WARNING LETTER

Kaleido Biosciences, Inc.

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Center for Drug Evaluation and Research | CDER
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WARNING LETTER

Ref: 21-HFD-45-08-01

Dear Mr. Menichella:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted from February 24 to March 3, 2021. Investigator Kent A. Conforti, representing FDA, reviewed the role of Kaleido Biosciences, Inc. (Kaleido) as the sponsor of the following clinical investigations of the investigational drug KB109:

- Protocol K031-120: "A Randomized, Open Label, Prospective, Parallel Group Study to Assess the Natural History of COVID-19[1] and Effects of KB109 in Addition to Supportive Self Care (SSC) Compared to SSC Alone on Measures of Health in Non-hospitalized Patients with Mild-to-Moderate COVID-19"
- Protocol K032-120: "An Exploratory, Open Label, Clinical Study to Evaluate the Physiologic Effects of KB109 in Adult Patients with Mild-to-Moderate COVID-19 on Gut Microbiota Structure and Function in the Outpatient Setting"

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Investigator Conforti presented and discussed with your staff the Form FDA 483, Inspectional Observations. We acknowledge our receipt of Kaleido's March 23, 2021, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and Kaleido's March 23, 2021, written response to the Form FDA 483, it appears that Kaleido did not adhere to the applicable statutory requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and applicable regulations contained in Title 21 of the Code of Federal Regulations, part 312 [21 CFR 312] governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

Failure to submit INDs for the conduct of clinical investigations with an investigational new drug that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a), 312.20(b), and 312.40(a)].

FDA regulations require a sponsor to submit, and to have in effect, an investigational new drug application (IND) before initiating a clinical investigation of a drug that is subject to 21 CFR 312.2(a) in human subjects, unless the clinical investigation qualifies for an IND exemption under 21 CFR 312.2 (see 21 CFR 312.20 and 312.40(a)). Kaleido failed to comply with these requirements. Specifically, Kaleido initiated and conducted the following clinical investigations of investigational drug products subject to section 505 of the FD&C Act without submitting and having in effect an IND[2]:

- The clinical investigation of the investigational drug KB109 conducted under Protocol K031-120
- The clinical investigation of the investigational drug KB109 conducted under Protocol K032-120

In Kaleido's March 23, 2021, written response to the Form FDA 483, Kaleido argued that it was not obligated to submit an IND before initiating these clinical investigations because the article under study, KB109, was a food rather than a drug. Specifically, Kaleido argued that the investigations were conducted "to evaluate the effect of KB109 on the microbiome[,] as well as to determine the safety and tolerability of KB109 in the diseased population[,]" that is, human subjects with mild to moderate COVID-19, and thus it investigated KB109 for use as a food rather than a drug.

To support this argument, Kaleido asserted that it did not intend for these "food studies" to evaluate whether KB109 would be an effective treatment or mitigation for COVID-19; rather, Kaleido argued that the secondary endpoints in these studies were determinative of safety and tolerability. For this reason, Kaleido stated that KB109 was a food intervention, and consistent with Agency guidance, it was appropriate to conduct these studies without an IND in a population with COVID-19.[3]

In further discussing the purported safety and tolerability endpoints of these two studies, Kaleido stated that because the medical community was still learning about risk factors for severe COVID-19, signs and symptoms of the disease were collected in both studies to support adequate safety monitoring, in order to capture signals of disease worsening that may warrant referral to emergency medical care. Kaleido argued that it collected information on symptoms related to worsening or improvement of disease conditions to determine if KB109 would have an impact on safety or tolerability in patients with COVID-19.

Kaleido stated that the FD&C Act specifically recognizes products used in the dietary management of a disease and subject to regulation as medical foods (when such products meet the definition of a medical food, comply with the requirements for medical foods, and are not subject to regulation as drugs). Although Kaleido did not explicitly argue that the clinical investigations were exempt from the IND requirement because they studied

KB109 for use as a medical food, it did state that the findings from these studies could "enhance our understanding of the distinct nutritional requirements (DNR) that may exist in individuals with respiratory viral illnesses such as COVID-19 and would support the positioning of KB109 as a medical food."

In further arguing that its clinical investigations studied KB109's use as a food, Kaleido stated that the Generally Recognized as Safe (GRAS) status of KB109 was determined by an outside firm that evaluated not only the composition of KB109, but also its consumption safety in patients with mild to moderate COVID-19. Kaleido asserted that this GRAS determination supported its conclusion that KB109 is a lawfully marketed food ingredient that could be evaluated in food studies such as Protocols K031-120 and K032-120.

Finally, Kaleido stated that subjects were instructed to follow the Centers for Disease Control and Prevention (CDC) guidelines and supportive self-care (SSC) measures to manage COVID-19 symptoms, and argued that KB109 therefore was given for nutritional purposes and was not studied as a COVID-19 treatment.

For the reasons described below, we conclude that the evidence collected during the inspection shows that KB109 was intended for use as a drug, not as a food, in the two clinical investigations named above.

Section 201(g)(1) of the FD&C Act [21 U.S.C. 321(g)(1)] defines *drug* as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals . . . ." Kaleido studied the efficacy and safety of KB109 to mitigate and treat COVID-19 in subjects who tested positive for COVID-19 as described below:

As shown by the protocol, a published article supported by Kaleido, and Kaleido's press releases, the objective of Protocol K031-120 was to compare the safety and efficacy of KB109 in combination with SSC under quarantine protocols set forth by the CDC, with SSC alone in human subjects with mild-to-moderate COVID-19. This study evaluated efficacy endpoints intended to assess KB109 for use in mitigating or treating COVID-19, including change from baseline in, and time to resolution of, overall composite and individual COVID-19-related symptom scores; time to resolution of fever; proportion of subjects with oxygen saturation <95% and <98%; and other endpoints, such as change from baseline in bedrest time, individual measures of quality of life (QOL), proportion of subjects with improvements in patient global impression on COVID-19 condition, proportion of subjects experiencing hospital admissions (all-cause and COVID-19-related), and number of healthcare utilizations.

As shown by the protocol and a published article supported by Kaleido, the objective of Protocol K032-120 was to compare KB109, in combination with SSC under quarantine protocols set forth by the CDC or local ordinances and practices as advised by a healthcare provider, against SSC alone in human subjects with mild-to-moderate COVID-19. Physiologic effects were assessed by measuring biomarkers of inflammation and antibodies, physiologic responses of health in subjects, QOL, and hospital utilization. This study also assessed the effects of KB109 on the gut microbiome structure and function, and evaluated endpoints related to measures of health, as well as changes in laboratory measures, specific biomarkers, serology, and viral load in the presence and absence of KB109.

For Protocol K031-120, the endpoints characterized in the protocol as secondary endpoints (for example, time to resolution of individual and composite COVID-19 symptoms, time to resolution of fever, and proportion of subjects hospitalized) clearly assessed the impact of KB109 on clinical manifestations of COVID-19 and were aligned with the recommended efficacy endpoints in published FDA guidances to aid sponsors in developing products to treat patients with COVID-19.[4, 5]

For Protocol K032-120, while some endpoints could be considered safety outcomes that might be evaluated only to ensure that treatment with KB109 was not worsening the course of COVID-19, other endpoints (for example, proportion of subjects experiencing hospital admission during the follow-up period, measures of healthcare utilization, and proportion of subjects with oxygen saturation below normal) clearly assessed the use of KB109 in combination with SCC for the treatment or mitigation of COVID-19.

We note that Kaleido itself described the purpose of KB109 in the clinical investigations conducted under Protocols K031-120 and K032-120 as "treatment of mild to moderate COVID-19" in a communication to FDA.[6]

To the extent that Kaleido intended to argue that KB109 was used as a medical food in these clinical investigations, this argument fails for the following reasons:

- A product is a medical food if it is "a food . . . intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."[7] No such distinctive nutritional requirements have been established for COVID-19. Dietary management of a disease is one way to treat or mitigate that disease; therefore, to the extent that a product that does not meet the medical food definition is intended for the dietary management of a disease, it is a drug under section 201(g)(1)(B) of the FD&C Act.
- Even if there were distinctive nutritional requirements established for COVID-19, Protocols K031-120 and K032-120 went beyond "dietary management" of COVID-19 to evaluate KB109's ability to treat COVID-19 by measuring the investigational product's effects on fever, oxygen saturation, viral load, and other biomarkers of COVID-19 infection, among other things.
- Finally, the purported GRAS status of an article for one or more uses in food does not exempt the article from IND requirements when it is studied for use as a drug. In other words, an article may be a drug as used in a clinical trial, even if it is considered a food as used in other contexts. In addition, the instruction for subjects to adhere to CDC guidelines and SSC measures does not preclude investigating KB109 as an add-on therapy in the management of COVID-19 for subjects who are not at high risk for disease worsening or hospitalization.

As Kaleido noted in its response to the Form FDA 483, whether an investigational article is a drug or a food depends on the intent of the investigation. Based on the study designs of Protocols K031-120 and K032-120, KB109 as used in these clinical investigations was a drug, per 201(g)(1) of the FD&C Act, because KB109 was studied for use in the mitigation and treatment of COVID-19.

Thus, before initiating the clinical investigations of KB109 conducted under Protocol K031- 120 and Protocol K032-120, Kaleido was required to submit an IND to FDA and to have an IND in effect under 21 CFR 312.40. FDA's records indicate that Kaleido failed to submit an IND before conducting these clinical investigations, in which 350 human subjects were randomized at 16 clinical sites for Protocol K031-120, and 49 human subjects were randomized at 7 clinical sites for Protocol K032-120.

In its response to the Form FDA 483, Kaleido stated that it is developing a procedure for determining the need for an IND (in consultation with FDA) when developing protocols for clinical studies in a disease population where endpoints may be viewed as diagnosing, mitigating, treating, preventing, or curing a disease. Kaleido's corrective action plan does not provide sufficient details about its new procedure for IND determination. Without these details, we are unable to determine whether Kaleido's corrective action plan is adequate to prevent similar violations in the future.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address any deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations.

Within 15 business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately address this matter may lead to regulatory action. If you believe you have complied with the FD&C Act and relevant FDA regulations, please include your reasoning and any supporting information for our consideration.

If you have any questions, please call Miah Jung, Pharm.D., at 240-402-3728. Alternatively, you may e-mail FDA at CDER-OSI-Communications@fda.hhs.gov. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
/S/

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1 Coronavirus Disease 2019 (COVID-19) is the respiratory disease caused by the novel coronavirus called *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2).

2 Also, neither of these clinical investigations qualified for any of the exemptions listed at 21 CFR 312.2 from the application of 21 CFR 312.

3 *Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND, September 2013*.

4 Guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020; updated February 2021).

5 Guidance for industry *Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment* (September 2020).

6 Pre-IND 151218 Type B Meeting Package for KB109, Kaleido Biosciences, Inc. (July 2, 2020).

7 21 U.S.C. 360ee(b)(3).

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