Aldeyra Therapeutics Provides Regulatory Update on ADX-2191

June 21, 2023

- **Based on U.S. Food & Drug Administration (FDA) Determination of Lack of Adequate and Well Controlled Investigations in the Scientific Literature, Complete Response Letter Received for New Drug Application (NDA) of ADX-2191 (methotrexate injection, USP) for the Treatment of Primary Vitreoretinal Lymphoma (PVRL)**
- **Due to Shortage of Methotrexate, Lack of Approved Therapy for PVRL, and Inbound Requests for ADX-2191, Expanded Access Program Planned to be Discussed with FDA**

LEXINGTON, Mass.--(BUSINESS WIRE)--Jun. 21, 2023-- (Nasdaq: ALDX) (Aldeyra), a biotechnology company devoted to discovering and developing innovative therapies designed to treat immune-mediated diseases, today announced receipt of a Complete Response Letter from the U.S. Food and Drug Administration (FDA) for the 505(b)(2) New Drug Application (NDA) of ADX-2191 (methotrexate for injection, USP), an investigational drug candidate, for the treatment of primary vitreoretinal lymphoma (PVRL). Although no safety or manufacturing issues with ADX-2191 were identified, the FDA stated that there was a “lack of substantial evidence of effectiveness” due to “a lack of adequate and well-controlled investigations” in the literature-based NDA submission. Based on prior discussions with the FDA, Aldeyra did not conduct any clinical trials of ADX-2191 in PVRL.

“While we appreciate the FDA’s position with respect to providing evidence from adequate and controlled trials, we do not currently believe that randomized clinical trials of ADX-2191 in PVRL, a rare and fatal cancer with no approved therapy, are feasible,” stated Todd C. Brady, M.D., Ph.D., President and Chief Executive Officer of Aldeyra Therapeutics. “Given the current shortage of methotrexate, the lack of approved therapy for PVRL, and the desire to avoid potential safety risks associated with ocular injection of compounded formulations, we look forward to discussing with the FDA the potential for making ADX-2191 available to PVRL patients under an Expanded Access Program.”

PVRL is a rare, high-grade, aggressive cancer, with a median survival of less than five years.[1] Methotrexate, the compounded intravitreal injection of which is the standard of care for the treatment of PVRL,[2] is currently in shortage, per the FDA Drug Shortages database. An Expanded Access Program allows for access to treatment options for serious diseases when other therapeutic options are not available. Aldeyra plans to discuss ADX-2191 for the treatment of PVRL with the FDA, including the potential to make ADX-2191 accessible to PVRL patients under an Expanded Access Program protocol.

ADX-2191 is also under development for the treatment of proliferative vitreoretinopathy and retinitis pigmentosa, both of which are rare, sight-threatening retinal diseases. Top-line results from a Phase 2 clinical trial of ADX-2191 in retinitis pigmentosa are expected to be announced in June of 2023. Additionally, Aldeyra plans to conduct a Type C meeting with the FDA in the second half of 2023 to discuss the completion of clinical development of ADX-2191 for the prevention of proliferative vitreoretinopathy.

About Aldeyra

Aldeyra Therapeutics is a biotechnology company devoted to discovering innovative therapies designed to treat immune-mediated diseases. Our approach is to develop pharmaceuticals that modulate immunological systems, instead of directly inhibiting or activating single protein targets, with the goal of optimizing multiple pathways at once while minimizing toxicity. Our product candidates include RASP (reactive aldehyde species) modulators ADX-629, ADX-246, ADX-248, and chemically related molecules for the potential treatment of systemic and retinal immune-mediated diseases. Our pre-commercial product candidates are reproxalap, a RASP modulator for the potential treatment of dry eye disease (under U.S. Food and Drug Administration New Drug Application Review) and allergic conjunctivitis, and ADX-2191, a novel formulation of intravitreal methotrexate for the potential treatment of proliferative vitreoretinopathy and retinitis pigmentosa.

Safe Harbor Statement

This release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the potential for an ADX-2191 Expanded Access Program, Aldeyra’s plans and expectations for ADX-2191 and future discussions with the FDA regarding ADX-2191. Aldeyra intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. In some cases, you can identify forward-looking statements by terms such as, but not limited to, “may,” “might,” “will,” “objective,” “intend,” “should,” "could," “can,” “would,” “expect,” “believe,” “anticipate,” “project,” “on track,” “scheduled,” “target,” “design,” “estimate,” “predict,” “contemplates,” “likely,” “potential,” “continue,” “ongoing,” “aim,” “plan,” or the negative of these terms, and similar expressions intended to identify forward-looking statements. Such forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions, and uncertainties. Aldeyra is at an early stage of development and may not ever have any products that generate significant revenue. All of Aldeyra's development timelines may be subject to adjustment depending on recruitment rate, regulatory review, preclinical and clinical results, funding, and other factors that could delay the initiation, enrollment, or completion of clinical trials. Important factors that could cause actual results to differ materially from those reflected in Aldeyra's forward-looking statements include, among others, the timing of enrollment, commencement and completion of Aldeyra's clinical trials, the timing and success of preclinical studies and clinical trials conducted by Aldeyra and its development partners; delay in or failure to obtain regulatory approval of Aldeyra's product candidates, including as a result of the FDA not accepting Aldeyra’s regulatory filings, issuing a complete response letter, or requiring additional clinical trials or data prior to review or approval of such filings; the ability to maintain regulatory approval of Aldeyra's product candidates, and the labeling for any approved products; the risk that prior results, such as signals of safety, activity, or durability of effect, observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or clinical trials involving Aldeyra's product candidates in clinical trials focused on the same or different indications; the scope, progress, expansion, and

costs of developing and commercializing Aldeyra's product candidates; the current and potential future impact of the COVID-19 pandemic on Aldeyra's business, results of operations, and financial position; uncertainty as to Aldeyra's ability to commercialize (alone or with others) and obtain reimbursement for Aldeyra's product candidates following regulatory approval, if any; the size and growth of the potential markets and pricing for Aldeyra's product candidates and the ability to serve those markets; Aldeyra's expectations regarding Aldeyra's expenses and future revenue, the timing of future revenue, the sufficiency or use of Aldeyra's cash resources and needs for additional financing; the rate and degree of market acceptance of any of Aldeyra's product candidates; Aldeyra's expectations regarding competition; Aldeyra's anticipated growth strategies; Aldeyra's ability to attract or retain key personnel; Aldeyra's commercialization, marketing and manufacturing capabilities and strategy; Aldeyra's ability to establish and maintain development partnerships; Aldeyra's ability to successfully integrate acquisitions into its business; Aldeyra's expectations regarding federal, state, and foreign regulatory requirements; political, economic, legal, social, and health risks, including the COVID-19 pandemic and subsequent public health measures, and war or other military actions, that may affect Aldeyra's business or the global economy; regulatory developments in the United States and foreign countries; Aldeyra's ability to obtain and maintain intellectual property protection for its product candidates; the anticipated trends and challenges in Aldeyra's business and the market in which it operates; and other factors that are described in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Aldeyra's Annual Report on Form 10-K for the year ended December 31, 2022, and Aldeyra's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, which are on file with the Securities and Exchange Commission (SEC) and available on the SEC's website at https://www.sec.gov/. Additional factors may be described in those sections of Aldeyra's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023, expected to be filed with the SEC in the third quarter of 2023.

In addition to the risks described above and in Aldeyra's other filings with the SEC, other unknown or unpredictable factors also could affect Aldeyra's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. The information in this release is provided only as of the date of this release, and Aldeyra undertakes no obligation to update any forward-looking statements contained in this release on account of new information, future events, or otherwise, except as required by law.

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[1]Annals of Oncology, 18(11): 1851–1855, 2007.

[2]British Journal of Haematology, 194: 92–100, 2021.

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