figure 1) shows a separation of the two curves beginning around Day 4, with a higher proportion of recovered patients in the baricitinib plus remdesivir arm. The separation becomes more pronounced after Day 8.

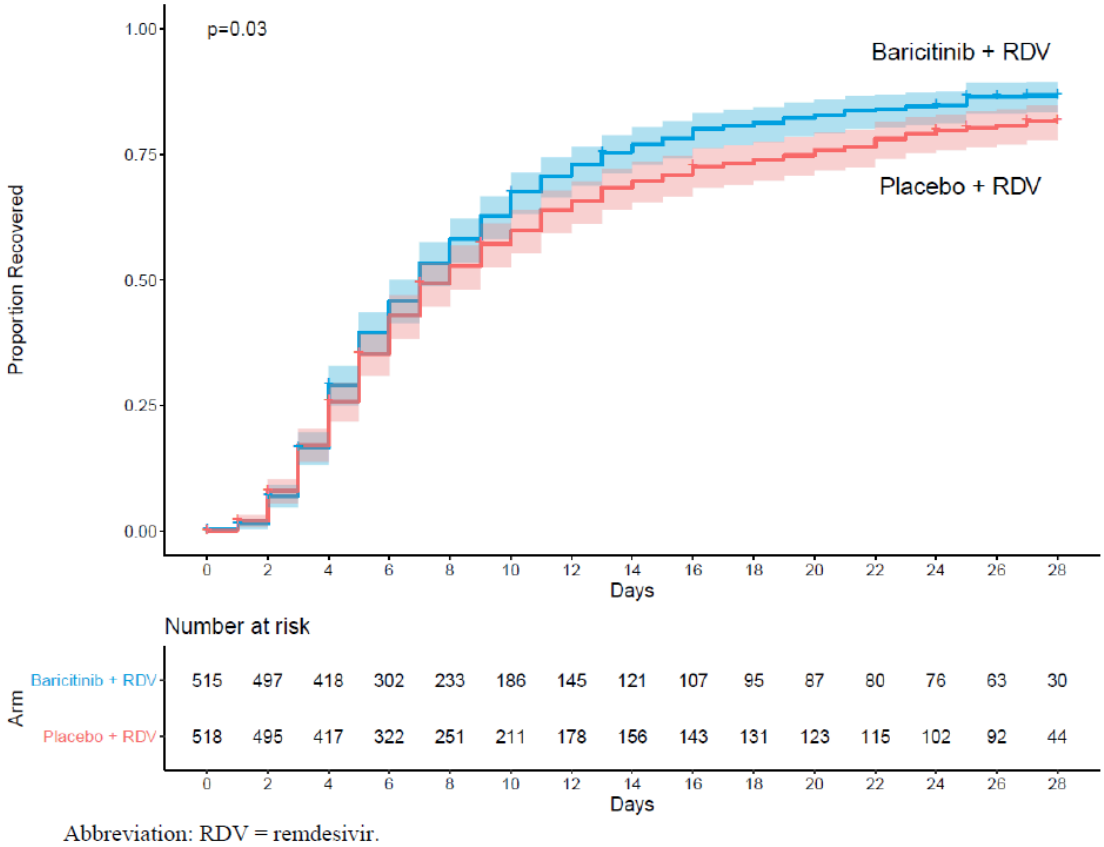
Table 3. Time to Recovery for All Randomized Patients (ITT Population)

	Placebo + Remdesivir (n=518)	Baricitinib + Remdesivir (n=515)
25th Percentile for Time to Recovery (95% CI)	4.0 (4.0, 5.0)	4.0 NE*
Median Time to Recovery Days (95% CI)	8.0 (7.0, 9.0)	7.0 (6.0, 8.0)
75th Percentile for Time to Recovery (95% CI)	20.0 (16.0, 23.0)	13.0 (12.0, 16.0)
Hazard Ratio[a] (95% CI)	1.15 (1.00, 1.31)	
P-value[b]	p=0.047	

[a] Hazard ratio is calculated from a Cox model stratified by disease severity
[b] P-value is calculated from a stratified log-rank test using baseline disease severity as a stratification factor
*Not Estimated
Source: Adapted from Table 9.5. (page 36) of Request for Emergency Use Authorization

SEE ATTACHED ADDENDUM

Figure 1. Kaplan-Meier Plot for Time to Recovery



Abbreviation: RDV = remdesivir.

Source: Figure 16.1. (page 80) of Pre-IND Meeting Briefing Document

The primary endpoint of time to recovery was based on a patient's initial recovery. Therefore, a patient could have potentially achieved recovery (OS ≤ 3) as defined in the primary endpoint and subsequently worsened. Among patients who recovered during the study, less than 6% were observed to relapse during the study period (i.e., a score ≥ 4 was observed on the NIAID OS after achieving a score ≤ 3). Less than 1% of recovered patients were observed to require invasive or non-invasive ventilation after recovery and only approximately 0.2% of recovered patients later died. Although the observed percentage of patients requiring ventilation or dying after recovering was small, the actual proportion of patients who progressed to ventilation or death after recovery could be higher as clinical status after recovery was unknown for approximately 7% of recovered patients. A slightly higher proportion of recovered patients relapsed in the baricitinib + remdesivir arm (5.8%) compared to the placebo + remdesivir arm (4.4%). An exploratory analysis of time to sustained recovery, where patients were considered to have achieved sustained recovery if they achieved an OS ≤ 3 and maintained an OS ≤ 3 for the remainder of their participation in study, did not achieve nominal statistical significance but still showed a favorable trend for the baricitinib + remdesivir arm with an estimated hazard ratio of 1.13 and a 95% CI of (0.98, 1.30).

Secondary Endpoint Planned Analyses

In addition to the primary endpoint, multiplicity adjusted analyses were to be performed for the following secondary endpoints:

- Proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 29. For patients who required non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) at baseline, worsening at least 1 point in NIAID-OS by Day 29 is required for the patient to be included in the numerator.
- Overall improvement on the NIAID-OS evaluated at Day 11 and Day 15
- All-cause mortality (Day 1-Day 29)
- Number of ventilator-free days (Day 1-Day 29)
- Duration of hospitalization (Day 1 to Day 29)
- Proportion of patients with at least 1-point improvement on the NIAID-OS or live discharge from the hospital at Day 15

For the analyses of endpoints based on continuous or ordinal scale measures, a modified last observation carried forward (mLOCF) analysis was used to handle missing data, unless otherwise noted. This was performed by carrying forward the last observed postbaseline assessment for the outcome. For time to event outcomes, patients who are lost to follow-up or terminate the study prior to Day 29 and prior to observing/experiencing the event were censored at the time of their last observed assessment, unless otherwise noted.

The proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation by Day 29 was analyzed using a logistic regression model which included baseline disease severity and treatment group as factors in the model. The SAP specified that if there were <5 responders in any category for any factor, the p-value from Fisher's exact test instead of the logistic regression model would be used. Missing values were imputed using mLOCF.

The secondary endpoint of the distribution of the 8-point ordinal clinical status scale at Day 15 was analyzed using a proportional odds logistic regression model with treatment arm and disease severity as factors in the model. The analysis was based on the ordinal scale outcome at the Day 15 visit, which had a window of ± 2 days. For patients who died on or prior to the end of the Day 15 window, they were considered dead in the analysis even if they had another clinical status outcome score on Day 15. For patients who were discharged but subsequently re-admitted prior to Day 15 without a reported clinical score, their clinical score was imputed as a 7 (the worst outcome for a hospitalized patient who was still alive). Randomized patients without pre- or post-randomization ordinal score data and patients transfer to hospice care prior to Day 15 also had their clinical score imputed as a 7. If patients were discharged from the hospital without a reported clinical score, then their clinical score at the time of discharge was imputed as 2 (the worst possible outcome for a non-hospitalized patient). For all other patient with missing data, the last available clinical score prior to the Day 15 visit was used.

The primary analysis of all-cause mortality was based on time to event analysis and used the same analysis methods as the primary endpoint of time to recovery. A p-value was computed using a log-rank test stratified by baseline disease severity and a Cox model which included baseline disease severity was used to estimate the hazard ratio. Patients who were lost to follow-up or terminated early were censored at the day of their last observation. If it was learned that a patient who terminated early had died prior to Day 29, the patient was classified as dead. Based on requests from the FDA, an additional analysis was performed to compare the estimated difference in the probability of mortality by Day 29 between the two arms using the Kaplan-Meier method.

A graphical multiple testing procedure was pre-specified in the SAP addendum to control the overall type I error.

Secondary Endpoint Results

Efficacy results for available secondary endpoints are presented in Table 4 for the proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation by Day 29, overall improvement on the NIAID-OS at Day 15 and all-cause mortality by Day 29. Statistical hypothesis tests of the other multiplicity controlled secondary endpoints were not submitted at this time. The analyses for all three secondary endpoints show favorable results for the baricitinib + remdesivir arm. The odds ratio of 0.74 indicates lowers odds of progression to ventilation or mortality by Day 29 for patients in the baricitinib + remdesivir arm, the common odds ratio of 1.26 indicates increased odds of patients having a more favorable clinical status at Day 15 for patients in the baricitinib + remdesivir arm, and the hazard ratio of 0.65 shows an estimated decrease in the hazard of dying for patients in the baricitinib + remdesivir arm. The secondary endpoints of proportion of patients progressing to ventilation and the NIAID-OS endpoint both achieved statistical significance based on the analyses and multiple testing procedures pre-specified in the SAP addendum. Although all-cause mortality was not statistically significant, the upper bound of the 95% difference in estimated probability of mortality by Day 29 was 0.5% and the upper bound for the hazard ratio from the stratified Cox model was 1.09, indicating that it is unlikely that the addition of baricitinib to remdesivir will lead to an unacceptable increase in mortality.

Table 4. Available Results for Secondary Efficacy Endpoints (ITT Population)

	Placebo + Remdesivir (n=518)	Baricitinib + Remdesivir (n=515)
Proportion of Patients Progressing to Ventilation or Mortality through Day 29		
Estimated Proportion (95% CI)	28 (25, 32)	23 (19, 26)
Odds Ratio[a] (95% CI)	0.74 (0.56, 0.99)	
P-value[a]	p=0.039	
NIAID-OS Evaluated at Day 15		
Common Odds Ratio[b] (95% CI)	1.26 (1.01, 1.57)	
P-value[b]	p=0.044	
All-cause Mortality by Day 29		
Number of Deaths (%)	37 (7.1)	24 (4.7)
Estimated Probability of Mortality[c] (95% CI)	7.8 (5.7, 10.6)	5.1 (3.5, 7.6)
Difference in Probability of Mortality[d] (95% CI)	-2.6 (-5.8, 0.5)	
Hazard Ratio[e] (95% CI)	0.65 (0.39, 1.09)	
P-value[e]	p=0.102	

[a]Calculated using a logistic regression model with disease severity included as a factor
[b]Calculated from a proportional odds logistic regression model with disease severity included as a factor
[c]Calculated using the Kaplan-Meier estimate for mortality by Day 29
[d]Calculated from an unadjusted difference in the Kaplan-Meier estimated probability of mortality
[e]Calculated from a stratified log-rank test using disease severity as a stratification factor
Source: Adapted from Table 9.1. (page 24) and Table 9.8. (page 42) of Request for Emergency Use Authorization. Kaplan-Meier estimates of 29 Day mortality are from page 29 of Response to IR (10/19/2020).

Early Study Withdrawal and Missing Data

There was a considerable number of randomized patients who terminated early from the study for reasons other than death as shown in Table 5. Approximately 11.8% of randomized patients in the baricitinib + remdesivir and 14.3% of randomized patients in the placebo + remdesivir arm terminated participation in the study early for reasons other than death. The majority of patients who withdrew early had already met the primary endpoint definition for recovery at the time of withdrawal (3.3% of randomized patients in the baricitinib + remdesivir and 4.4% of randomized patients in the placebo + remdesivir arm were hospitalized at the time of early withdraw). The plurality of patients who withdrew early before recovery had not received study treatment. As such, only a small number of treated patients were missing with respect to the analysis of the primary endpoint using the As Treated population. Only 1.9% of randomized patients in the baricitinib + remdesivir and 2.7% of randomized patients in the placebo + remdesivir arm received study drug and withdrew before recovery. Overall missing data rates for the proportion of patients who died or progressed to ventilation by Day 29 and all-cause mortality at Day 29 are around 10.5% among all randomized patients. A slightly higher proportion of patients in the placebo + remdesivir arm had missing outcomes for these two secondary endpoints (approximately 1-2 percentage points higher). Most of the

missing outcomes for the Day 29 secondary endpoints resulted from patients who withdrew from the study after meeting the definition for recovery.

As decribed above, for time to event endpoints, patients with missing outcomes were censored at the time of their last observation. This assumes that patients who withdrew early had similar outcomes to patients who remained in the study, conditional on the covariates included in the model. For endpoints that used the NIAID OS, mLOCF was used to imputed missing data. This approach makes the strong assumption that the expected outcome of a patient does not change after the observed postbaseline assessment. Furthermore, as mLOCF is a single imputation approach, it does not account for the uncertainty added by missing data and is generally not recommended. However, given that missing data rates were similar in both treatment arms and most of the missing data resulted from patients who withdrew after hospital discharge, missing data were considered unlikely to have altered the conclusion that baricitinib, in combination with remdesivir, may be effective for treatment of COVID-19.

Table 5. Early Study Termination for Reasons Other than Death

	BARI+RDV (N = 515)		**PBO+RDV (N = 518)**		**Total (N = 1033)**	
	n	%	n	%	n	%
Early termination for any reason	**61**	**11.8**	**74**	**14.3**	**135**	**13.1**
Recovered before early termination	44	8.5	51	9.8	95	9.2
Lost to follow-up	40	7.8	41	7.9	81	7.8
Other	1	0.2	3	0.6	4	0.4
Voluntary withdrawal by subject	3	0.6	7	1.4	10	1.0
Not recovered at early termination	**17**	**3.3**	**23**	**4.4**	**40**	**3.9**
Not treated	7	1.4	9	1.7	16	1.5
Voluntary withdrawal by subject	5	1.0	9	1.7	14	1.4
Withdrawal by investigator	1	0.2	2	0.4	3	0.3
Ineligible after enrollment	1	0.2	1	0.2	2	0.2
AE or SAE, other than death	2	0.4	1	0.2	3	0.3
Transfer to another hospital	0	0.0	1	0.2	1	0.1
Other	1	0.2	0	0.0	1	0.1

Source: Table 4.4. (page 15) Response to IR (10/23/2020)

Subgroup Analyses

Table 6 shows subgroup analyses of the efficacy results for time to recovery based on the baseline clinical status as determined by NIAID OS. The estimated time to recovery favors the baricitinib + remdesivir arm for all subgroups except patients who were hospitalized but did not require supplemental oxygen (OS 4). The observed treatment effect on time to recovery is largest for patients on non-invasive ventilation or high flow oxygen devices (OS 6). The median time to recovery for patients on invasive mechanical ventilation or ECMO could not be estimated as less than half of all patients within that subgroup had recovered by Day 29.

Table 6. Time to Recovery by Baseline NIAID OS Score (ITT Population)

		NIAID OS = 4	NIAID OS = 5	NIAID OS = 6	NIAID OS = 7
Placebo + Remdesivir	Sample Size	72	276	113	57
	Median Time to Recovery (95% CI)	4.0 (4.0, 6.0)	6.0 (5.0, 6.0)	18.0 (13.0, 21.0)	NE* (26.0, NE*)
Baricitinib + Remdesivir	Sample Size	70	287	104	54
	Median Time to Recovery (95% CI)	5.0 (4.0, 6.0)	5.0 (5.0, 6.0)	10.0 (9.0, 13.0)	NE* (25.0, NE*)
	Hazard Ratio[a] (95% CI)	0.88 (0.62, 1.23)	1.17 (0.98, 1.40)	1.52 (1.11, 2.09)	1.08 (0.59, 1.97)

[a] HR is calculated from a Cox model stratified by disease severity
*Not Estimated
Source: Adapted from Table 2 (page 41) of Pre-IND Meeting Briefing Document

Subgroup results for the proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation by Day 29 are displayed in Table 7. The definition of progression to ventilation or death differed by baseline ventilation subgroup, i.e., patients not on ventilation could progress to non-invasive ventilation, invasive ventilation, or death; patients on non-invasive ventilation/high-flow oxygen could progress to invasion mechanical ventilation or death; patients on invasive ventilation could only progress to death. For patients that met the definition of progression, the worst clinical status to which patients progressed is displayed.

Table 7. Progression to Ventilation or Death by Baseline Ventilation Status

Baseline Clinical Status	Worst Disease Progression	Placebo + Remdesivir	Baricitinib + Remdesivir
Not on Ventilation at Baseline	Proportion who Progressed to Non-invasive Ventilation	17% (58/348)	15% (53/358)
	Proportion who Progressed to Invasive Ventilation	5% (18/348)	4% (14/358)
	Proportion who Died	3% (12/348)	1% (5/358)
Non-invasive Ventilation or High Flow Oxygen	Proportion who Progressed to Invasive Ventilation	30% (34/113)	24% (25/103)
	Proportion who Died	12% (13/113)	7% (7/103)
Invasive Ventilation or ECMO	Proportion who Died	21% (12/57)	22% (12/54)

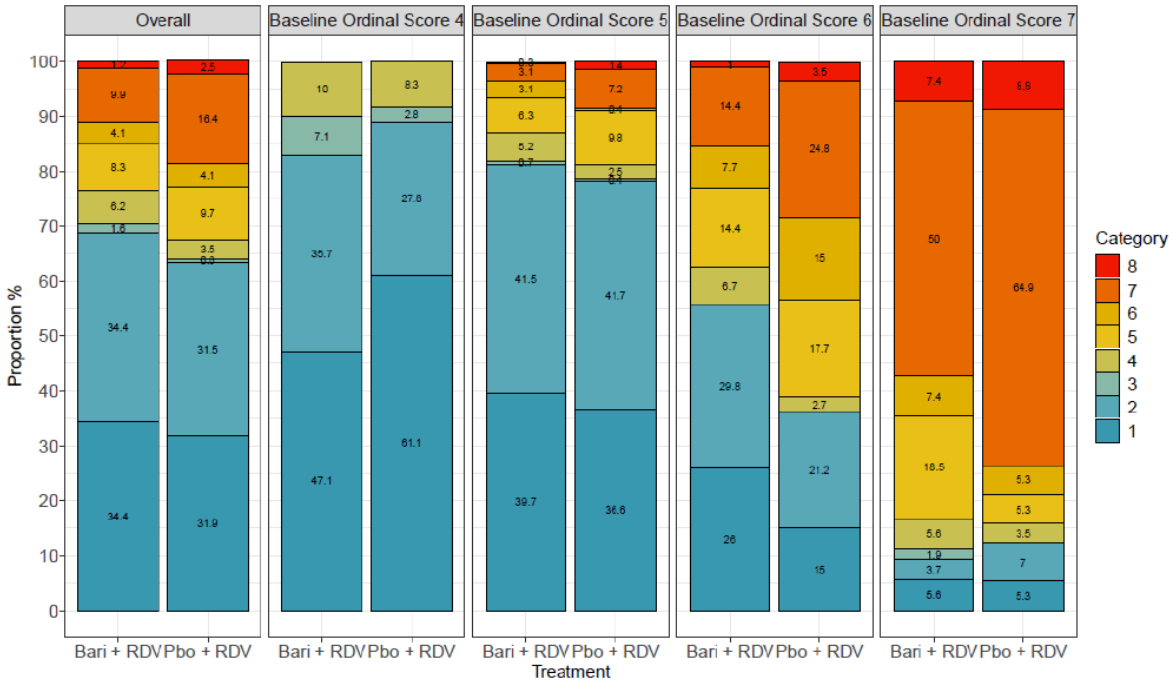
Source: Adapted from Table 5.2. (Page 31) Response to IR (10/19/2020)

Figure 2 and Figure 3 display stacked bar charts for the distribution of the NIAID OS overall and by baseline clinical status at Day 15 and Day 29, respectively. The

distributions show favorable results for the baricitinib + remdesivir arm for patients with a baseline clinical status of 5, 6, and 7 on the NIAID ordinal scale. Among patients with a baseline status of 5 and 6, there is a lower proportion of patients who died (OS 8) or were on invasive ventilation (OS 7) and a higher proportion of recovered patients (OS 1-3) at both timepoints for the baricitinib + remdesivir arm. The difference between the two arms, in terms of lower proportions of progression and higher proportions of improvement, appears to be larger for patients with a baseline status of 6. While the observed mortality rate at Day 29 was slightly worse for the baricitinib + remdesivir arm for patients with a baseline status of 7, a large decrease in the proportion of patients on invasive ventilation (OS 7) and an increase in the proportion of recovered patients at Day 29 was observed (OS 1-3). It is possible that the increase in recovered patients and decrease in patients on invasive ventilation would translate into a mortality benefit at a later timepoint for this subgroup; however, follow-up beyond Day 29 is not available.

There was very little difference in the observed distribution of the ordinal scale for patients with a baseline clinical status of 4 (hospitalized but did not require supplemental oxygen) at Day 15 and Day 29. The Sponsor has not proposed to include this population as part of the EUA due to the lack of observed benefit within this subgroup. We note that the study was not powered to detect a significant difference between treatment arms within baseline OS subgroups (there were only 142 randomized patients who had a baseline OS of 4) and exploratory analyses were performed on multiple baseline OS subgroups. Therefore, the lack of a positive trend for the subgroup with a baseline clinical status of 4 may be due to chance; however, there is likely insufficient evidence at this time to support effectiveness for this subgroup.

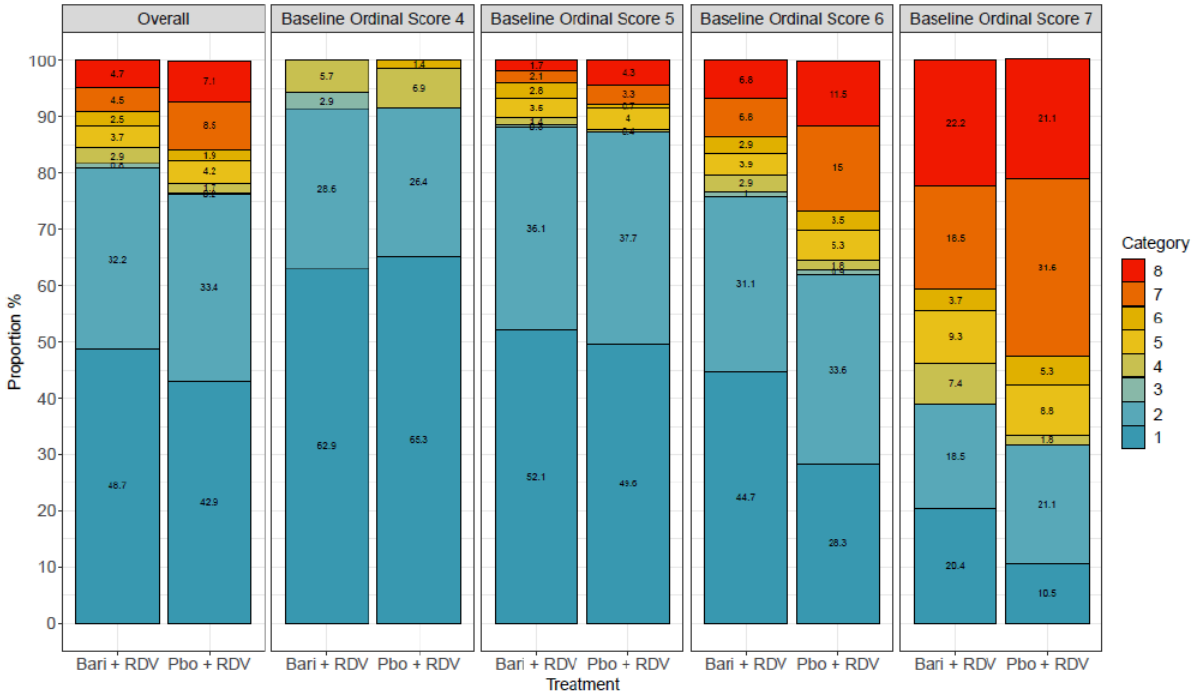
Figure 2. Distribution of NIAID Ordinal Scale at Day 15



Abbreviations: Bari + RDV = baricitinib plus remdesivir; Pbo + RDV = placebo plus remdesivir.

Source: Figure 4.1. (page 7) Response to IR (10/29/2020)

Figure 3. Distribution of NIAID Ordinal Scale at Day 29



Abbreviations: Bari + RDV = baricitinib plus remdesivir; Pbo + RDV = placebo plus remdesivir.

Source: Figure 4.2. (page 8) Response to IR (10/29/2020)

Another subgroup analysis of interest was defined by baseline corticosteroid use. When study enrollment had begun in ACTT-2, corticosteroid usage was not yet part of standard of care treatment for COVID-19 and actively prohibited by the protocol for COVID-19 treatment. However, corticosteroid usage was permitted for other disease indications. As a result, very few patients (50 in the baricitinib + remdesivir arm and 51 in the placebo + remdesivir arm) were using corticosteroids at the time of enrollment. Efficacy results for time to recovery and the NIAID OS at Day 15 appear favorable among patients on baseline corticosteroids; however, interpretation of results is difficult given the small sample size. A slightly higher proportion of patients initiated corticosteroids after randomization in the placebo + remdesivir arm compared to the baricitinib + remdesivir arm (14.3% vs 12.0%).

Efficacy Conclusions From ACTT-2 Study

The efficacy results from the ACTT-2 study provide evidence that baricitinib in combination with remdesivir may be effective in treating hospitalized COVID-19 patients reqiuring supplemental oxygen,[5] invasive mechanical ventilation or ECMO and support issuance of an EUA. The primary efficacy analyses for time to recovery, progression to ventilation or death, and NIAID OS outcome at Day 15 achieved statistical significance. The results for all-cause mortality were not statistically significant, but were able to rule out an unacceptable increase in mortality. Although there is considerable uncertainty in subgroup analyses, estimated effects for all four endpoints trended in the direction of benefit for the subgroups of patients requiring supplemental oxygen and patients requiring non-invasive ventilation or high-flow oxygen at baseline. While there were similar mortality rates between arms for patients on invasive ventilation at baseline, estimates for time to recovery and the proportion of patients who died or required invasive ventilation at Day 29 showed a positive trend for the baricitinib + remdesivir arm compared to the placebo + remdesivir arm.

IX. Human Clinical Safety

Baricitinib is approved at a dose of 2 mg a day for chronic treatment in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. Clinical trials in rheumatoid arthritis also included a 4 mg baricitinib dose which provide additional safety information regarding the 4 mg dose. While efficacy in rheumatoid arthritis was demonstrated with the 2 mg and 4 mg doses the overall benefit-risk profile of the 2 mg dose was determined to be more favorable.

As of August 2020, approximately 548 healthy volunteers and 10,759 patients have received baricitinib in clinical trials across multiple indications. In clinical trials 52 patients

[5] Supplemental oxygen also includes non-invasive ventilation

were 12 years of age or younger, and 55 patients were between the ages of 12 years to 18 years. Single doses of up to 40 mg of baricitinib and multiple doses of up to 20 mg daily for 10 days have been administered. An estimated 222,700 patients have been exposed to baricitinib worldwide.

The United States Prescribing Information (USPI) for baricitinib contains a boxed warning for the risk of serious infections, thrombosis and malignancy. Additional safety risks in the USPI Warnings and Precautions include risks for gastrointestinal perforations, risks associated with live vaccinations and hypersensitivity reactions. Laboratory abnormalities including decreases in lymphocytes, neutrophils, and hemoglobin, and increases in platelets, liver enzymes, and lipid parameters have been associated with use of baricitinib in clinical trials in rheumatoid arthritis. The rheumatoid arthritis clinical program evaluated safety with chronic dosing in clinical trials. In the setting of chronic dosing, some safety risks appeared dose dependent with increased safety risk observed with the 4 mg dose.

In this EUA the proposed dosing regimen is 4 mg daily for 14 days or until discharge. While higher than the FDA approved dose for rheumatoid arthritis, the dosing period is limited to 14 days and significant safety information is available for this dose in patients treated with baricitinib for indications other than COVID-19. Inclusion criteria for the ACTT-2 study required patients to have laboratory confirmed 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$\leq$ 94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or ECMO. In the ACTT-2 study patients were excluded based on the following:

- Lab parameters:
    - ALT or AST > 5x ULN, eGFR <30 ml/min or if a patient was receiving hemodialysis or hemofiltration at screening.
    - Neutropenia (ANC <1000 cell/µL), or lymphopenia (ALC <200 cell/µL).
- Received convalescent plasma or intravenous immunoglobulin (IVIg) for COVID-19.
- A diagnosis of current active tuberculosis or latent TB treated for less than 4 weeks.
- Other suspected serious, active bacterial, fungal, viral or other infections besides COVID-19.
- History of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (>1) VTE or DVT/PE.
- Received a live vaccine within 4 weeks before screening.
- Pregnancy or breast feeding.
- Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
- Received three or more doses of remdesivir, including the loading dose, outside of the study under the EUA (or similar mechanism) for COVID-19.
- Received small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatibib, genfinitib), in the 1 week prior to screening.

- Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], 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, and including any targeting multiple cell lines including B-cells) 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.
- Use of probenecid that cannot be discontinued at study enrollment.
- Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who, in the judgment of investigator, are at increased risk for serious infections or other safety concerns given the study products.

Safety data is available for 507 patients hospitalized with COVID-19 (moderate, or severe) treated with 4 mg of baricitinib once daily for up to 14 days in combination with remdesivir in the ACTT-2 study. Background remdesivir in the clinical study was dosed with 200 mg IV on day 1, followed by 100 mg IV daily on days 2-10. Safety data of the baricitinib arm on a background of remdesivir was compared to 509 patients treated with placebo along with background remdesivir. Based on the known safety profile for baricitinib, the overall conclusion was no new safety signals were identified. The Sponsor has provided a summary of the safety data for patients in the ACTT-2 clinical trial. Safety data is presented from the “As Treated” population, defined as subjects who received at least one dose of study drug:

- All-cause mortality at Day 29 was higher in the placebo arm compared to the baricitinib arm with 23 (4.5%) events in the baricitinib arm and 37 (7.3%) events in the placebo arm. Although the difference in all-cause mortality was not statistically significant, the upper bound of the 95% difference in probability of mortality by Day 29 among all randomized patients was 0.5% and the upper bound for the hazard ratio from the stratified Cox model including all randomized patients was 1.09. This indicates that it is unlikely that the addition of baricitinib to remdesivir will lead to an unacceptable increase in mortality. Nineteen patients (4%) in the baricitinib and 31 patients (6%) in the placebo arm were considered to have treatment emergent adverse events (beginning after receiving study drug) with a fatal outcome. The most common cause of death reported in the study population was due to respiratory causes (Preferred terms [PTs]: acute respiratory distress, acute respiratory failure, hypoxia, respiratory failure, respiratory arrest and respiratory distress). Overall fewer respiratory events leading to death were observed in the baricitinib arm compared to placebo.

- A higher proportion of patients in the placebo arm (20%) had serious adverse events compared to the baricitinib arm (15%). The most commonly reported SAEs were due to respiratory failure.
- A higher proportion of patients had any treatment emergent adverse event in the placebo arm (47.5%) compared to the baricitinib arm (41.3%). The most commonly reported non-serious AEs were due to laboratory abnormalities. Common non-serious AEs reported in 5 or more patients and at a rate of >1% higher in the baricitinib arm compared to placebo were: glomerular filtration rate decreased (baricitinib 9.7%, placebo 8.3%), and hypertension (baricitinib 2.2%, placebo 1.2%).
- A higher proportion of patients had AEs of infections in the placebo arm (10% [n=50]) than the barcinib arm (6% [n=32]).
- An increase in thrombotic events was observed in the baricitinib arm compared to the placebo arm. Overall 21 patients (4%) in the baricitinib arm had a thrombic event compared to 16 patients (3%) in the placebo arm. Five patients (1.0%) in the baricitinib arm had a serious pulmonary embolism compared to 1 patient in the placebo arm (0.2%). The risk of thromboembolism has previously been identified as a risk with the use of baricitinib; more thrombotic events were observed with the higher dose (4 mg) of baricitinib in clinical trials in patients with rheumatoid arthritis as compared to placebo. The Warnings/Precautions sections of the Fact Sheet will provide wording that clearly describes the risk for thrombosis including an increased risk for thrombotic events including pulmonary embolism.
- Discontinuations due to AE in the ACTT-2 clinical trial were higher in the placebo arm (11.6%) compared to baricitinib arm (6.7%). The most common AEs leading to treatment discontinuation in the baricitinib arm were due to infections, investigations (elevations in liver enzymes), respiratory events, renal and urinary disorders (acute kidney injury) and thrombotic events (pulmonary embolism, deep vein thrombosis). The types of adverse events leading to discontinuation were similar in the baricitinib and placebo arm.

Summary of safety in ACTT-2 is presented in Table 8.

Table 8. Summary of Safety in ACTT-2

	placebo + remdesivir N=509 n (%)	baricitinib + remdesivir N=507 n (%)
Subjects with at least one:		
Adverse Event (AE)	242 (48)	210 (41)
Grade 3-4 AE	238 (47)	207 (41)
Serious Adverse Event (SAE)	103 (20)	77 (15)
SAE/AEs with fatal outcome[a]	31 (6)	19 (4)
All Cause Mortality	37 (7)	23 (5)
AE leading to discontinuation of study drug	59 (12)	34 (7)
Infections	50 (10)	32 (6)
Thrombotic events	16 (3)	21 (4)
Pulmonary Embolism	2[b] (<1%)	5 (1%)

N=Number of subjects in the As Treated population
[a] Reflects SAE and AE that started after the first dose of study treatment and were considered treatement emergent events with a fatal outcome.
[b]One pulmonary embolism was reported as non-serious.
Source: Reviewer, adapted from Table 10.4, 10.5 Sponsor's request for Emergency Use Authorization and Information Request 10/19/2020.

- The Sponsor provided analysis of safety with baricitinib compared to placebo with background use of corticosteroids. While a higher proportion of patients receiving corticosteroids had infections and serious infections, no increase in serious infection were observed in patients receiving corticosteroids, remdesivir and baricitinib compared to patients receiving corticosteroids and remdesivir alone. Conclusions based on the risk of background corticosteroid treatment, however, is limited by the lack of information on the corticosteroid use, dose and duration as well as the small number of patients with available data in this subgroup.
- The ACTT-2 study protocol included temporary interruption of study treatment with resumption of study treatment when the criteria was no longer met for:
    - Total white blood cells (WBC) <1000 cells/μL
    - Absolute neutrophil count (ANC) <500 cells/μL
    - Absolute lymphocyte count (ALC) <200 cells/μL
    - ALT or AST >5 times ULN
    - Infection that, in the opinion of the investigator, merits study drug being withheld
    - eGFR < 30 mL/min, resume when eGFR returns to ≥ 30 mL/min. Oral study drug and remdesivir would be discontinued if renal function worsened and hemodialysis or hemofiltration was required,.
- The safety profile observed in patients with COVID-19 in the ACTT-2 clinical trial was consistent with the known safety profile for baricitinib. Baricitinib is a JAKi and a potent immunosuppressant. The warnings and precautions section

of the fact sheet will include wording reflecting the known risks associated with baricitinib.

X. Specific Populations

- No data is currently available for children or pregnant or lactating women with COVID-19 treated with baricitinib.
- The safety and tolerability of baricitinib 4 mg was assessed in 91 patients (range 6 years - 17 years with median age 14 years of age) enrolled in ongoing Study 14V-MC-JAHV.Total patient years of exposure from this study is 24.98 patient-years. Safety and tolerability of the 4 mg dose was also evaluated in 27 patients (20 patients aged 10 years 17 years, and 7 patients aged 6 years - 9 years of age) who participated in a 14 day, open-label, PK lead-in ongoing study 14V-MC-JAIP. In both ongoing studies there were no deaths, venous thrombotic events, MACE, TB or serious herpes zoster events reported. Safety and tolerability was also assessed in 71 pediatric patients with type 1 interferonopathies in study 14V-MC-JAGA. The mean duration of exposure was 1.8 years. The mean dose in this clinical trial was 6 mg/day and the study period is up to 7 years. The reported AEs in the clinical trial were consistent with safety profile for baricitinib and expected in patients with serious interferonopathies.
- The recommended dose for pediatric patients 9 years to <18 years of age is 4 mg of baricitinib once daily dose for 14 days or until hospital discharge, whichever occurs first. The recommended dose for pediatric patients 2 years to < 9 years of age is 2-mg of baricitinib once daily dose for 14 days or until hospital discharge, whichever occurs first.
- Renal function was found to significantly affect baricitinib exposure. The recommended dose of baricitinib in patients 9 years of age and older with moderate renal impairment is 2 mg once daily. The recommended dose of baricitinib in pediatric patients 2 to < 9 years of age with moderate renal impairment is 1 mg once daily. The recommended dose of baricitinib in patients 9 years of age and older with severe renal impairment is 1 mg once daily. Baricitinib is not recommended for patients on dialysis or those who develop acute kidney injury.
- No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Baricitinib has not been studied in adult or pediatric patients with severe hepatic impairment. Baricitinib should only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk. It is not known if dosage adjustment is needed in patients with severe hepatic impairment.
- Embryo-fetal toxicities were observed in animal studies when dosed at an excess of the maximum human exposure. These toxicities included skeletal

anomalies and reduced fertility in animals. These are not considered clinically relevant to the proposed duration of 14-day dosing of baricitinib.

XI. Human Clinical Pharmacology

- Pharmacokinetics

The PK of baricitinib is not available in patients with COVID-19. The following absorption/distribution/metabolism/elimination (ADME) information of baricitinib is listed from the approved label of NDA 207924:

Following oral administration of OLUMIANT, peak plasma concentrations are reached approximately at 1 hour. A dose-proportional increase in systemic exposure was observed in the therapeutic dose range. The pharmacokinetics of baricitinib do not change over time. Steady-state concentrations are achieved in 2 to 3 days with minimal accumulation after once-daily administration.

- Absorption – The absolute bioavailability of baricitinib is approximately 80%. An assessment of food effects in healthy subjects showed that a high-fat meal decreased the mean AUC and Cmax of baricitinib by approximately 11% and 18%, respectively, and delayed the tmax by 0.5 hours. Administration with meals is not associated with a clinically relevant effect on exposure. In clinical studies, OLUMIANT was administered without regard to meals.

- Distribution – After intravenous administration, the volume of distribution is 76 L, indicating distribution of baricitinib into tissues. Baricitinib is approximately 50% bound to plasma proteins and 45% bound to serum proteins. Baricitinib is a substrate of the Pgp, BCRP, OAT3 and MATE2-K transporters, which play roles in drug distribution.

- Elimination – The total body clearance of baricitinib is 8.9 L/h in patients with RA. Elimination half-life in patients with rheumatoid arthritis is approximately 12 hours.

- Metabolism – Approximately 6% of the orally administered baricitinib dose is identified as metabolites (three from urine and one from feces), with CYP3A4 identified as the main metabolizing enzyme. No metabolites of baricitinib were quantifiable in plasma.

- Excretion – Renal elimination is the principal clearance mechanism for baricitinib through filtration and active secretion as baricitinib is identified as a substrate of OAT3, Pgp, BCRP and MATE2-K from in vitro studies. In a clinical pharmacology study, approximately 75% of the administered dose was eliminated in the urine, while about 20% of the dose was

eliminated in the feces. Baricitinib was excreted predominately as unchanged drug in urine (69%) and feces (15%).

- Drug interactions

There were no clinically meaningful changes in the pharmacokinetics of simvastatin, ethinyl estradiol, or levonorgestrel (CYP3A substrates), digoxin (Pgp substrate) or methotrexate (substrate of several transporters) when co-administered with baricitinib. There were no clinically meaningful changes in the pharmacokinetics of baricitinib when co-administered with fluconazole (CYP3A/CYP2C19/CYP2C9 inhibitor), methotrexate (substrate of several transporters), cyclosporine (Pgp and BCRP inhibitor), diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential), or rifampicin (CYP3A inducer).

o Organic anion transporter 3 inhibitor probenecid

The same dosing strategy (i.e., 2 mg once daily) is recommended by the reviewer in COVID-19 patients taking probenecid as a concomitant medicine as in the approved label of NDA 207924.

Refer to the approved label of NDA 207924, "*in a clinical study, probenecid administration (strong OAT3 inhibitor) resulted in an approximately 2-fold increase in baricitinib AUC0-inf with no effect on Cmax and tmax*". Therefore, the label recommends "*the dose of OLUMIANT in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (e.g., probenecid) is 1 mg once daily*".

Upon FDA's recommendation, the Sponsor agreed to adjust baricitinib dosage in patients taking strong OAT3 inhibitors (such as probenecid) as reflected in the factsheet:

- If the recommended dose is 4 mg once daily, reduce dose to 2 mg once daily.
- If the recommended dose is 2 mg once daily, reduce dose to 1 mg once daily.
- If the recommended dose is 1 mg once daily, consider discontinuing probenecid.

o Remdesivir

There is unlikely a drug-drug interaction between remdesivir and baricitinib at PK level.

Regarding the approved label of NDA 214787, In vitro, remdesivir is a substrate for drug metabolizing enzyme CYP3A4, and is a substrate for OATP1B1 and P-gp transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.

Regarding the approved label of NDA 207924, renal elimination is the principal clearance mechanism for baricitinib and only 6% of the orally administered baricitinib dose is identified as metabolites. In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). In clinical pharmacology studies there were no clinically meaningful effects on the PK of of simvastatin, ethinyl estradiol, or levonorgestrel (CYP3A substrates), digoxin (Pgp substrate) or methotrexate (substrate of several transporters) when co-administered with baricitinib.

- Corticosteroids

There is unlikely a drug-drug interaction between baricitinib and corticosteroids at PK level.

Corticosteroids are commonly prescribed for more severe COVID-19 cases. Some major CYP enzymes including CYP3A4 are involved in metabolism of commonly prescribed corticosteroid such as dexamethasone and prednisone. However, baricitinib did not significantly inhibit or induce the activity of the major CYP enzymes in vitro. In addition, clinical studies did not find that baricitinib has clinically meaningful effect on CYP3A substrates (simvastatin, ethinyl estradiol, or levonorgestrel).

- Hepatic impairment

Refer to the approved label of NDA 207924, "b*aricitinib systemic exposure and Cmax increased by 1.19- and 1.08-fold for the moderate hepatic impairment group, respectively, compared to subjects with normal hepatic function. Baricitinib has not been studied in subjects with sever hepatic function."* Therefore, the Sponsor proposed in the EUA that (b) (4) *Baricitinib has not been studied in patients with severe hepatic impairment. Baricitinib should only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk. It is not known if dosage adjustment is needed in patients with severe hepatic impairment*."

- Renal impairment

Refer to the approved label of NDA 207924, *"baricitinib systemic exposure in AUC was increased by 1.41-, 2.22-, 4.05- and 2.41-fold for mild, moderate, severe, and ESRD (with hemodialysis) renal impairment sub-groups, respectively, compared to subjects with normal renal*

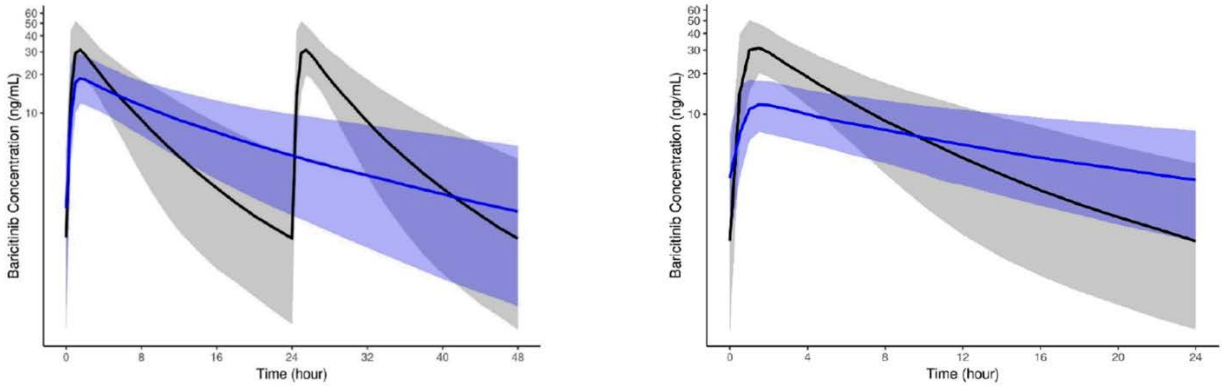
function. The corresponding values for increase in Cmax were 1.16-, 1.46-, 1.40- and 0.88-fold, respectively".

Therefore, the approved label of NDA 207924 recommends "*dose of OLUMIANT in patients with moderate renal impairment (estimated glomerular filtration rate (GFR) between 30 and 60 mL/min/1.73 m^2) is 1 mg once daily".*

The reviewer considers Sponsor's proposed half dose strategy in patients with moderate renal impairment (i.e., 2 mg once daily dose in patients 9 years age and older and 1 mg once daily dose in pediatric patients 2 to <9 years of age) is acceptable.

In patients 9 years of age with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2) and pediatric patients 2 years to < 9 years with moderate impairment, the Sponsor proposed either 1 mg QD or 2 mg QOD regimen. The simulated PK profiles following either 2 mg QOD or 1 mg QD in adults with severe renal impairment were provided by the Sponsor in response to IR dated October 23, 2020 (Figure 4).

Figure 4. Comparison of PK Profiles Following Two Dosing Regimens



Comparison of PK profiles following two dosing regimens (left: first 2-day PK profile following 2 mg QOD; right: first day PK profile following 1 mg QD) in adults with severe renal impairment (blue line and blue shade representing 90% prediction interval) and PK profile following 4 mg QD in adults with normal renal function (black line and grey shade representing 90% prediction interval).
Source: response to IR dated October 23, 2020, page 31, Figure 4.1)

Based on the results obtained from Study JADL, the reviewer estimated that at steady state, the mean Cmax and AUC values following 1 mg QD regimen in patients with severe renal impairment would match to about 52% and 101% of the values of Cmax and AUC following 4 mg QD in patients with normal renal function. On the other hand, although the steady state mean Cmax and AUC values following 2 mg QOD regimen in patients with severe renal impairment would match to about 73% and 101% of the values of Cmax and AUC following 4 mg QD in patients with

normal renal function, the Cmax only occur every other day. It is estimated that the highest baricitinib concentration on the second day following 2 mg QOD regimen in patients with severe renal impairment is only about 22% of the Cmax value following 4 mg QD regimen in patients with normal renal function. The second day AUC value following 2 mg QOD regimen in patients with severe renal impairment is only about half the AUC value following 4 mg QD regimen in patients with normal renal function.

By considering the following factors:

- Baricitinib is a reversible JAK inhibitor.
- The ex vivo IC50 value (as measured inhibition of STAT3 phosphorylation status from peripheral blood cells in healthy subjects) is close to the Cmax value following the approved 2 mg QD regimen in RA adults.
- The QOD regimen was not investigated in adult RA clinical program.
- The baricitinib dose-response curve in adults with RA is projected to a steeper decline when the dose is lower than 1 mg (approved dose is 2 mg).

There are uncertainties related to the efficacy on the every second day (the non-dosing day) following 2 mg QOD regimen in patients with severe renal impairment due to a much lower systemic exposure of baricitinib on the every second day compared to patients with normal renal function following 4 mg QD regimen. Therefore, the reviewer recommended 1 mg QD regimen in adult and pediatric patients 9 years and older with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2) and pediatric patients 2 to < 9 years of age with moderate renal impairment (eGFR 30 - <60 mL/min/1.73 m^2).

Due to the different baricitinib PK profiles in patients of ESRD with and without hemodialysis, and the uncertainty of the hemodialysis schedule in patients with COVID-19, Sponsor's recommendation not to use baricitinib in patients who are on dialysis is reasonable. Further, acute kidney injury with rapid deterioration of renal function has been reported in patients with COVID-19, who may need dialysis during the course of the disease. Baricitinib dose adjustment may not catch up with the rapid dynamic deterioration of eGFR. Therefore, Sponsor's recommendation in patients who have acute kidney injury (i.e., is not recommended) is also reasonable.

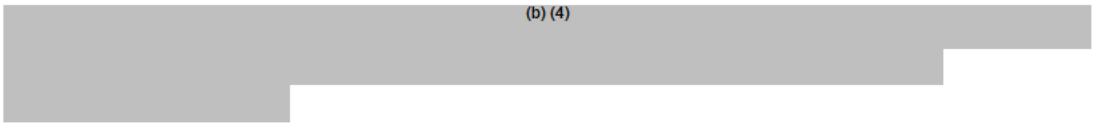
- Pediatric patients

The PK of baricitinib is not available in pediatric patients with COVID-19. However, the PK of baricitinib has been evaluated in pediatric patients

with juvenile idiopathic arthritis (JIA), atopic dermatitis (AD), and diseases referred to as type I interferonopathies. At the investigated dosing regimens in pediatric patients, the exposure of baricitinib is within the same range with that in adult patients in the respective indications, as detailed in this section below. Further, there are no known COVID-19-specific pathophysiological differences which can significantly impact the ADME profile of baricitinib between adult and pediatric patients with COVID-19. Therefore, it is reasonable to estimate the PK and dosing in pediatric patients with COVID-19 from adults with COVID-19 based on the PK relationship established between adult and pediatric patients in other indications.

- Adult RA/pediatric juvenile idiopathic arthritis (JIA) program

  The Sponsor currently has a pediatric juvenile idiopatic arthritis (JIA) study (Study JAHV) ongoing in Europe. The investigated dose in Study JAHV is 4 mg QD in pediatric patients 9 years to <18 years of age and 2 mg QD in pediatric patients 6 years to < 9 years of age. (b) (4)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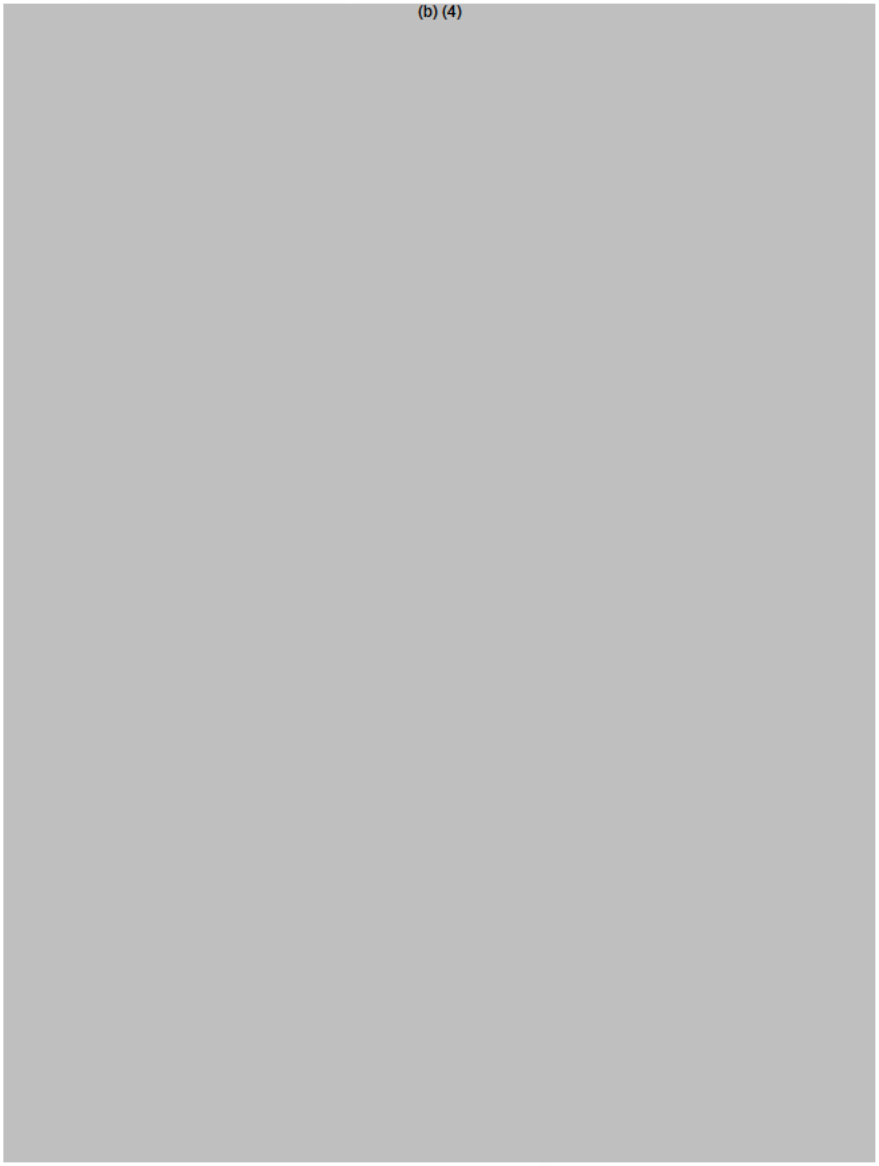
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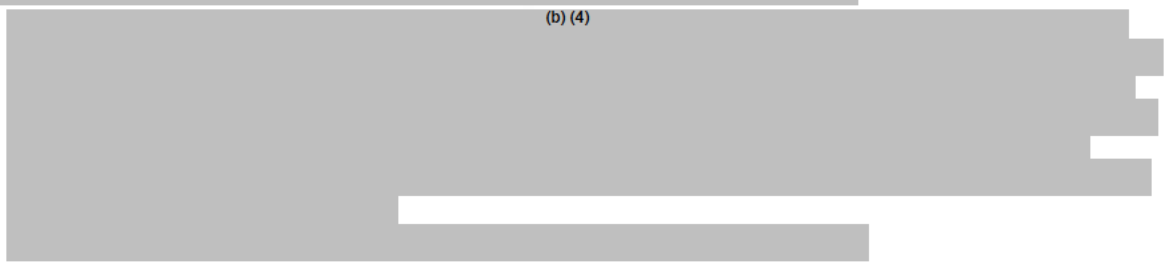
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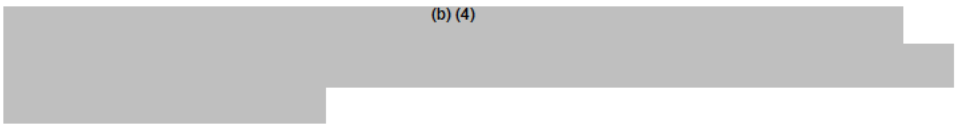
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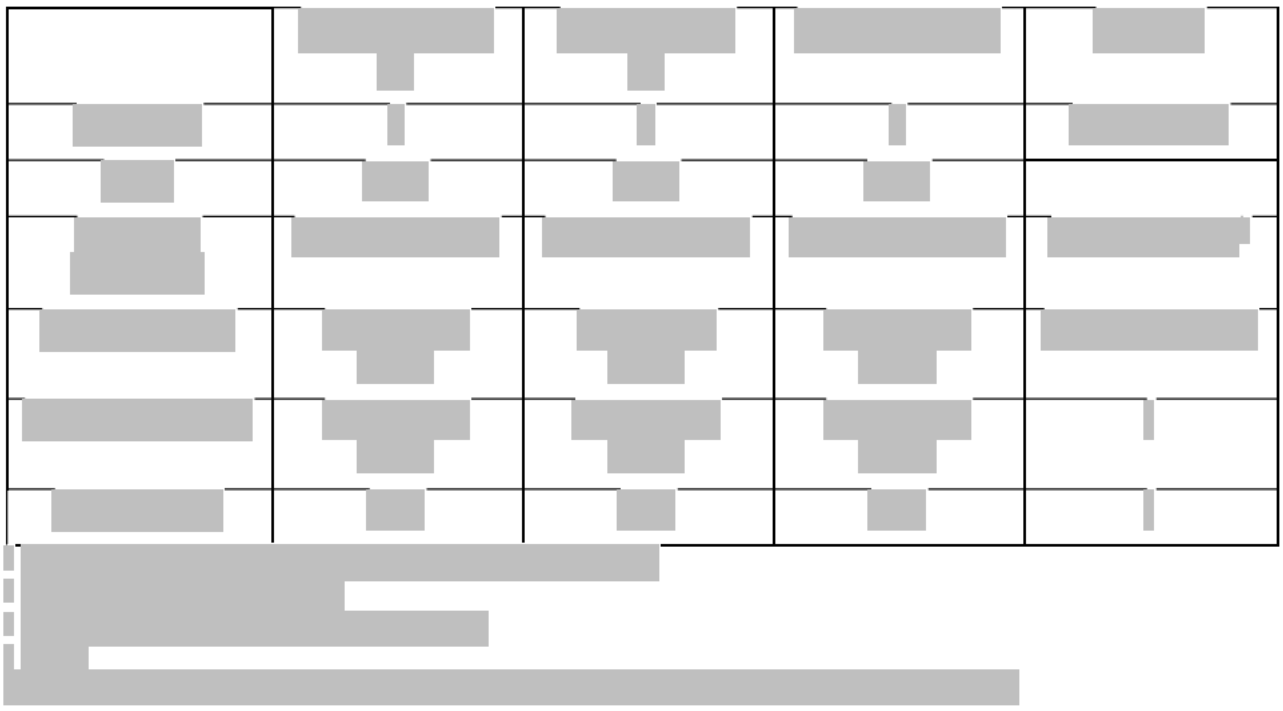

- Adult/pediatric atopic dermatitis (AD) program

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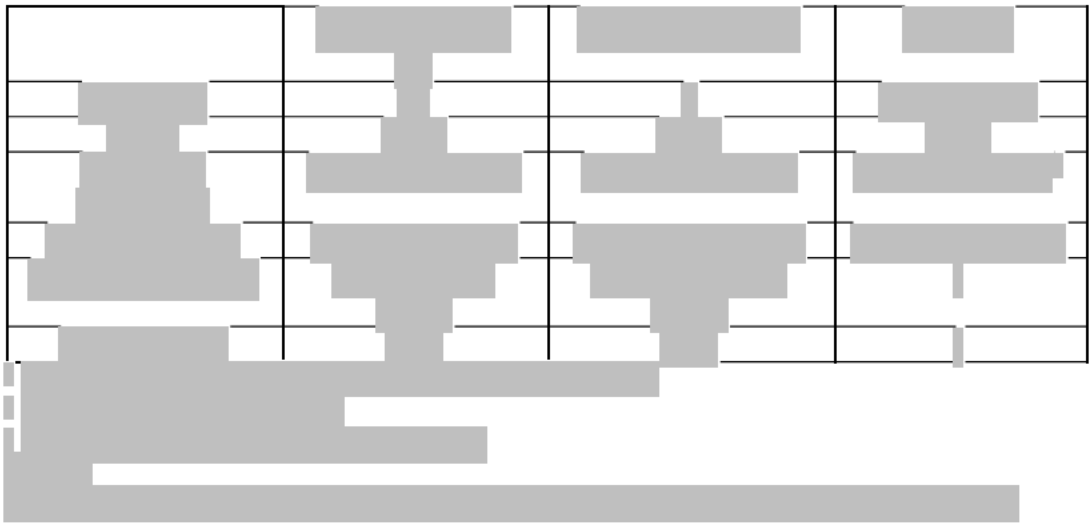

(b) (4)

- Adult/pediatric type I interferonopathies

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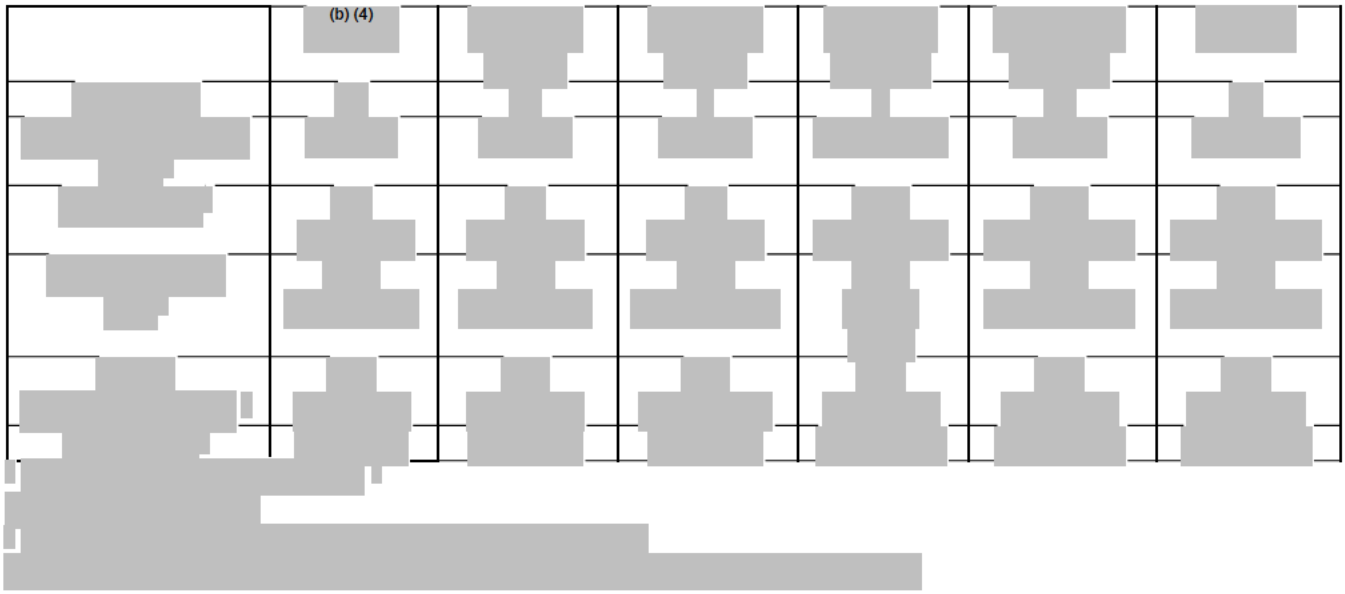

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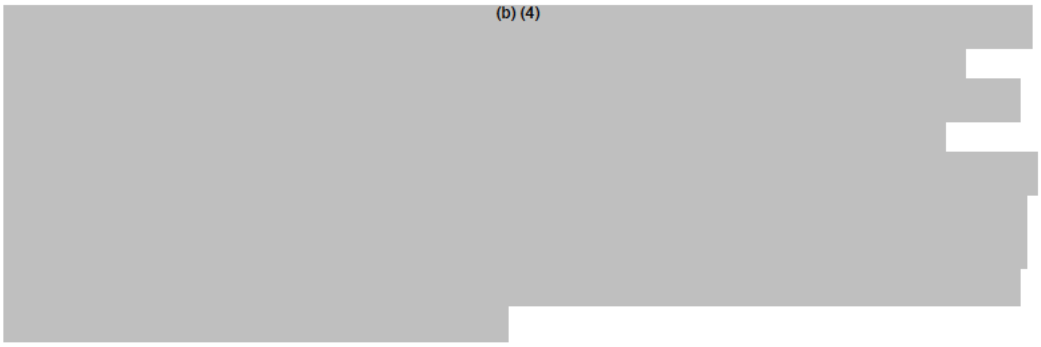

- Physiologically based pharmacokinetic (PBPK) modeling

The Sponsor conducted a PBPK modeling to predict the baricitinib PK in pediatric subjects 2 years of age and older. The Sponsor's approach was to match the baricitinib exposure in pediatric subjects with those observed in adult patients with RA following 4 mg QD regimen. The Sponsor previously submitted a PBPK model for adult healthy volunteers (HVs) under NDA 207924 which was deemed adequate. In this EUA submission, the Sponsor revised the PBPK model and simplified the kidney model where the clearance obtained from adults with RA was incorporated into the PBPK model. The revised PBPK model was then coupled with the virtual pediatric populations developed by Simcyp to predict the baricitinib PK in pediatric populations (2 years -18 years of age). In response to FDA's IR dated on October 19, 2020, the Sponsor repeated the analysis using the originally developed HV model which incorporated a mechanistic kidney model to capture the ontogeny of

OAT3 (a transporter involved in baricitinib' s excretion). The Sponsor compared the predicted baricitinib PK with the observed PK in pediatric patients with JIA, AD, and type I interferonopathies, and simulated target exposure in adults with RA following 4 mg QD.

As previously mentioned, due to the known disease's effect on baricitinib PK, cross-disease PK comparison might not be appropriate and within 'disease group' comparison approach was adopted. Three PBPK models were tested by the reviewer: (1) linear renal and non-renal clearance obtained from HVs; (2) linear renal and non-renal clearance obtained from adults with RA; and (3) mechanistic renal and non-renal (assigned to CYP3A) clearance obtained from HVs. Simulations were conducted for age groups 2 yrs - 6 yrs, 6 yrs -9 yrs, 9 yrs -12 yrs, 12 yrs -18 yrs of age, and adults. The model predictions were compared to the observed PK in adult HVs, adult patients with RA, pediatric subjects (6 yrs-18 yrs) with JIA as JIA is considered as a similar disease as RA in adults. Overall predicted vs. observed AUCtau,ss (the AUC for a dosing internal, i.e., 24 hours, at steady state) and Cmax,ss ratios were within the range of 0.5-1.5.

Simulations using the linear clearance models suggested that within the same 'disease group', in general, the exposure in pediatric subjects 9 years -18 years of age is within 2-fold of that in adults, and the exposure in pediatric subjects 2 years - 9 years of age is about 2-3-fold of that in adults following the same dosing regimen (i.e., 4 mg once daily). Simulated exposures using the mechanistic kidney model are generally higher than those using the linear clearance model. Using the mechanistic kidney model, the simulated exposure in pediatric subjects 9 years - 18 years of age is within 2.1-fold of that in adults, and the exposure in pediatric subjects 2 years - 9 years of age is about 3-4-fold of that in adults following the same dosing regimen. Overall, simulations supported the proposed dosing regimens in pediatric populations.

In conclusion, the proposed dose in pediatric patients with COVID-19 (i.e., 4 mg in pediatric patients 9 years to <18 years if age and 2 mg in pediatric patients 2 years to < 9 years of age) is reasonable based on the considerations that the disease in adults and pediatric patients is sufficiently similar once patients progress to require supplemental oxygen, invasive mechanical ventilation, or ECMO, and that there are no known COVID-19-specific pathophysiological differences which can significantly impact the ADME profile of baricitinib between adult and pediatric patients with COVID-19. The pediatric AUC values following the proposed doses are expected to be within the adults' reference range. The Cmax values in most pediatric patients are expected to be within the adults' reference range with some values in pediatric patients 9 years to < 11 years of age distributed at the high end of adults' reference range.

For discussion related to dose adjustment in pediatric patients with renal impairment, refer to section of "Assessment of baricitinib in patients with renal impairment".

- Assessment of baricitinib with alternate administration

It is unlikely the compounding process and administration via gastrotomy tube or nasogastric tube will significantly affect the bioavailability of baricitinib.
For patients who are unable to swallow whole tablets (including children), the Sponsor proposed alternate administrations:

- Oral dispersion
- Gastrostomy tube (G tube)
- Nasogastric tube (NG tube)

Procedure for preparation of alternate administration is listed below:

- Swirl to disperse whole tablets in room temperature water using at least the minimum dispersion volume in Table 12 below.

- Intact tablets are not hazardous. Tablets may be crushed to facilitate dispersion. It is not known if powder from the crushed tablets may constitute a reproductive hazard to the preparer. Use proper control measures (e.g. ventilated enclosure) or personal protective equipment (i.e. N95 respirator). Ensure complete transfer of crushed tablet.

- Ensure appropriate dispersion for administration and administer immediately.

- Rinse container using at least the minimum rinse volume in Table XI.6 below and administer immediately.

Table 12. Minimum Dispersion and Rinse Volume for Alternate Administration

Administration via	Dispersion Volume	Container Rinse Volume
Oral dispersion	10 mL	10 mL
Gastrostomy tube (G tube)	15 mL	15 mL
Nasogastric tube (NG tube)	30 mL	15 mL

Source: annotated-eua-factsheet-hcp.pdf, page 4, Table 2.

Division of Biopharmaceutics have examined section 13.2.2 (Alternate Administration) of the Sponsor's EUA application and module 3.2.P.2 (Pharmaceutical Development) of IND 102204 (SDN 420, submitted April 30, 2020) that address the plan to administer baricitinib as a suspension to patients who cannot swallow the tablet. The suspension is prepared by crushing the tablet(s) and dispersing in a predetermined volume of water,

depending on the dose or number of tablets. The suspension may be administered orally or via a nasogastric tube. On pages 10 and 24 of the pediatric study plan for JIA indication submitted under IND 102204 SDN 438 on August 21, 2020, the Sponsor states that the orally administered 4 mg/2 mL suspension (a pediatric formulation with composition listed on page 26) has been demonstrated in an in vivo pharmacokinetic study to be bioequivalent to the 4 mg tablet. Therefore, the administration of the baricitinib suspension via a nasogastric tube is expected to provide bioavailability similar to the tablet. There is no concern from a biopharmaceutics perspective (See Section XV for additional details).

XII. Nonclinical Data to Support Safety

- Nonclinical studies with baricitinib were previously reviewed under NDA 207924 to support the approval of OLUMIANT (Dated in DARRTS November 18, 2016; Authored by Dr. Matthew Whittaker)
- Nonclinical studies in adult animals identified immunosuppressive effects (e.g. decreased peripheral blood leukocytes and lymphoid depletion/atrophy in the bone marrow, spleen, lymph nodes) as the major treatment-related toxicities. Development of demodicosis (mange) in dogs was attributed to immunosuppression. Dose limiting toxicities were identified in the gastrointestinal tract (inflammation, infiltrates) and liver (infiltrates/inflammation, bile duct hyperplasia).
- In embryofetal development studies, baricitinib was teratogenic (skeletal malformations including bent limb bones and rib anomalies) in both rats and rabbits. No observed adverse effect levels were identified that provide safety margins for baricitinib as an oral therapy in adults at 4 mg/day.
- (b) (4)

(b) (4)

- The nonclinical data provides coverage for the use baricitinib as an oral therapy for the treatment of COVID-19 in adults at 4 mg/day.

XIII. Nonclinical Data to Support Efficacy

- JAKs serve as transducers of extracellular signals from multiple cytokines and growth factors that are involved in inflammatory diseases (e.g., rheumatoid arthritis). Inhibition of JAK enzymes is a therapeutic strategy for treatment of this condition.
- Baricitinib was developed to inhibit intracellular signaling pathways associated with cytokine receptor activation through selective inhibition of JAK1 and JAK2. In in vitro pharmacology studies, baricitinib showed selectivity for JAK1 and JAK2 relative to JAK3 and TYK2. These effects were not recapitulated in cell-based assays conducted in human leukocyte preparations, which demonstrated inhibition of JAK1, JAK2, JAK3, and TYK2, but no selectivity for JAK1 and JAK2 relative to JAK3 and TYK2.
- Baricitinib inhibited IL-2 induced phosphorylation of JAK2, STAT3 and STAT5 with IC_{50} values between 3 – 30 nM in human T cells and inhibited IL-2 stimulated T-cell proliferation with an IC_{50} of approximately 29 nM
- There are no directly relevant animal studies showing that baricitinib inhibits cytokine release in the context of SARS-CoV-2 infection.

XIV. Supply Information

- For patients 9 years and older, two tablets are needed for treatment
- For patients 2 years to less than 9 years of age, one tablet is needed for treatment.
- One treatment course is14 days or until a patient is discharged from the hospital whichever occurs first.
- Lilly indicates that the annual US demand for Olumiant is approximately (b) (4) 2-mg tablets for treatment of RA. There currently are (b) (4) Olumiant 2-mg commercial 30-count oval bottles (b) (4) tablets) for US supply that would be available for the EUA (2 x 2-mg tablet = 4-mg daily dose). Additional production of roughly (b) (4) 2-mg tablets is anticipated through the rest of 2020 to support the expected US demand for COVID-19 treatment. Lilly confirms adequate supply of 1-mg tablet is available for distribution to treat patients with COVID-19 and severe renal impairment if emergency use is authorized.

XV. Chemistry, Manufacturing, and Controls Information

- The EUA product is the approved drug products of NDA 207924, which are 1 a 2 mg tablets of baricitinib for oral administration, with Proprietary name OLUMIANT.
- OLUMIANT tablets are composed of baricitinib and the following inactive ingredients: microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate (b) (4) polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, lecithin (soya), and ferric oxide.
- The Sponsor submitted *in vitro* data to support the dispersion of the tablets in room temperature water and delivery by oral administration or by a gastrostomy (see 30-APR-2020 amendment of IND 102204), nasogastric or orogastric tubes (see 10-NOV-2020 amendment of IND 102204), of various sizes and compositions.

  Dispersed in 5 mL of water with a 5 mL rinse, a 1 mg (n=3) tablet provided 99.2-100.7% and three 2 mg tablets (n = 3) provided 95.9-97.8% of the target doses for **oral administration.** Dispersed in 10 mL of water with a 10 mL rinse, a 1 mg tablet (n = 3) provided 97.8-100.7% and three 2 mg tablets (n = 3) provided 95.8-98.6% of the target doses for **oral administration**. These solutions were demonstrated to have sufficient stability for up to 4 hours.

  The G tubes were silicone (12 and 24 FR) and polyurethane (12 and 20 FR) and NG/OG enteral tubes studied were silicone (8 Fr), polyvinylchloride (PVC, 16 Fr), and polyurethane (8 Fr). Tube lengths were the maximum available to represent the worst case with regard to internal surface area.

  The G, NG/OG tube study results are summarized in the table P.2.3-4 below reproduced from the 10-NOV-2020 amendment.

Table P.2.3-4 Summary of Enteral Tube Study

Tablet	Silicone size, type, (dispersion/rinse vol.)	Polyurethane size, type, (dispersion/rinse vol.)	PVC size, type, (dispersion/rinse vol.)
1 x 1-mg	**8 Fr**, NG/OG (20/10 mL or 25/5 mL) **12 Fr**, G (15/15 mL or 10/10 mL) **24 Fr**, G (15/15 mL or 10/10 mL)	**8 Fr**, NG/OG (20/10 mL or 25/5 mL) **12 Fr**, G (15/15 mL or 10/10 mL) **20 Fr**, G (15/15 mL or 10/10 mL[a])	**16 Fr**, NG/OG (20/10 mL or 25/5 mL)
1 x 2-mg	8 Fr, NG/OG (25/14 mL)[b]	**8 Fr**, NG/OG (30/14 mL or 25/14 mL)	NS
2 x 2-mg	8 Fr, NG/OG clog[c]	8 Fr, NG/OG (30/15 mL[d])	**16 Fr**, NG/OG (30/15 mL or 25/15 mL)
3 x 2-mg	**12 Fr**, G (15/15 mL or 10/10 mL) **24 Fr**, G (15/15 mL or 10/10 mL)	**12 Fr**, G (15/15 mL or 10/10 mL) **20 Fr**, G (15/15 mL or 10/10 mL)	NS
Material of Construction Compatibility	Pass (24 Fr, G)	Pass (20 Fr, G)	Pass (16 Fr, NG/OG)

NS= not studied.

[a] Robustness study (10 mL dispersion/10 mL rinse) did not meet protocol criterion of 95% to 105% for 1 x 1mg tablet in 20 Fr G-tube, however, were within 90% to 110% considered acceptable per EMA guidance.

[b] Robustness study (25 mL dispersion /14 mL rinse) passed. Nominal volume study (30/14 mL) had a replicate clog, but three replicate data generated suggests as long as tube does not clog, the dose will be delivered.

[c] One replicate at each condition of nominal and reduced dispersion volume clogged and study was not continued.

[d] Robustness study (25 mL dispersion/15 mL rinse) had a replicate clog and study was not continued.

From the above table it is evident that adequate 1 x 1 mg target doses could be delivered by all of the types and sizes of G, NG/OG tubes studied. However, for both the 1 x 2 mg and 2 x 2 mg target doses, there was some tube clogging observed for the 8 Fr silicone tube and for the 2 x 2 mg target dose with the 8 Fr polyurethane tube.

Samples were found to be compatible in the silicone 24 Fr and polyurethane 20 Fr G tubes for up to 30 minutes, still providing doses within 90-110% of the targets of 1 and 6 mg. Samples of 1 x 1 mg and 2 x 2 mg doses were compatible in PVC 16 Fr NG/OG tubes for up to 30 minutes as well, providing 99% of the average doses as compared to the doses that were delivered immediately.

In summary, for silicone and polyurethane G and NG/OG tubes, the minimum size that provides adequate delivered doses are 12 Fr and larger. For PVC NG/OG tubes, the Sponsor only studied the 16 Fr size, but these could achieve delivered target doses of 1 x 1 mg, 2 x 2 mg.

Table 2 of the healthcare provider factsheet is reproduced below and it provides the following dispersion and rinse volumes of room temperature water to use for alternate administration by oral dispersion, G, or NG tubes:

Administration via	Dispersion Volume	Container Rinse Volume
Oral dispersion	10 mL	10 mL
Gastrostomy tube (G tube)	15 mL	15 mL
Nasogastric tube (NG tube)	30 mL	15 mL

The Sponsor proposes the following additional instructions for NG/OG tube administration (from the 10-NOV-2020 IND 102204 amendment):

"***Administration via nasogastric feeding tube:***

For patients with an enteral feeding tube, 1-mg, 2-mg (b) (4) *baricitinib tablet(s), or a combination of tablets necessary to achieve the desired dose may be placed into a container with approximately 30 mL of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw the entire contents from the container into an appropriate syringe and immediately administer through the enteral feeding tube. To avoid clogging of small diameter tubes, the syringe can be held horizontally and shaken during administration. Rinse container with a sufficient amount (minimum of 15 mL) of room temperature water, withdraw the contents into the syringe, and administer through the tube.*"

From a quality perspective, the results of the various alternate administration studies provide reasonable support for the dispersion/rinse volumes and the additional NG tube instructions, however, depending on the likelihood that G, NG/OG tubes of diameters less than 12 Fr are used in a clinical setting, it is reasonable to include a description of the tube size in the above instructions, e.g., "*To avoid clogging of small diameter tubes (i.e., less than 12 Fr), the syringe can be held horizontally and shaken during administration.*"

Refer to section XI above for the clinical pharmacology/biopharmaceutic perspective regarding the alternative administration methods proposed in the Healthcare Provider fact sheet.

XVI. Manufacturing Site Inspections

Table 13. provides list of all manufacturing sites for drug substance through to the drug product for the EUA product.

Table 13. Manufacturing Sites

Manufac-turing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Sponsor	Inspection Dates	GMP Status (if known)
Eli Lilly S.A. Irish Branch (FEI# 3002806888)	Drug Substance Manufacturing, Control and Stability Testing	County Cork, Ireland	NDA-207924	Eli Lilly and Co.	1/13-17, 2020 (MRA GMP inspection review) 6/13-17, 2016 (PAI, Baricitinib)	Compliant, CSN profile acceptable
Lilly del Caribe, Inc (FEI# current: 3004525072 merged: 2619243)	Drug Product Manufacturing, Control and Stability Testing	Puerto Rico, US	NDA-207924	Eli Lilly and Co.	7/9-12, 2019 (PoAI, TCM) 9/10-21, 2018 (GMP)	Compliant, TCM profile acceptable
Eli Lilly and Company (FEI# 1819470)	Drug Product Packaging	IN, US	NDA-207924	Eli Lilly and Co.	03/16-20, 2020 (BIMO) 5/15-25, 2017 (GMP)	Compliant, TCM profile acceptable

XVII. Clinical Trial Site Inspections

No site inspection was performed or deemed necessary for the COVID-19 study.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

No site inspections were performed or deemed necessary.

XIX. Recommendations From Treatment Guidelines and Other Sources

The NIH COVID-19 Treatment Guidelines (covid19treatmentguidelines.nih.govhttps://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/; as of November 3, 2020) state that, data from randomized controlled trials, prospective and retrospective observation cohorts, and case series studies are rapidly emerging. The guidelines provide recommendations regarding use of remdesivir and/or dexamethasone for hospitalized patients requiring supplemental oxygen, high-flow device or non-invasive ventilation and hospitalized patients requiring invasive mechanical ventilation treatment. The guidelines currently recommend against the use of immununomodulators including Janus kinase inhibitors except in a clinical trial and those guidelines have not been updated. NIH notes that this document will be updated as clinical trial data becomes available.

XX. Benefit-Risk Assessment and Recommendations for Emergency Use

Baricitinib is a Janus kinase inhibitor (JAKi) approved by the FDA for the treatment of rheumatoid arthritis at a dose of 2 mg daily. The safety of baricitinib at 2 mg and 4 mg has been evaluated in clinical trials in patients with rheumatoid arthritis. In addition, clinical trials using chronic doses of baricitinib are ongoing in several other patient populations as part of the Sponsor's development program for other chronic conditions.

The effectiveness and safety of baricitinib in adult patients with COVID-19 infection on a background of remdesivir was evaluated in the NIAID sponsored ACTT-2 trial. This phase 3, double-blind, randomized trial included a total of 1033 hospitalized patients with laboratory-confirmed SARS-CoV-2 infection. Patients were randomized to receive either baricitinib or placebo for 14 days or until discharge on a background of remdesivir. Patients in this trial were classified as having either moderate or severe COVID-19 at baseline. In the topline efficacy data provided, the study met the primary endpoint of time to recovery measured in days. The estimated hazard ratio of 1.15 (intent to treat population, p=0.047) indicated a decrease in time to recovery for the baricitinib arm. Median time to recovery was 7 days in the baricitinib arm compared to 8 days in the placebo arm for a difference of one day in median time to recovery.

The largest decrease in the time to recovery was identified in patients with severe disease who were receiving non-invasive ventilation or high flow oxygen devices (NIAID OS=6) but were not receiving mechanical ventilation or ECMO. A smaller decrease in the time to recovery was also seen in hospitalized patients requiring supplemental oxygen at baseline (NIAID OS=5). No effect was seen for patents who did not require supplemental oxygen at baseline (NIAID OS=4). For patients who were receiving mechanical ventilation or ECMO at baseline (NIAID OS=7), a small decrease in time to recovery was observed; however, there was a large amount of uncertainty in the estimated hazard ratio due to the small sample size.

Furthermore, not enough patients recovered for the median time to recovery to be estimated in this subgroup.

The ACTT-2 trial also evaluated the secondary endpoints of the proportion of patients who died or progressed to non-invasive ventilation/ high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 29, overall improvement on the NIAID-OS evaluated at Day 15, and all-cause mortality (Day 1-Day 29). Additional secondary endpoints that were evaluated included the number of ventilator-free days and duration of hospitalization, though comparative results for these endpoints were not available for the EUA submission. The secondary endpoints of the proportion of patients progressing to mechanical ventilation or mortality through day 29 and overall improvement on the NIAID-OS at Day 15 supported the primary endpoint. A numerical trend was also observed for a reduction in all-cause mortality in patients receiving baricitinib compared to those receiving placebo. This reduction in mortality was not statistically significant but the confidence intervals reflect that an unacceptable increase in mortality is unlikely. The numerical trend for decrease in overall mortality through Day 29 was predominantly observed in the patients in the NIAID-OS=5 and NIAID-OS=6 categories at baseline with no mortality benefit observed in patients receiving mechanical ventilation or ECMO (NIAID-OS=7) at baseline. However, there were fewer patients who were either on mechanical ventilation or dead at Day 29 in the baricitinib group for the NIAID-0S=7 subgroup. These results suggest that, although a mortality benefit was not observed in the subgroup requiring mechanical ventilation or ECMO at baseline, baricitinib may provide some benefit in reduction of time on mechanical ventilation or reduction in the requirement for mechanical ventilation, which are considered clinically meaningful.

In the ACTT-2 clinical trial, baricitinib dosed with background remdesivir did not show an increase in adverse events or serious adverse events compared to patients receiving placebo with background remdesivir. The safety profile of baricitinib in hospitalized patients with COVID-19 was consistent with the safety of baricitinib observed in patients with rheumatoid arthritis. Although baricitinib is an immunosuppressant there was no increase in overall infections observed following 14 days of treatment compared to patients on the placebo arm. A numerical increase in thrombotic events including pulmonary embolism was observed in patients treated with baricitinib, compared to placebo; however the numerical imbalance was based on a small number of events such that there is considerable uncertainty around the observed difference. Further, the overall events of serious respiratory failure were lower in the baricitinib group compared with placebo. In the ACTT-2 study, VTE prophylaxis was recommended unless contraindicated. Information on thromboembolic events and pulmonary embolism from the study will be described in the Fact Sheets along with the Warning on thrombosis and instructions for VTE prophylaxis and monitoring for deep vein thrombosis and pulmonary embolism. The review team concluded that the potential risk of thromboembolic events is adequately conveyed in the Fact Sheets and does not outweigh the potential benefits from the use of baricitinib under this EUA, based on the available data.

The benefits and risks of baricitinib use in adults observed in ACTT-2 study are expected to be similar for pediatric patients 2 years of age or older with COVID-19 requiring supplement oxygen, invasive mechanical ventilation or ECMO, based on the considerations that the disease in adults and pediatric patients is sufficiently similar once patients progress to require supplemental oxygen, invasive mechanical ventilation, or ECMO and that there are no known COVID-19-specific pathophysiological differences which can significantly impact the ADME profile of baricitinib between adult and pediatric patients with COVID-19. The appropriate dosing for pediatric patients is informed by the accumulated PK and safety information with baricitinib in multiple adult and pediatric populations, as detailed in the sections on Human Clinical Pharmacology and Special Populations above.

The standard of care for patients with COVID-19 continues to evolve rapidly. ACTT-2 was not designed to evaluate baricitinib with background use of corticosteroids. In the small subgroup of patients who were receiving corticosteroids at baseline, there were some trends for favorable efficacy and the frequency of adverse events in patients receiving baricitinib was similar to those receiving placebo. However, interpretation of results is difficult given the small sample size and considerable uncertainty around estimates. Given that the study was not designed to evaluate the effect of baricitinib on top of corticosteroids such that there were few patients receiving corticosteroids in the trial, and given that information around dose, timing and duration of corticosteroid use are not available, limited conclusions can be made regarding the efficacy and safety of baricitinib with background corticosteroids to provide specific recommendations. There is currently limited information on the use of baricitinib in combination with systemic corticosteroids for treating patients with COVID-19. However, use of baricitinib in patients receiving corticosteroids is not precluded.

ACTT-2 was also not designed to evaluate baricitinib without background use of remdesivir. While baricitinib may abrogate the hyperinflammatory state resulting from SARS-CoV-2 infection, it is not known how it could impact the anti-viral response. The cytokine response in severe COVID-19 infection is complex, with both beneficial and potentially detrimental effects[6,7]. Given the complexity of the immune response in SARS-CoV-2 infection, it is unclear, based on the review of the available efficacy data in which baricitinib is dosed with background antiviral therapy, if baricitinib may provide a benefit in SARS-CoV-2 without background remdesivir.

Based on the safety and efficacy information available, it is reasonable to believe that baricitinib, in combination with remdesivir, may be effective for the treatment of hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation or ECMO and that the

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[6] Jamilloux Y, et al., Should we stimulate or suppress the immune responses in COVID-19? Cytokine and anti-cytokine interventions, *Autoimmunity Reviews* 2020;19:102567.
[7] Zhou T, et al., Immune asynchrony in COVID-19 pathogenesis and potential immunotherapies, Journal of Experimental Medicine 2020;217 (10).

known and potential benefits of baricitinib, in combination with remdesivir, outweigh its known and potential risks for this population. Therefore, the review Division recommends issuance of an EUA for baricitinib for the treatment of hospitalized adults and pediatric patients 2 years of age or older with COVID-19 requiring supplement oxygen, invasive mechanical ventilation, or ECMO and receiving background remdesivir.

In addition, and per Lilly's request, Lilly intends to use the commercially available baricitinib product for use under the EUA, subject to the conditions of authorization, including conditions related to authorized labeling. FDA is including certain conditions in the Letter of Authorization to ensure suitable quality, including the submission and consideration by FDA of any changes to the manufacturing for the authorized baricitinib. FDA believes that such conditions are necessary to ensure that issues and/or changes do not adversely impact the use of baricitinib under the EUA; for instance, these conditions will help to ensure that notifications from the manufacturer regarding changes to the manufacturing of the authorized product are appropriately directed to the EUA file.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice. If used in clinical trials done under IND, FDA IND safety reporting regulations will apply. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

The prescribing health care provider and/or the provider's designee will be responsible for reporting medication errors and adverse events (death, serious adverse events*) considered to be potentially related to baricitinib occurring during baricitinib treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Baricitinib Treatment under Emergency Use Authorization (EUA)."

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheets for Health Care Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Fact Sheet for Patients, Parents and/orCaregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps

Not applicable.

XXV. References

References are listed in the relevant sections of the review, where applicable.

XXVI. Appendices

Appendix 1. FDA-approved baricitinib labeling from drugs@FDA

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207924s002lbl.pdf

Appendix 2. Submitted Literature Reports are summarized in Table 14.

Table 14. Listing of Published Observational Studies, Retrospective Studies, and Case Reports

Study Number/ Publication	IND, NDA, or Literature Reference	Study Design and Type of Control	Population (N)	Background Therapy	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Outcome
NCT04438629 - Bronte et al. 2020	**Literature**	Open- label observational longitudinal trial; single center	20	hydroxychloroquine and/or lopinavir/ritonavir	4 mg BID x 2 days, 4 mg QD x 7 days 2 mg BID x 2 days, 4 mg QD for 7 days in patients >75 yrs	1 death; Baricitinib-treated patients reportedly had: a reduction in serum levels of IL-6, IL-1β, and TNFα, recovery in circulating T and B cells, and increased antibody production against SARS-CoV-2 spike protein.
Cantini et al. 2020a NCT04358614	**Literature**	Open-label Observational	12	lopinavir/ritonavir, hydroxychloroquine	4 mg QD x 14 days	58% discharged after 2 weeks
Cantini et al. 2020b	**Literature**	Retrospective analysis; multicenter	113 (Baricitinib) 78 (control), moderate pneumonia	Baricitinib group: lopinavir/ritonavir Control group: hydroxychloroquine, lopinavir/ritonavir	4 mg QD x 14 days	After 2 weeks; Baricitinib group: 78% discharged, 0 deaths Control group: 13% discharged, 5 deaths

Lo Caputo et al. 2020	**Literature**	Case report	1 (Family of 4)	lopinavir/ritonavir, hydroxychloroquine	Patient (87 year-old Female) was receiving for >1 year for treatment of RA	Recovered; Family of 4. Two other members of family (husband and son) also received lopinavir/ritonavir and hydroxychloroquine but did not receive baricitinib and died of respiratory failure
Cingolani et al. 2020	**Literature**	Case report	1, 71 year-old, severe respiratory failure	sequential combination of lopinavir/ritonavir, hydroxychloroquine and azithromycin, followed by sarilumab, followed by baricitinib	4 mg QD x 14 days	Recovered
Stebbing et al. 2020	**Literature**	Case report	4	combined oral contraception, losartan, propanol, omeprazole, aspirin, low-molecular-weight heparin, hydrochlorothiazide, inhaled beclomethasone, antibiotics	2 mg to 4 mg for 10 to 12 days	All 4 patients showed improvement with baricitinib treatment in signs and symptoms such as cough, fever, and reduction in plasma IL-6 levels, along with a reduction in the SARS-CoV-2 RNA viral
Titanji et al. 2020	**Literature**	Retrospective Study, uncontrolled	15 patients moderate-to-severe	hydroxychloroquine 200 mg to 400 mg po QD	2 mg to 4 mg QD	3 deaths, 12 recovery
Rodriguez-Garcia et al. 2020	**Literature**	Prospective nonrandomized observational trial	112 total Bari (n= 62)	All on background lopinavir/ritonavir and hydroxychloroquine; one group with corticosteroids only (n=50), one group with corticosteroids + baricitinib (n=62)	2 mg and 4 mg QD x 5-10 days 4 mg once daily if <75 years of age, loading dose of 4 mg followed by 2 mg if ≥75 years old corticosteroids: methylprednisolone at 80, 125, or 250 mg once daily	Greater improvement in pulmonary function with baricitinib + steroids than on steroids alone
Sodani et al. 2020	**Literature**	Case report	1, 50 year-old patient with severe pneumonia and moderate ARDS	Sequential hydroxychloroquine, azithromycin, other antibiotics, baricitinib, tocilizumab, steroids, followed by remdesivir	4 mg QD	Baricitinib 4 mg once daily, steroids, and tocilizumab were added sequentially with partial response. Recovered when remdesivir was added
Source: Adapted from Sponsor's request for Emergency Use Authorization						

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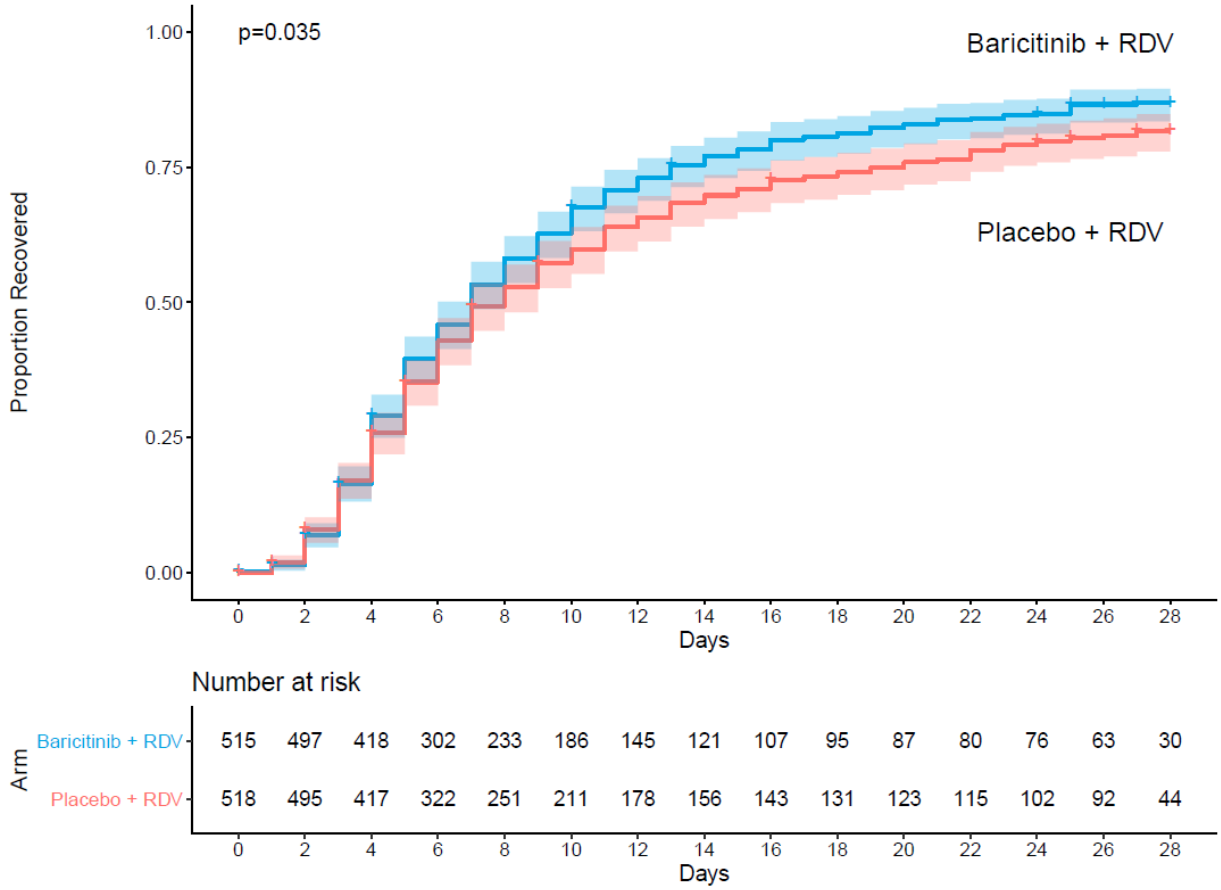
RE: Emergency Use Authorization (EUA) for baricitinib
Addendum: December 14, 2020

This addendum references the summary EUA review for baricitinib for the treatment of hospitalized COVID-19 patients, dated November 19, 2020. Page 10 of the summary EUA review Section VIII, Human Clinical Efficacy, indicated that severe disease in the ACTT-2 study was defined as hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. The definition of severe disease in ACTT-2 included hospitalized patients on non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO but did not include patients on supplemental oxygen. This corrected definition of severe disease replaces the definition in the November 19, 2020 summary EUA review. Randomization stratified by baseline classification disease severity was based on the corrected definition where patients requiring supplemental oxygen were not considered to be severe.

The summary EUA review Section VIII also included a Kaplan-Meier plot for time to recovery (Figure 1). This figure displayed an incorrect p-value of p=0.03 at the top of the Kaplan-Meier plot. A corrected figure shows the p-value to be p=0.035 and replaces Figure 1 in the November 19, 2020 summary EUA review.

Figure 1: Kaplan-Meier Plot for Time to Recovery



Abbreviation: RDV = remdesivir

Source: Appendix 1 (Page 10) of Response to IR (12/10/2020)

The summary EUA in Section VI, Related Regulatory Submission, Page 8, includes an IND cross-reference to NDA 207942. The correct NDA number should be NDA 207924. The summary EUA references study 14V-MC-KHAA. The correct study identification number should be I4V-MC-KHAA. In Section X, Specific Populations, Page 26, three studies are referenced beginning with the study identifier of 14V (14V-MC-JAHV, 14V-MC-JAIP and 14V-MC-JAGA). The correct study identifier for these three studies is I4V.

In Section XI. Human Clinical Pharmacology, procedure for preparation of alternate administration there is a reference to minimum rinse volume for alternate administration. The reference for Table XI.6 should be corrected to Table 12. The corrected bulleted text follows:

- Rinse container using at least the minimum rinse volume in Table 12 below and administer immediately.

The Supporting Document Numbers (SDN) were updated to reflect the correct number. SDN420 should be SDN 438 and SDN 430 should be SDN 456.

In Section IV. Product Information, the bullet stating “description of product as packaged (e.g., round pink tablets in blisters, packaged 6 per card, with code “ASD” debossed on one side)” is incorrect and should be removed.

On Table 13 Manufacturing Sites, the FEI#30004525072 should be deleted. The FEI#2619243 is correct.

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