Aldeyra Therapeutics Receives Special Protocol Assessment Agreement Letter from the U.S. Food and Drug Administration for ADX-2191 for the Treatment of Primary Vitreoretinal Lymphoma

June 26, 2025

LEXINGTON, Mass.--(BUSINESS WIRE)--Jun. 26, 2025-- Aldeyra Therapeutics, Inc. (Nasdaq: ALDX) (Aldeyra) today announced receipt of a Special Protocol Assessment Agreement Letter from the U.S. Food and Drug Administration (FDA) for ADX-2191 (methotrexate injection, USP), an investigational drug candidate, for the treatment of primary vitreoretinal lymphoma (PVRL), a rare and potentially fatal cancer currently lacking FDA-approved therapy.

“Primary vitreoretinal lymphoma is treated today off label with intravitreal injections of compounded methotrexate,” stated Todd C. Brady, M.D., Ph.D., President and Chief Executive Officer of Aldeyra. “ADX-2191, a novel, vitreous-compatible formulation of methotrexate that is specifically designed for intraocular injection, potentially allows for a reduced injection volume relative to compounding.”

Based on a pre-New Drug Application (NDA) meeting with the FDA in December 2022, Aldeyra submitted a literature-based NDA of ADX-2191 for the treatment of PVRL, which was accepted for Priority Review in March 2023. In June 2023, Aldeyra received a Complete Response Letter that stated that the available literature was not sufficient to demonstrate efficacy and that adequate and well-controlled trials were required for approval. The FDA subsequently agreed that a single clinical trial in addition to literature references will be sufficient to support NDA resubmission.

The clinical trial proposed in the Special Protocol Assessment will compare cancer cell clearance after 30 days of therapy in up to 20 patients following 1:1 randomization to receive either a single intraocular injection or eight intraocular injections of ADX-2191. The frequency of methotrexate injections has been linked to cancer cell clearance in patients with PVRL,[1] and approximately five injections are required on average to achieve cancer cell clearance.[2] The clinical trial is expected to begin in the second half of 2025 and conclude in 2026.

About ADX-2191

ADX-2191 (methotrexate injection, USP) is a sterile, non-compounded intravitreal formulation of methotrexate for the potential treatment of specific rare retinal diseases, including primary vitreoretinal lymphoma and retinitis pigmentosa. The ADX-2191 intravitreal formulation is preservative-free, is designed to be vitreous-compatible, and is optimized for excipient composition, viscosity, density, tonicity, pH, concentration, and volume of administration. ADX-2191 has received FDA Orphan Drug Designation for the treatment of primary vitreoretinal lymphoma and retinitis pigmentosa.

About Primary Vitreoretinal Lymphoma

Primary vitreoretinal lymphoma is a rare, aggressive, and potentially fatal retinal cancer that is diagnosed in approximately 300 to 600 patients in the United States per year. The median survival for newly diagnosed patients is less than five years. No approved treatments are currently available, though intravitreal injection of compounded methotrexate represents the current standard of care.

About Aldeyra

Aldeyra Therapeutics is a biotechnology company devoted to discovering innovative therapies designed to treat immune-mediated and metabolic diseases. Our approach is to develop pharmaceuticals that modulate protein 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-248, ADX-743, ADX-631, ADX-246, and chemically related molecules for the potential treatment of systemic and retinal immune-mediated and metabolic diseases. Our late-stage product candidates are reproxalap, a RASP modulator for the potential treatment of dry eye disease and allergic conjunctivitis, and ADX-2191, a novel formulation of intravitreal methotrexate for the potential treatment of primary vitreoretinal lymphoma 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 Aldeyra’s future expectations, plans, and prospects, including without limitation statements regarding: the goals, opportunity, and potential for ADX-2191; the outcome and timing of any clinical trials of ADX-2191; and the outcome and timing of the FDA’s acceptance, review, or approval of a potential NDA resubmission for ADX-2191 and the adequacy of the data expected to be included in such potential resubmitted NDA. 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 or in connection with resubmissions 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; 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, 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, 2024, and Aldeyra's Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, which are on file with the Securities and Exchange Commission (SEC) and available on the SEC 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, 2025, expected to be filed with the SEC in the third quarter of 2025, and Aldeyra's other filings with the SEC.

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] Am J Ophthalmol 251: 189–196, 2023

[2] Br J Haematol, 194, 92–100, 2021; Cancer Sci. 107:1458-1464, 2016

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