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

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
Submission Date(s)	May 7, 2021
Receipt Date(s)	May 7, 2021
OND Division / Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII)
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)	Hospitalized adult and pediatric patients 2 years and older with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation or ECMO

I. Issue Summary

The November 19, 2020, Emergency Use Authorization (EUA) 092 authorized use of baricitinib, in combination with remdesivir, for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults

[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.

and pediatric patients 2 years or older requiring supplemental oxygen[2], invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The Letter of Authorization for EUA 092 did not authorize the use of baricitinib in patients who were not receiving remdesivir. Baricitinib should only be administered in a hospital or healthcare setting capable of providing acute care comparable to inpatient hospital care[3].

As described below, the review team recommends that the EUA be revised to authorize the use of baricitinib alone[4]. Based on the totality of the scientific information available, which now includes results of trial 14V-MC-KHAA, A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of Baricitinib in Patients with COVID-19 Infection, (COV-BARRIER) described below, it is reasonable to believe that baricitinib may be effective for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, non-invasive or 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]. When used under such conditions, the known and potential benefits of baricitinib outweigh the known and potential risks of the product. There is no adequate, approved, and available alternative to the emergency use of baricitinib for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). On October 22, 2020, Veklury (remdesivir) was approved to treat COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization. Veklury 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. This is distinct from Veklury, which acts as an antiviral agent. We also note that Veklury's FDA-approved indication is for a narrower population than the use authorized for baricitinib under this EUA.

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[2] Supplemental oxygen also includes non-invasive ventilation. The review team recommends adding a reference to "non-invasive ventilation" to the authorized use, for clarity and consistency with the terminology used in the letter of authorization for Actemra

[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.

[4] While the review team recommends that the EUA be revised to authorize the use of baricitinib alone for the uses detailed below, we note that the COV-BARRIER trial supporting our recommendation did not raise questions about the safety or efficacy of baricitinib used in combination with remdesivir for the treatment of patients hospitalized due to COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). As such, the use of baricitinib in combination with remdesivir should not be contraindicated under the terms and conditions of an authorization.

Detailed Rationale for Revision of the Authorized Use

The primary support for the initial issuance of the EUA was based on results of the ACTT-2 study. In the ACTT-2 study, all patients received background remdesivir and patients were randomized to receive either baricitinib or placebo. The sponsor has now proposed to revise the EUA based on new information. Support for the proposed EUA revision is provided by results from study 14V-MC-KHAA, A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of Baricitinib in Patients with COVID-19 Infection (referred to as COV-BARRIER by the sponsor). This study randomized 1525 hospitalized patients (corresponding to NIAID ordinal scale 4, 5 and 6[5] at baseline) to receive up to 14 days of baricitinib or placebo on background standard of care. The majority of patients (87.8%) required supplemental oxygen at baseline (NIAID-OS 5 or 6 at baseline). The study was conducted both within and outside of the US and approximately 19% of patients were receiving background remdesivir at baseline. An additional 3.3% of patients received remdesivir post-baseline. Approximately 80% of patients enrolled in the KHAA (COV-BARRIER) study received corticosteroids at baseline as standard of care (SOC) therapy. An additional 5% of patients received corticosteroids starting post-baseline.

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Table 1. Summary of 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 and EUA amendment 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 14V-MC-KHAA (COV-BARRIER) NCT04421027	149,279	Efficacy, Safety	1525 Baricitinib +SOC (n=764) Placebo +SOC (n=761)	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	Completed**

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[5] NIAID-Ordinal Scale (OS)-4 defined as hospitalized not requiring supplemental oxygen but requiring ongoing medical care; NIAID-OS 5 defined as hospitalized, requiring any supplemental oxygen; NIAID-OS-6 defined as hospitalized, on non-invasive ventilation or high flow oxygen devices.

IND=investigational new drug, SOC=standard of care, *ACTT master protocol remains active, ** OS7 sub-study remains active

KHAA Study Description

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Study 14V-MC-KHAA (referred to as KHAA or COV-BARRIER) is a Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of baricitinib 4 mg in addition to SOC versus placebo and SOC in hospitalized adult patients with COVID-19. In this study the SOC was predominantly corticosteroid use. This study was conducted in the US, EU, Asia, India, and Latin America.

The study enrolled hospitalized male and female patients, aged 18 years or older, with a confirmed SARS-CoV-2 infection. Per the initial protocol, patients needed to have evidence of active COVID-19 including clinical symptoms (corresponding to NIAID OS 4, OS 5, or OS 6, shown below) and patients were excluded if they required invasive mechanical ventilation or ECMO, at study entry (NIAID OS 7).

The 8-Point NIAID Ordinal Scale (OS) is defined as follows:

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

Patients were also required to have at least 1 elevated marker of inflammation (CRP, D-dimer, LDH, ferritin > upper limit of normal (ULN) with at least at least 1 instance of elevation >ULN within 2 days before study entry).

In October 2020, a protocol amendment narrowed the patient population to patients requiring supplemental oxygen at baseline (NIAID OS 5 or OS 6). The amendment was informed by data from ACTT-2, suggesting that patients who did not require oxygen support at baseline were not predicted to progress during KHAA and would be unlikely to contribute to the primary endpoint of progression to death or ventilation. Based on FDA feedback, another protocol addendum in December 2020 modified the exclusion criteria to allow inclusion of patients who were NIAID OS 7 in a sub-study of KHAA. The sub-study is planned to enroll approximately 100 patients (50 per treatment arm) and will evaluate the efficacy and safety of baricitinib compared to placebo in exploratory analyses separate from analyses of the main study. The sub-study is ongoing, and no data from the baseline OS 7 group are currently available to support the EUA revision.

Patients in the KHAA study were randomized 1:1 to receive treatment with baricitinib 4 mg or placebo once daily for 14 days, or up to the day of hospital discharge, whichever came first, followed by treatment evaluations up to Day 28. Follow-up visits occurred at approximately Day 28 and Day 60. Patients could remain on background SOC therapy, as defined per local guidelines, which could include antimalarials, antivirals, corticosteroids, and/or azithromycin.

Randomization was stratified by: disease severity (OS 4 [not on supplemental oxygen], OS 5 [those on low-flow oxygen devices, by prongs or mask], and OS 6 [non-invasive ventilation/high-flow oxygen devices]), age (younger than 65 years; 65 years or older), region (US, Europe, and rest of the world), and dexamethasone and/or other systemic corticosteroid use at baseline for primary study condition (Yes or No).

The study enrolled and randomized 1525 patients (placebo, N= 761; baricitinib, N=764) and 1502 were dosed (placebo, N=752; baricitinib, N=750). Countries with the highest patient enrollment included Brazil (22.1%), US (20.3%), Mexico (18.4%) and Argentina (13.6%). Patients were also enrolled in Europe, India, Japan, Korea and Russia. The mean age of patients was 57.6 years with 32.7% of patients over age 65. Most patients (69.0%) had onset of symptoms 7 days or more prior to the enrollment in study KHAA. The demographics and baseline characteristics were similar between the baricitinib and placebo arms.

In the KHAA study, approximately 19% of patients received remdesivir at baseline (19.3% in placebo arm and 18.3% in baricitinib arm). An additional 3.3% of patients in each arm received treatment with remdesivir that was initiated post-baseline. Most patients (~80%) in the KHAA study were receiving corticosteroids as background standard of care at baseline (79.9% in placebo arm and 81.9% in baricitinib arm). Approximately 5% of patients received corticosteroids which were initiated post-baseline (4.8% in placebo arm and 5.2% in baricitinib arm). Of the patients receiving remdesivir at baseline, approximately 92% were also receiving corticosteroids.

The primary endpoint for study KHAA was a composite endpoint of progression to death, non-invasive ventilation/high-flow oxygen, or invasive mechanical ventilation (including ECMO) by Day 28. Patients on non-invasive ventilation/high-flow oxygen at baseline were only counted as progressing if they progressed to invasive mechanical ventilation or death. Key secondary endpoints included: all-cause mortality by Day 28, time to recovery, the proportion of patients with at least 1-point improvement on NIAID OS at Day 10 and 14, the distribution of NIAID OS at Day 4, 7, and 14, the number of ventilator-free days, the duration of hospitalization, and the proportion of patients with a change in oxygen saturation from less than 94% to 94% or greater from baseline at Day 4, 7, 10, and 14.

KHAA Efficacy

Primary Endpoint

The primary endpoint of the proportion of patients who progressed to death, non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) by Day 28 was tested in two study populations: population 1, which included all randomized patients, and population 2, a subset of the randomized patients who required oxygen support at baseline (OS 5 or OS 6) and were not receiving systemic corticosteroids for the treatment of COVID-19. Alpha was split between the two populations allowing the study to meet its primary objective if the primary endpoint was significant for either study population. The final testing procedure allocated 99% of alpha for testing population 1 and 1% of alpha for testing population 2. The primary endpoint was analyzed using a logistic regression model with baseline stratification factors and treatment included as covariates in the model. Missing data was multiply imputed using a Markov model to impute missing NIAID-OS scores through Day 28.

The primary endpoint did not achieve statistical significance for either population ($p = 0.180$ in population 1 and $p = 0.728$ in population 2), though a positive trend for a reduction in progression to death, non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation in the baricitinib arm was observed for population 1 with an odds ratio of 0.85 [95% confidence interval (0.67, 1.08)]. Among all randomized patients, 30% (228/761) of patients in the placebo arm were observed to progress to death, non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation compared to 27% (206/764) of patients in the baricitinib arm.

This composite primary endpoint can be broken into three distinct components, (1) progression to high flow oxygen or non-invasive ventilation without progression to invasive ventilation, (2) any progression to invasive ventilation, and (3) progression to death without first progressing to high flow oxygen, non-invasive ventilation, or invasive ventilation. The proportion of patients that progressed to each component was similar between arms but numerically favored the baricitinib arm: Progressed to high flow oxygen or non-invasive ventilation in placebo arm 9.7% (74/761) vs. baricitinib arm 9.2% (70/764), progressed to intubation in placebo arm 17.9% (136/761) vs. baricitinib arm 16.4% (125/764), died (without prior progression to OS-6 or OS-7) in placebo arm 2.4% (18/761) vs. baricitinib arm 1.4% (11/764).

Primary and Supplemental Analyses of All-Cause Mortality by Day 28

As the primary endpoint was not met, no secondary endpoints met multiplicity-controlled statistical significance. Most secondary endpoints, including time to recovery, the proportion of patients with at least 1-point improvement on NIAID OS, the number of ventilator-free days, and the duration of hospitalization, demonstrated numerical trends for improvements in the baricitinib arm compared to placebo. The distribution of NIAID OS at Day 4, Day 7, and Day 14 all demonstrated nominally significant improvements in the clinical status of patients in the baricitinib arm

compared to the placebo arm. In addition, a nominally significant reduction in the secondary endpoint of all-cause mortality was observed at Day 28. Extra focus is given to evaluation of the mortality results as mortality is arguably the most relevant endpoint for determining benefit in this patient population. Furthermore, the Agency has emphasized that analyses of all-cause mortality will be important regardless of the selected primary endpoint. While statistical significance cannot be established for mortality based on the pre-specified testing hierarchy, evidence for a potential reduction in mortality should be taken into consideration when determining whether a drug may be effective and whether the known and potential benefits outweigh the known and potential risks.

The results of Day 28 all-cause mortality are displayed in Table 2. The pre-specified analysis comparing all-cause mortality by Day 28 was based on a log-rank test, with a Cox proportional hazards model adjusted for baseline stratification factors used to estimate the hazard ratio. For these analyses, patients were censored at the date of the last non-missing OS or visit on or prior to Day 28, unless there was other information indicating the patients were alive at Day 28. Additional supplemental analyses analyzing the proportion of patients who died by Day 28 were performed using a logistic regression model adjusted for baseline stratification factors.

For the proportion of patients who died, missing data was multiply imputed using a Markov model to impute missing NIAID-OS scores through Day 28. It should be noted that the regression-based analyses (i.e., the Cox and logistic regression model) excluded 5 patients in the placebo arm and 2 patients in the baricitinib arm due to missing baseline NIAID OS scores. These 7 patients were randomized but did not receive study drug.

All analyses show similar results and indicate a reduction in Day 28 all-cause mortality and the p-value for the log-rank test is well below the usual 0.05 threshold for evaluating statistical significance. The upper bound for the 95% confidence interval for the difference in proportions appears to rule out reductions in mortality of less than 1.9%. However, because the primary endpoint was not statistically significant based on the testing hierarchy, these results are not appropriately adjusted for multiplicity and care must be taken with their interpretation. The consistency in the estimated treatment effects for mortality across the trials provides additional support that the results observed in KHAA represent a true treatment effect. While the estimated difference in mortality between the baricitinib arm and the placebo arm at Day 28 is larger than the estimated difference in mortality at Day 29 from the ACTT-2 study (-2.6%), the findings are not inconsistent given the uncertainty around the point estimates [95% CI for difference in mortality from ACTT-2 study (-5.8%, 0.5%)]. The estimated hazard ratio for time to death from the ACTT-2 study was 0.65 [95% CI = (0.39, 1.09)].

While a nominally significant reduction in mortality was observed, the primary endpoint, which was a composite of mortality and progression to ventilation, did not achieve significance. It is possible that a reduction in mortality without a reduction in

progression to ventilation could occur if patients in the baricitinib arm were more likely to receive ventilation and the receipt of ventilation prevented death. However, based on analyzing the components of the primary endpoint, this scenario seems unlikely given fewer patients in the baricitinib arm progressed to ventilation. Further, the observed mortality difference for patients who did progress to ventilation was only around 1% in favor of the baricitinib arm, indicating that the observed reduction in mortality primarily occurred in patients who had progressed to ventilation.

Table 2: KHAA All-Cause Mortality by Day 28 (ITT Population)

	Placebo + SoC (N=761)	Baricitinib +SoC (N=764)
Proportion of patient who died by Day 28, n (%)	101 (13.3%)	62 (8.1%)
Difference in proportions (95% CI)[1]	-4.9% (-8.0%, -1.9%)	
Odds ratio (95% CI)[2]	0.52 (0.37,0.75)	
Hazards ratio (95% CI)[3]	0.56 (0.41, 0.77)	
P-value[4]	0.0015	

SOC= standard of care, CI= confidence interval
[1]Computed from stratified risk difference adjusted for baseline stratification factors using Cochran-Mantel-Haenszel weights with missing data multiply imputed
[2]Computed from logistic regression model adjusted for baseline stratification factors with missing data multiply imputed
[3]Computed from Cox proportional hazards model adjusted for baseline stratification factors.
[4]Computed from log-rank test. Includes all randomized subjects
Source: Sponsor's Analysis from Table 4.1 of response to Question 3 of 16July2021 IR and Figure APP.1 of response to 10Jun2021 IR.

Missing Data Sensitivity Analyses of All-Cause Mortality by Day 28

A total of 41 out of 761 (5.4%) patients in the placebo arm and 50 out of 764 (6.5%) patients in the baricitinib arm had an unknown vital status at Day 28. Of the patients with a missing Day 28 mortality outcome, only 13 patients in the placebo arm (31.7% and 13 patients in the baricitinib arm (26.0%) were known to have been discharged from the hospital (OS 1 or OS 2). The distribution of the last known available NIAID OS score among missing patients is displayed in Table 3. The 7 patients categorized as missing did not have an observed baseline NIAID OS score and did not receive study drug. More patients with missing data in the baricitinib arm were hospitalized at their last available OS score compared to patients in the placebo arm, mostly due to more baricitinib patients having a final observed OS score of 4 and 5. The number of patients who had missing mortality data and had an OS score of 6 and 7 at their final observed visit were fairly similar between arms. There were also more patients with missing NIAID OS scores in the placebo arm.

Table 3: Last Available NIAID OS Score in Patients with Missing Day 28 Vital Status

	Placebo + SoC (N=761)	Baricitinib +SoC (N=764)
Missing Day 28 Vital Status n (%)	41 (5.4)	50 (6.5)
Last Available NIAID OS Score n (%)*		
OS 1	10 (24.4)	10 (20.0)
OS 2	3 (7.3)	3 (6.0)
OS 3	0 (0.0)	0 (0.0)
OS 4	1 (2.4)	5 (10.0)
OS 5	12 (29.3)	19 (38.0)
OS 6	4 (9.8)	6 (12.0)
OS 7	6 (14.6)	5 (10.0)
Missing	5 (12.2)	2 (4.0)

SOC= standard of care, OS= NIAID Ordinal Scale
*Percentage out of the number of patients with missing Day 28 vital status
Source: Table APP.1. of Response to 10Jun2021 IR

To explore the plausibility of missing data assumptions under which the conclusions regarding mortality at Day 28 would change, the Sponsor performed tipping point analyses which systematically vary assumptions about the missing outcomes on the two treatment arms. These analysis results indicated that if the true underlying mortality rate in placebo patients with missing Day 28 mortality data was 3%, the true underlying mortality rate in among patients with missing Day 28 mortality data in the baricitinib arm would have to be greater than 30% in order for the Day 28 mortality results to no longer demonstrate nominal significance at the 0.05 level. Alternatively, if the true underlying mortality rate was higher at 12-15% in placebo arm, the true underlying mortality rate in the baricitinib arm would have to be greater than 36% to no longer demonstrate nominal significance at the 0.05 level. Finally, if the true underlying mortality rate was 21% in placebo arm, the true underlying mortality rate in the baricitinib arm would have to be greater than 42% to no longer demonstrate nominal significance at the 0.05 level.

To evaluate if such scenarios are plausible, we considered the distribution of last known OS score among the missing patients and the mortality rates among subjects with these OS scores at baseline. Among all patients who were discharged from the hospital who had an observed Day 28 vitality status, less than 0.5% died by Day 28. There was an estimated Day 28 mortality rate of 4.2% (0.2%, 8.3%) in placebo patients with a baseline OS score of 4, 9.0% (6.4%, 11.7%) in placebo patients with a baseline OS score of 5, and 30.9% (24.2% ,37.7%) in placebo patients with a baseline OS score of 6, and an overall estimated mortality rate of 13.8% (11.3%,16.3%) in placebo patients. The observed Day 28 morality rate among placebo patients known to have progressed to OS 7 was 56.6% (77/136), 95% Wald confidence interval of (48.3%, 64.9%). Assuming (1) patients with a last observed OS of 4, 5, or 6 had the same Day 28 mortality rate as placebo patients in that ordinal

scale category at baseline, (2) patients with a last observed OS of 7 had a Day 28 mortality rate equal to the overall placebo mortality rate among patients who progressed to OS 7, (3) patients with a missing baseline OS score had the same mortality rate as observed in the overall placebo arm, and (4) no patients died by Day 28 after hospital discharge, there would be an expected mortality rate of around 16% among missing patients in the placebo arm and 14% among missing patients in the baricitinib arm. If this analysis is repeated assuming no patients died after hospital discharge but using the upper bounds of the 95% confidence intervals for Day 28 mortality rates instead of the point estimates, there would be an expected mortality rate of around 19% among missing patients in the placebo arm and 17% among missing patients in the baricitinib arm. Instead assuming a 10% mortality rate among missing patients who were discharged from the hospital, a 20% mortality rate in patients whose last OS score was 4, a 30% mortality rate in patients whose last OS score was 5, a 60% mortality rate in patients whose last OS score was 6, and 100% mortality rate in patients whose last OS score was 7 or missing would produce an expected mortality rate of approximately 37% in baricitinib patients with missing Day 28 mortality data.

Considering these estimated mortality rates and the distribution of last known OS score among the missing patients in combination with the Sponsor's tipping point analyses, scenarios under which the analysis for Day 28 all-cause mortality is no longer nominally significant appear to be unlikely.

Subgroup Analyses of All-Cause Mortality by Day 28

A numerical reduction in all-cause mortality by Day 28 was seen across all baseline severity subgroups and across regions (US, Europe, and the rest of the world). Subgroup analyses of time to death by Day 28 based on baseline use of corticosteroids and remdesivir are displayed in Table 4. A nominally significant increase in time to death was seen in both patients who were receiving background corticosteroids at baseline and patients not receiving background corticosteroids. A nominally significant benefit was observed for patients treated with baricitinib who were not receiving background remdesivir. In the subgroup that was receiving background remdesivir, the analysis for time to death through Day 28 showed little difference between the baricitinib and placebo arm [hazard ratio of 0.81 with a 95% CI of (0.38, 1.73)]; however, there was a small numerical reduction in the Kaplan-Meier estimated mortality rate for the baricitinib arm at Day 28 (9.2% versus 11.3%). The overall number of patients receiving remdesivir at baseline was small (147 patients in the placebo arm and 140 of patients in the baricitinib arm) making it challenging to estimate differences in mortality rate with precision. The majority of patients receiving remdesivir were also receiving concomitant corticosteroids as background standard of care. It should be noted that the ACTT-2 study demonstrated statistically significant benefits on multiple efficacy endpoints for the use of baricitinib in combination with remdesivir.

Table 4: Subgroup Analyses of Day 28 Mortality

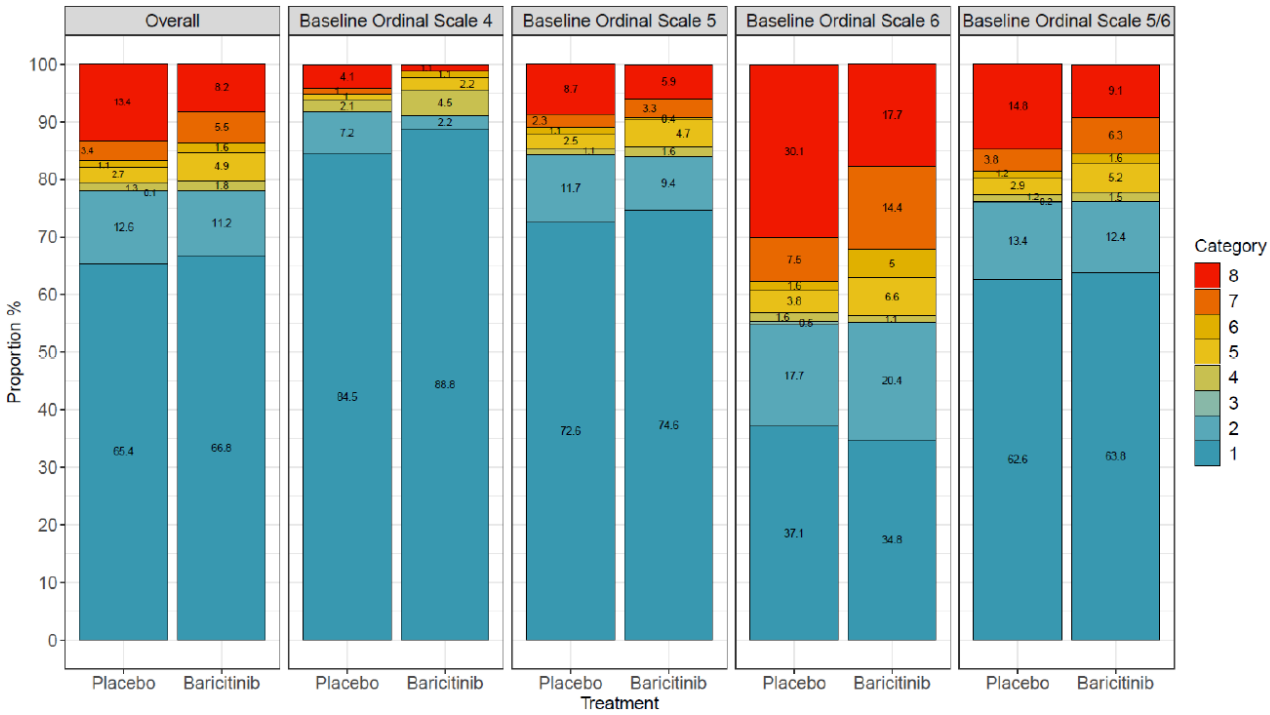
Subgroup	N (Placebo)*	N (Baricitinib)*	Day 28 Placebo Mortality Rate[1] (95% CI)	Day 28 Baricitinib Mortality Rate[1] (95% CI)	Hazard Ratio[2] (95% CI)
Baseline Steroid: Yes	592	612	14.2% (11.2%, 17.9%)	9.8% (7.1%, 12.8%)	0.63 (0.45, 0.89)
Baseline Steroid: No	164	150	11.5% (6.9%, 18.9%)	3.6% (1.3%, 9.5%)	0.28 (0.10, 0.77)
Baseline Remdesivir: Yes	147	140	11.3% (6.5%, 19.1%)	9.2% (4.9%, 17.1%)	0.81 (0.38, 1.73)
Baseline Remdesivir: No	609	622	14.2% (11.3%, 17.9%)	8.4% (6.0%, 11.3%)	0.52 (0.36, 0.74)

CI = confidence interval
*Patients with missing baseline covariates were excluded from subgroup analyses, excluding 5 patients randomized to placebo and 2 patients randomized to baricitinib
[1]Mortality rate and 95% CI computed based on Kaplan-Meier estimator. Vital status information after study withdrawal is not included
[2]Hazard Ratio and 95% CI computed based on Cox proportional hazards model adjusting for baseline randomization factors. Vital status information after study withdrawal is not included
Source: Sponsor's analysis created from Table APP.8. of Request for EUA Amendment

Distribution of NIAID Ordinal Scale Scores at Day 28

Figure 1 displays the distribution of NIAID OS scores at Day 28 by treatment arm and baseline OS category. For this figure, missing NIAID OS scores were singly imputed using last observation carried forward. While there is a smaller proportion of patients who died in the baricitinib arm compared to the placebo arm for each subgroup, the proportion of patients discharged from the hospital at Day 28 (OS 1 and OS 2) are similar between arms and there are more hospitalized patients in the baricitinib arm (OS 3, 4, 5, 6, and 7). For baseline OS 5 and OS 6 patients, a higher proportion of patients in the baricitinib arm are on invasive mechanical ventilation at Day 28 (OS 7) compared the placebo arm.

Figure 1: Distribution of Day 28 NIAID OS



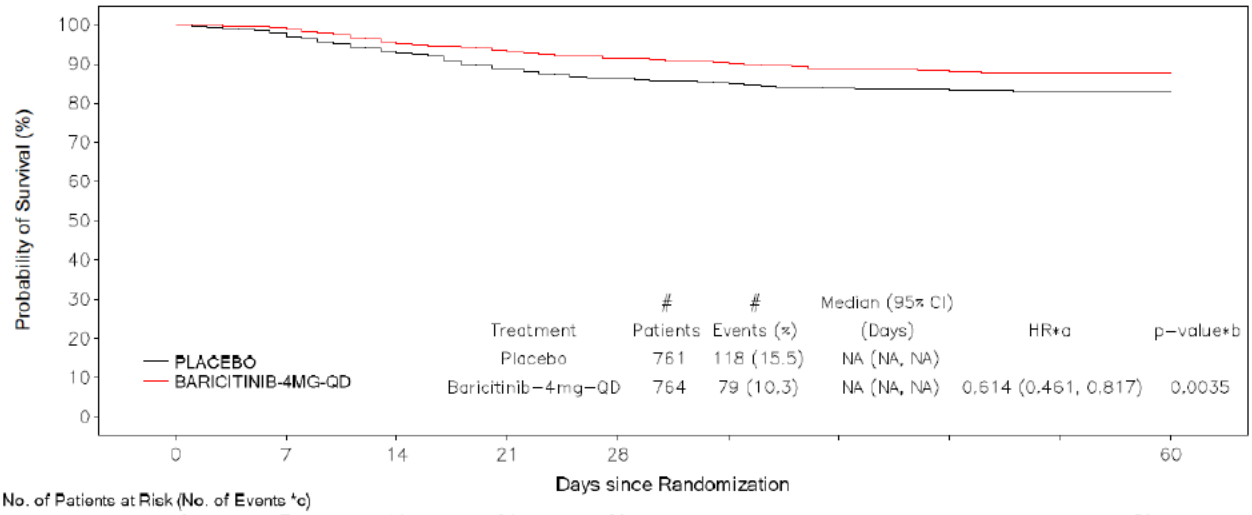
Source: Figure 2 of Response to 16July2021 IR Questions 1, 2, 4, and 5

All-Cause Mortality by Day 60

Due to the higher proportion of patients who remained hospitalized at Day 28 in the baricitinib arm, it is possible that the mortality benefit for patients in the baricitinib arm would not be observed at a later timepoint. Day 60 efficacy data was examined to address this potential scenario. Figure 2 displays the Kaplan-Meier plot of time to death up to Day 60. There is a clear separation in the cumulative number of observed deaths between treatment arms, and this separation remains through Day 60.

Reference ID: 4833044

Figure 2: Kaplan-Meier Plot for Time to Death



Treatment	# Patients	# Events (%)	Median (95% CI) (Days)	HR*a	p-value*b
Placebo	761	118 (15.5)	NA (NA, NA)		
Baricitinib-4mg-QD	764	79 (10.3)	NA (NA, NA)	0.614 (0.461, 0.817)	0.0035

No. of Patients at Risk (No. of Events *c)

Time	0	7	14	21	28	59
Placebo	761 (24)	720 (30)	684 (29)	645 (18)	616 (17)	236 (0)
Baricitinib-4mg-QD	764 (9)	728 (27)	687 (14)	669 (12)	648 (17)	242 (0)

CI = confidence interval, HR = hazard ratio, NA = not applicable, No. = number, OS = ordinal scale, QD = once daily

*a HR was calculated using Cox proportional hazards regression model adjusted for randomization stratification factors

*b p-value is from unstratified log-rank test.

*c Number of patients who died between end of this time period and end of the next time period.

Source: Figure 1 of Response to 16July2021 IR Questions 1, 2, 4, and 5

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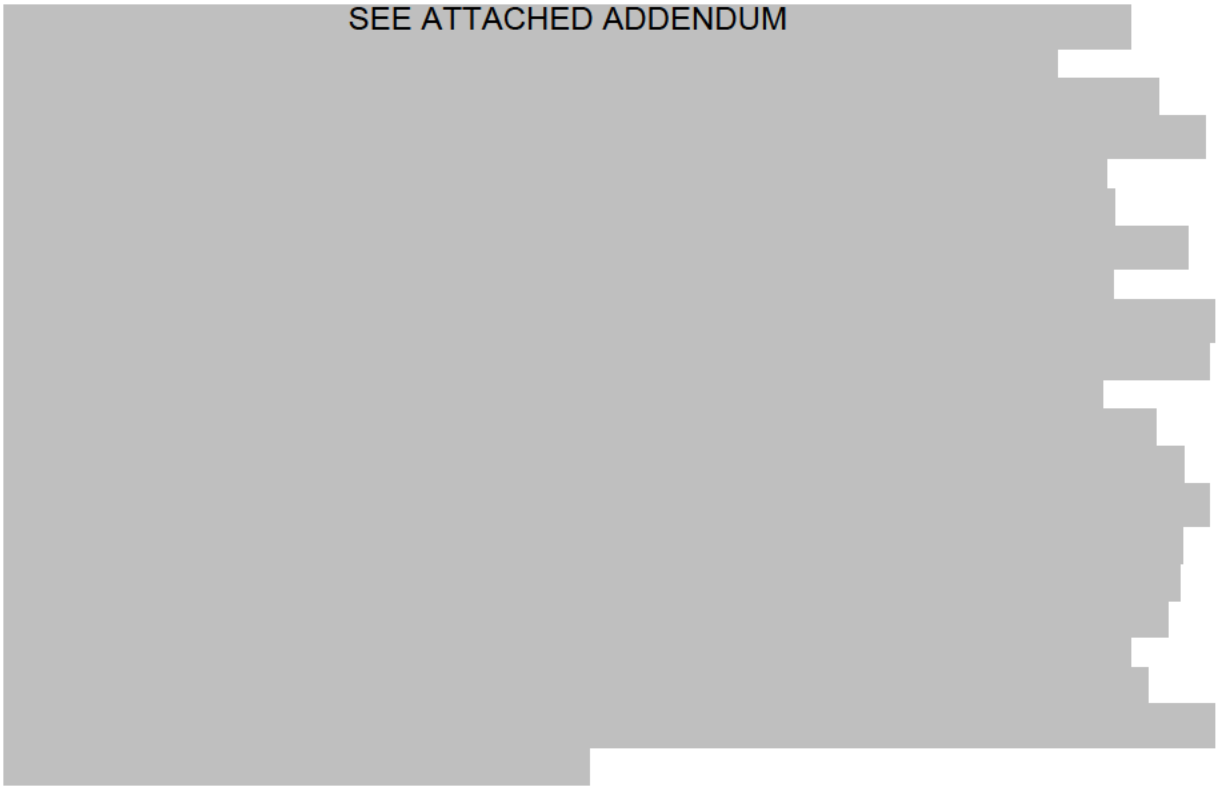
A larger percentage of patients in the baricitinib arm who were enrolled or ongoing in the study after amendment (d) was implemented (i.e., patients eligible for Day 60 follow-up) were on invasive mechanical ventilation (OS 7) at Day 28 compared to patients in the placebo arm (6.3% versus 3.3%). Additionally, more patients in the baricitinib arm who were enrolled or ongoing in the study after amendment (d) was implemented were on supplemental oxygen (OS 5) at Day 28 compared to the placebo arm (2.9% versus 1.0%). However, the proportion of patients on non-invasive ventilation and high flow oxygen (OS 6) and the proportion of hospitalized patients not receiving supplemental oxygen (OS 4) were similar between arms. The larger number of patients on invasive mechanical ventilation or on supplemental

oxygen in the baricitinib arm is consistent with the Day 28 results for the overall study population.

SEE ATTACHED ADDENDUM



While the large amount of missing data at Day 60 makes it difficult to interpret Day 60 mortality results and it cannot be fully known whether there was a differential mortality rate between the two arms after Day 28, the observed data at Day 60 did not raise concerns that the mortality benefit observed at Day 28 would disappear by Day 60. There was a similar observed number of deaths between the two arms after Day 28 and there was no information to suggest that, among all patients eligible for Day 60 follow-up, patients with missing Day 60 data had a substantially higher expected mortality rate in the baricitinib arm compared to the placebo arm.

Efficacy Conclusions

The analysis of the primary endpoint was not statistically significant, but the secondary endpoint of all-cause mortality at Day 28 showed a nominally significant effect. Because the primary endpoint failed to demonstrate significance, results for all-cause mortality are not appropriately controlled for multiplicity and testing multiple endpoints could lead to an inflation in type I error. However, because all-cause mortality is probably the most meaningful endpoint for this study population, the results for all-cause mortality are more important than other secondary endpoints in determining clinical benefit. Furthermore, the p-value for the primary analysis of all-cause mortality of 0.0015 was well below the 0.05 threshold. The very small p-value and the similarity of mortality results with the ACTT-2 study make it less likely that the

mortality results for KHAA were due to chance. Tipping point analyses indicated that the results at Day 28 were robust to missing data. There are limitations in the Day 60 data due to the large amount of missing data, however, the available data did not raise additional concerns that a mortality benefit would not be observed after Day 28.

A mortality benefit was observed both in patients receiving corticosteroids and in patients not on remdesivir. Neither of these populations were well studied in ACTT-2. A nominally significant reduction in mortality was seen in both patients who were receiving background corticosteroids at baseline and patients not receiving background corticosteroids. A nominally significant benefit in all-cause mortality was also observed for patients treated with baricitinib who were not receiving background remdesivir at baseline. In the subgroup that was receiving background remdesivir, the analysis for time to death through Day 28 showed little difference between the baricitinib and placebo arm [hazard ratio of 0.81 with a 95% CI of (0.38, 1.73)]; however, there was a small numerical reduction in the Kaplan-Meier estimated mortality rate for the baricitinib arm at Day 28 (9.2% versus 11.3%). It should be noted that the ACTT-2 study demonstrated statistically significant benefits on multiple efficacy endpoints for the use of baricitinib in combination with remdesivir and therefore such use should not be contraindicated under the terms and conditions of an authorization. Given the totality of evidence, KHAA provides evidence that baricitinib alone may be effective in reducing mortality rates in hospitalized patients not on invasive mechanical ventilation. KHAA provides support for the use of baricitinib in combination with corticosteroids and support for the use of baricitinib in patients who are not receiving remdesivir as part of standard of care.

KHAA Safety

In the KHAA study 1525 patients were randomized and of these 1502 were dosed; 750 patients received baricitinib (for a mean of 8.1 days) and 752 patients received placebo (for a mean of 8.3 days). The safety profile observed in the patients with COVID-19 in the KHAA study was consistent with the safety observed in the ACTT-2 clinical trial and with the known safety profile for baricitinib.

Overall a similar proportion of patients in the baricitinib and placebo arms had treatment emergent adverse events and serious adverse events. Overall infections, serious infections and opportunistic infections were similar between treatment arms. The safety summary including adverse event of interest are shown in Table 5. The majority of patients in the KHAA trial were also receiving background corticosteroids.

In the KHAA study venous thromboembolic event (VTE) prophylaxis was required for all patients unless a contraindication was observed. Patients with a history of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) within 12 weeks prior to randomization or a history of recurrent DVTs or PEs were excluded. VTEs were observed in 2.5% of placebo treated patients and 2.7% of baricitinib treated patients. Pulmonary embolism was reported in 9 patients in the placebo arm (1.2%) and 13 patients in the baricitinib arm (1.7%).

Table 5. COV-BARRIER (KHAA) Overall Safety and Adverse Events of Interest

	Placebo (n=752)	Baricitinib 4 mg (n=750)
Treatment-emergent adverse event (TEAE)	334 (44.4)	334 (44.5)
TEAE severity*		
Mild	115 (15.3)	133 (17.7)
Moderate	89 (11.8)	90 (12.0)
Severe	130 (17.3)	111 (14.8)
Serious adverse event	135 (18.0)	110 (14.7)
Discontinuation from study treatment due to adverse event†	70 (9.3)	56 (7.5)
Deaths‡	100 (13.3)	61 (8.1)
Infections	123 (16.4)	119 (15.9)
Serious infections	74 (9.8)	64 (8.5)
Opportunistic infections	7 (0.9)	6 (0.8)
Venous thromboembolic events	19 (2.5)	20 (2.7)
Pulmonary embolism	9 (1.2)	13 (1.7)
Deep Vein Thrombosis	2 (0.3)	4 (0.5)

*Patients with multiple events are counted in highest severity. Includes TEAEs in KHAA study through Day 28.

† Including death due to adverse event.

‡Based on safety population defined as all patients randomly assigned to study intervention who received at least one dose of study intervention, and who did not discontinue from the study as "Lost to Follow-up" at the first postbaseline visit.

Source: Adapted from tables APP 27, APP 41, APP 42 Sponsor's Request for EUA Amendment and Table 1 Response to Information Request EUA IR 16Jul2021a.

All-cause mortality in the safety population, as noted above, was higher at Day 28 in the placebo arm compared to the baricitinib arm (placebo 13.3%, baricitinib 8.1%). As previously discussed, although there is missing data beyond Day 28, based on the available data all-cause mortality in the safety population remained higher in the placebo arm with 117 deaths (15.6%) compared to the baricitinib arm with 78 deaths (10.4%) through Day 60. Between Day 28 and Day 60 a similar number of deaths were reported in both study treatment arms (placebo n=17, baricitinib n=17).

ACTT-2 and KHAA Integrated Safety

In the ACTT-2 and KHAA studies 1257 patients received baricitinib (mean exposure of 8.0 days) and 1261 received placebo (mean exposure of 8.1 days). In the ACTT-2 study all patients received remdesivir as part of background standard of care. In the KHAA study the majority of patients, received corticosteroids as background standard of care and approximately 19% of patients received remdesivir at baseline. The majority of patients who were receiving remdesivir in the KHAA study also received corticosteroids (91.6%). The pooled safety analysis of the two studies allows for further identification of any additional safety signals, however there are some

limitations in the currently pooling strategy. There were differences in collection of non-serious TEAEs between the two studies that should be taken into consideration. In the ACTT-2 study per protocol defined AE collection was focused primarily on Grade 3 and 4 events. The KHAA study included collection of all non-serious TEAEs. Displayed AE percentages were also based on naïve pooling of treatment arms and were not adjusted by study. However, because the ACTT-2 study and KHAA study used the same randomization allocation (1:1) and within each study there was a small difference in the number of patients in each arm who received study drug, differences between study-adjusted percentages and unadjusted percentages should be minimal.

The overall TEAEs, were similar between baricitinib and placebo treatment arms in the individual studies and in the integrated safety data. The summary of TEAEs and adverse events associated with infections, major adverse cardiac events and venous thromboembolic events are show below in Table 6. The integrated safety data for the studies through Day 28/29 is consistent with the known safety profile for baricitinib.

Table 6. TEAEs and AESIs studies (KHAA and ACTT-2) in COVID-19

Treatment Emergent Adverse Events, n (%)	Placebo + SoC (N = 1261)	Baricitinib + SoC (N = 1257)
TEAEs	576 (45.7)	544 (43.3)
SAE	244 (19.3)	197 (15.7)
Discontinuations due to AE*	145 (11.5)	104 (8.3)
Deaths	137 (10.9)	84 (6.7)
Infections	183 (14.5)	159 (12.6)
Serious Infections	94 (7.5)	76 (6.0)
Herpes Zoster	3 (0.2)	1 (0.1)
Tuberculosis	0	1 (0.1)
Opportunistic Infections	11 (0.9)	12 (1.0)
Major Adverse Cardiac events	15 (1.2)	12 (1.0)
Cardiovascular Deaths	10 (0.8)	5 (0.4)
Myocardial Infarction	3 (0.2)	4 (0.3)
Stroke	4 (0.3)	4 (0.3)
Venous thromboembolic events	35 (2.8)	41 (3.3)
Deep Vein Thrombosis (DVT)	16 (1.3)	19 (1.5)
Pulmonary Embolus (PE)	11 (0.9)	18 (1.4)

TEAEs ACTT-2 through Day 29, KHAA through Day 28. SOC= standard of care
* Including death due to adverse event.

Source: Adapted from Table 6.3, APP. 40, APP. 31 Sponsor's Request for EUA Amendment and Response to Information Request EUA IR 16Jul2021a

In the integrated COVID-19 studies (KHAA and ACTT-2) elevations in liver enzymes (ALT and AST ≥ 3 x upper limit of normal [ULN]) were observed more frequently in the baricitinib arm compared to placebo. In the integrated COVID-19 trials ALT elevations of ≥3xULN occurred in 15.6% of patients in the placebo arm and in 18.0% of patients in the baricitinib arm. AST elevation of ≥3xULN occurred in 9.1% of patients in the placebo arm and in 11.5% of patients in the baricitinib arm. Thrombotic events including DVTs and pulmonary embolism were also seen more commonly in the baricitinib arm (Table 5). Neutropenia (<1000 cells/mm3), was reported more frequently in COVID-19 patients receiving baricitinib (2.2%) than placebo patients (1.9%). Liver enzyme elevations, thrombotic events, and neutropenia have all been observed with baricitinib treatment of patient with rheumatoid arthritis[6]. In COVID-19 patients in the ACTT-2 and KHAA studies these events were seen more frequently than in studies in RA patients. Other laboratory changes associated with baricitinib treatment including thrombocytosis (>600,000 cells/mm3) was observed more frequently in the baricitinib arm (8.2%) compared to placebo (4.3%) and at a similar frequency to that observed in studies in RA patients. Creatine phosphokinase (CPK) levels were evaluated in the KHAA study and elevations in CPK > 5 x ULN occurred in 3.7% of patients in the baricitinib arm and in 3.3% of patients in the placebo arm.

Conclusions

The ACTT-2 study, which was conducted in patients receiving concomitant background remdesivir, provided the primary support for the initial EUA for baricitinib (EUA-092, 11/19/2020). Results from the KHAA study have now become available. Although the KHAA had a similar study design to ACTT-2, a key difference included the background standard of care. The majority of patients in the KHAA study received background corticosteroids as standard of care treatment for COVID-19 with only approximately 19% of patients receiving remdesivir at baseline. The primary endpoints for the two studies were also different; however, there was substantial overlap in the primary and key secondary endpoints for the two studies. The ACTT-2 study enrolled patients with baseline NIAID OS score of 4-7 while the KHAA study enrolled patients only with OS scores of 4-6. When results of the ACTT-2 study became available, enrollment in OS-4 group in KHAA was stopped. A substudy for OS-7 was added to KHAA; however, the results are not currently available and do not contribute to this review. Patients enrolled in KHAA were also required to have an elevation in at least one inflammatory marker. The ACTT-2 study was primarily conducted in the US with over 90% of patients enrolled from North America. In the KHAA study approximately 21% of patients were from the US.

Although the KHAA study did not meet its primary endpoint of the proportion of patients who progressed to death, non-invasive ventilation/high-flow oxygen or

[6]FDA Approved United States Prescribing Information (USPI). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207924s002lbl.pdf

invasive mechanical ventilation (including ECMO) by Day 28 there was an observed reduction of all-cause mortality at day 28 (8.1% mortality in baricitinib arm vs. 13.1% in placebo). Evidence for a potential reduction in mortality should be taken into consideration when determining whether a drug may be effective and whether the known and potential benefits outweigh the known and potential risks. The primary endpoint as well as other key secondary endpoints did demonstrate a trend that favored the baricitinib arm and were consistent with findings in the ACTT-2 study.

The reduction in all-cause mortality was observed in the overall study population as well as in the patients who did not receive remdesivir at baseline. A smaller treatment effect on all-cause mortality was observed in patients receiving background remdesivir. However, interpretation of this finding is complicated by the smaller number of patients who received remdesivir as well as the majority of patients receiving remdesivir at baseline were also receiving concomitant corticosteroids as background standard of care.

There are limitations to the data beyond Day 28, with missing data at Day 60 limiting assessment of additional mortality after Day 28. However, based on the available data it does not appear that after Day 28 there is increased mortality in the baricitinib arm compared to the placebo arm. The KHAA results provided in this submission do not provide any additional data regarding patients who are receiving mechanical ventilation or ECMO at baseline.

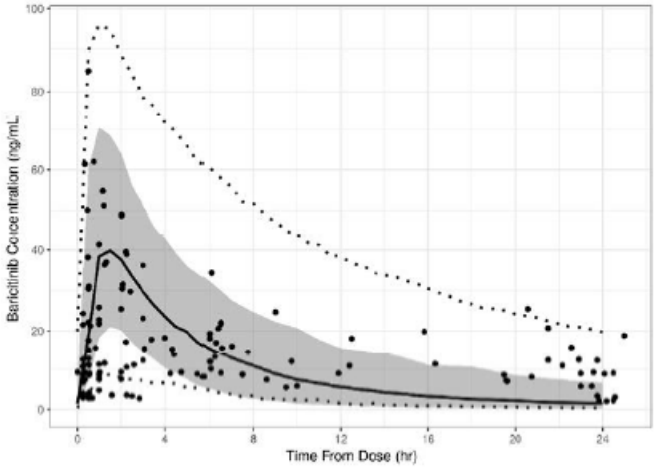
These additional study results from KHAA continue to support that baricitinib may be effective for treatment of hospitalized patients with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO consistent with the prior EUA and supports the revision of the EUA to dosing of baricitinib alone. As most patients in the KHAA study were receiving corticosteroids as background standard of care, the KHAA study provided additional information on the use of baricitinib in combination with corticosteroids that was not available from ACTT-2. Safety in the KHAA study was consistent with the safety observed in the ACTT-2 study and the known safety profile for baricitinib. The review staff have therefore concluded it is reasonable to believe baricitinib alone may be effective for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

II. Summary of clinical pharmacology

In this amendment, the Sponsor submitted the PK data of baricitinib from 30 adult patients with COVID-19 who progressed to mechanical ventilation and received baricitinib as a solution of crushed tablets administered via nasogastric (NG) tube. The administration of the baricitinib suspension via a NG tube is expected to provide bioavailability similar to the tablet (Original EUA92 review). As shown in Figure 3, the observed PK data from these patients are most comparable to those in healthy

subjects and are in the range of the PK of baricitinib in patients with RA following a 4-mg QD dose administered as an oral tablet.

Figure 3. Pharmacokinetic profile of 4 mg once daily baricitinib in hospitalized adult patients with COVID-19 in Study I4V-MC-KHAA



Abbreviations: COVID-19 = coronavirus disease; PK = pharmacokinetics; QD = once daily; RA = rheumatoid arthritis.
Note: Black symbols are observed concentration data from Study KHAA. The black line and grey band are the model-estimated median and 90% prediction interval, respectively, of PK profile at 4 mg QD based on Phase 1 clinical pharmacology studies conducted in healthy subjects. Dashed lines are model-estimated 90% prediction interval of PK profiles at 4 mg QD based on Phase 3 studies conducted in patients with RA.

Source: Request for Emergency Use Authorization Amendment, Table 6.1

III. Summary of Revision to EUA Facts Sheets

- Authorized Use:
  - Removal of the requirement to dose baricitinib with concomitant remdesivir. To authorize the emergency use of baricitinib for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- Dosing:
  - Removed statement regarding limited information on use of baricitinib in combination with corticosteroids based on new data from study KHAA.
- Pharmacology:
  - Added pharmacokinetics information for patients with COVID-19 who are administered baricitinib though NG tube.
- Warnings:

    - Added clarification that there is limited safety information regarding use of baricitinib and patients with concomitant active serious infections
    - Added clarification that there is limited safety information regarding use of baricitinib in patients with ANC <1000 cell/mm^3, ALC<200 cell/mm^3 and hemoglobin <8 g/dL.
- Efficacy Summary:
    - Added study design description for study COV-BARRIER (KHAA) and results for the primary and key secondary endpoint of mortality.
- Safety Summary:
    - Added integrated safety and Adverse Reactions Table from ACTT-2 and COV-BARRIER (KHAA) studies.
- Other:
    - Editorial revision for clarity, readability, and consistency.

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RE: Emergency Use Authorization (EUA) for baricitinib
Addendum: August 20, 2021

This addendum references the summary EUA review for baricitinib for the treatment of hospitalized COVID-19 patients, dated July 28, 2021.

On pages 2, 3 and 4 references to study 14V-MC-KHAA should be to study I4V-MC-KHAA.

On page 16 the formatting of Table 5 has been adjusted for clarity.

Table 1. COV-BARRIER (KHAA) Overall Safety and Adverse Events of Interest

	Placebo (n=752)	**Baricitinib 4 mg (n=750)**
Treatment-emergent adverse event (TEAE)	334 (44.4)	334 (44.5)
TEAE severity*		
Mild	115 (15.3)	133 (17.7)
Moderate	89 (11.8)	90 (12.0)
Severe	130 (17.3)	111 (14.8)
Serious adverse event	135 (18.0)	110 (14.7)
Discontinuation from study treatment due to adverse event†	70 (9.3)	56 (7.5)
Deaths‡	100 (13.3)	61 (8.1)
Infections	123 (16.4)	119 (15.9)
Serious infections	74 (9.8)	64 (8.5)
Opportunistic infections	7 (0.9)	6 (0.8)
Venous thromboembolic events	19 (2.5)	20 (2.7)
Pulmonary embolism	9 (1.2)	13 (1.7)
Deep Vein Thrombosis	2 (0.3)	4 (0.5)

*Patients with multiple events are counted in highest severity. Includes TEAEs in KHAA study through Day 28.
† Including death due to adverse event.
‡Based on safety population defined as all patients randomly assigned to study intervention who received at least one dose of study intervention, and who did not discontinue from the study as "Lost to Follow-up" at the first postbaseline visit.
Source: Adapted from tables APP 27, APP 41, APP 42 Sponsor's Request for EUA Amendment and Table 1 Response to Information Request EUA IR 16Jul2021a.

The Sponsor provided additional tables on 8/13/2021 (SN 0034) and 8/19/2021 (SN 0035) related to a programming error that was identified which impacted study results reported for Day 60. Changes based on these corrected tables are as follows:

1. On page 13, the number of patients who were alive and had an observed Day 60 ordinal scale value and the number of those patients who were still hospitalized at Day 60 are incorrectly listed. The first paragraph on page 13 should be corrected to read, “Unfortunately, there are limitations in interpreting Day 60 results due to the large amount of missing data. While the study began enrolling in June of 2020, the Day 60 study visit was added in protocol amendment (d) on 20 October 2020 and implementation of the amendment varied by sites. As a result, around 47% (361/761) of patients in the placebo arm and 50% (379/764) of patients in the baricitinib arm completed the study before the Day 60 study visit was added. Only a total of 224 placebo patients and 225 baricitinib patients were alive and had an observed Day 60 ordinal scale value. Among those patients, only 10 patients were still hospitalized at Day 60: 3 patients (2 placebo and 1 baricitinib) did not require supplemental oxygen, 1 baricitinib patient required non-invasive mechanical ventilation, and 6 patients (2 placebo and 4 baricitinib) required invasive mechanical ventilation. An additional 17 placebo patients and 17 baricitinib patients were observed to have died between Day 28 and Day 60.”

2. On page 14, the within treatment arm percentage of patients with missing Day 60 clinical status among patients who were eligible for Day 60 follow-up whose last observed clinical status on or before Day 28 indicated use invasive mechanical ventilation is incorrect. The first paragraph starting on page 14 should be corrected to read, “Among patients with missing Day 60 clinical status who were eligible for Day 60 follow-up, there was a small difference between treatment arms in the percentage of patients who were on supplemental oxygen based on last observed clinical status on or before Day 28 (3.4% of baricitinib patients versus 1.8% of placebo patients). Only a few patients on supplemental oxygen at Day 28 were observed to die by Day 60, and it seems unlikely that the higher proportion of patients with a missing Day 60 vital status who were on supplemental oxygen in the baricitinib arm would substantially bias the estimated difference in Day 60 mortality. For patients eligible for Day 60 follow-up with missing Day 60 clinical status, the proportion of patients on invasive ventilation, the proportion of patients on non-invasive ventilation and/or high flow oxygen, and the proportion of patients hospitalized but not receiving supplemental oxygen based on the last observed clinical status on or before Day 28 were similar between arms. Assuming that Day 60 outcomes were similar for patients enrolled in the study prior to the implementation of Day 60 follow-up and mortality rates between Day 28 and Day 60 among missing patients who were eligible for Day 60 follow-up were not substantially worse for the baricitinib arm after controlling for Day 28 severity, the missing data would be unlikely to have significantly biased the treatment effect of Day 60 mortality in favor of the baricitinib arm.”

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