July 21, 2021

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Dear Drs. Abrams, Carome, and Wolfe:

Thank you for your email and letter of April 21, 2021, to Drs. Woodcock and Cavazzoni in which you request that the Food and Drug Administration (FDA) convene an Antimicrobial Drugs Advisory Committee meeting to evaluate all currently available evidence regarding the safety and effectiveness of Veklury (remdesivir) and whether FDA approval of the drug should be rescinded.

Under the Federal Food, Drug & Cosmetic Act (FD&C Act) and FDA's implementing regulations, FDA has discretion in deciding whether to refer a matter to an advisory committee.[1] FDA acknowledges the important role that advisory committees can play in considering specified issues about a development program. However, as outlined below, due to the rigorous design of the ACTT-1 clinical trial in which Veklury demonstrated a robust, statistically significant treatment benefit compared to placebo for the clinically meaningful primary efficacy endpoint of time to recovery, we determined that there were no issues that necessitated referral to an advisory committee.[2]

As you mention in your letter, on October 22, 2020, FDA approved Veklury for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of

[1] See section 505(s)(2) of the FD&C Act and 21 CFR part 14.
[2] See FDA's Approval Letter for NDA 214787 covering Veklury at:
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/214787Orig1s000ltr.pdf

COVID-19 requiring hospitalization. As detailed in FDA's review memos for this application, the approval of Veklury was supported by the Agency's independent, in-depth analysis of data from three randomized, controlled clinical trials that included patients hospitalized with mild to severe COVID-19. This included the ACTT-1 trial sponsored by NIH's National Institute of Allergy and Infectious Diseases (NIAID) and the "SIMPLE" trials sponsored by Gilead Sciences Inc. The most compelling evidence of effectiveness was provided by the NIAID-sponsored ACTT-1 trial, given its rigorous trial design. [3,4,5,6,7]

The ACTT-1 trial was a randomized, placebo-controlled, double-blinded trial in hospitalized subjects with mild, moderate, or severe COVID-19 who received Veklury or placebo, in addition to standard of care. The primary goal of the ACTT-1 trial was to assess the time to recovery of hospitalized patients. Recovery was defined as either being discharged from the hospital or being hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery from COVID-19 was 10 days for the Veklury group compared to 15 days for the placebo group, a strongly statistically significant difference. The odds of clinical improvement at Day 15 were also statistically significantly higher in the Veklury group compared to the placebo group. The overall 29-day mortality was 11% for the Veklury group compared to 15% for the placebo group; this difference was not statistically significant. FDA's review of the scientific evidence from the ACTT-1 trial, combined with its review of the "SIMPLE" trials sponsored by Gilead Sciences Inc., supported the Agency's determination that the standard for substantial evidence of effectiveness and demonstration of safety as required for the approval of a new drug application under section 505 of the FD&C Act was met and supported the approved indication.[8]

The SOLIDARITY trial was a World Health Organization-sponsored, open-label, randomized trial comparing different investigational interventions plus standard of care to standard of care alone in hospitalized patients with COVID-19. One of the drugs studied in SOLIDARITY was Veklury. The SOLIDARITY trial's primary goal was to assess for effects of treatment interventions on in-hospital mortality. The SOLIDARITY trial did not find a statistically significant difference in mortality between the Veklury arm and the standard-of-care arm. While both the SOLIDARITY trial and the ACTT-1 trial contribute to our understanding of interventions to help treat COVID-19, the two clinical trials had different trial designs and primary goals. The design of ACTT-1 (i.e., randomized, placebo-controlled, double-blinded) was better suited to rigorously assess a time to recovery endpoint compared to a trial with an open-

[3] Food and Drug Administration, Center for Drug Evaluation and Research. Summary review. Application number: 214787Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000SumR.pdf.
[4] Food and Drug Administration, Center for Drug Evaluation and Research. Statistical review(s). Application number: 214787Orig1s000 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000StatR.pdf.
[5] Food and Drug Administration, Center for Drug Evaluation and Research. Clinical Review(s). Application number: 214787Orig1s000.https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000MedR.pdf.
[6] Rubin D, Chan-Tack K, Farley J, Sherwat A. FDA Approval of Remdesivir - A Step in the Right Direction. *N Engl J Med*. 2020;383(27):2598-2600 (https://www.nejm.org/doi/pdf/10.1056/NEJMp2032369).
[7] Frequently Asked Questions for Veklury (remdesivir). https://www.fda.gov/media/137574/download.
[8] See supra notes 3,4,5,6 and 7.

label design, such as the SOLIDARITY trial. Based on the findings of the ACTT-1 trial, combined with its review of the "SIMPLE" trials sponsored by Gilead Sciences Inc, FDA determined that Veklury provides clinical benefit to patients, including a shorter time to recovery and better odds of clinical improvement. The FDA carefully considered the results from SOLIDARITY and concluded that they do not refute the persuasive evidence of effectiveness from the randomized, placebo-controlled ACTT-1 trial.[9]

Thank you again for contacting FDA regarding this important matter.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2021.07.21 18:09:41 -04'00'

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[9] Supra at Note 2.

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