Evelo Biosciences Provides Clinical and Business Updates

– Data from first three cohorts of EDP1815 Phase 2 trial in atopic dermatitis did not meet primary endpoint; unusually high placebo response rate observed –
– Clear path to registration trials for EDP1815 in psoriasis based on recently completed interactions with FDA, EMA and MHRA –
– Dosing commenced in clinical study with first extracellular vesicle (EV) product candidate EDP2939 in January; Phase 2 data in psoriasis anticipated in 2H 2023 –
– Optimizing operations and reducing workforce to focus resources on strategic priorities –
– CEO Simba Gill, Ph.D., will continue to lead the organization, halting search for successor –
– Management to host conference call today at 8:30 a.m. ET –

CAMBRIDGE, Mass., February 1, 2023 – Evelo Biosciences, Inc. (Nasdaq:EVLO), a clinical stage biotechnology company developing a novel platform of orally delivered medicines acting on the small intestinal axis (SINTAX) today announced updates to its clinical pipeline as well as business updates.

"We observed an unusually high placebo response rate in the first three cohorts of the EDP1815 Phase 2 atopic dermatitis study, resulting in a missed primary endpoint," said Simba Gill, Ph.D., CEO of Evelo. "We are working through the data to understand the very high placebo rates observed in the trial, which occurred with greater prevalence in certain geographic regions. The fourth cohort of the trial, which is designed to test the faster release formulation, is fully recruited and we expect to report data from this cohort in the second quarter of this year. The results of this cohort will inform our path forward in atopic dermatitis."

Dr. Gill continued, "We have recently completed interactions with the FDA, EMA and MHRA around proposed Phase 3 plans in psoriasis. Based on their feedback, we believe we have a clear path towards a global registration program for EDP1815 in psoriasis. As a reminder, EDP1815 was well-tolerated and demonstrated positive efficacy results in a Phase 2 psoriasis clinical trial, supporting further development of EDP1815 for the broad treatment of psoriasis patients with mild and moderate disease for which there are few treatment options."

"Additionally, we are pleased to announce that we have begun dosing in the first clinical trial of a microbial extracellular vesicle (EV)," Dr. Gill said. "EVs have the potential to be a new type of potent SINTAX-based medicine and we are looking forward to reporting Phase 2 data for EDP2939 in psoriasis expected in the second half of this year."

"Given the challenging financial macro-environment, we have implemented cost-saving initiatives in order to extend our cash runway. As part of this initiative, we have reduced our workforce and are prioritizing investment in our core clinical programs. I am deeply thankful to our people, who have helped advance a new area of science and create the potential for a new treatment modality. I want to particularly thank those who are leaving for their exceptional contributions and commitment," Dr. Gill stated.

Clinical and Business Updates

EDP1815 Phase 2 in Atopic Dermatitis – Topline Data from First Three Cohorts; Data from Fourth Cohort Expected 2Q 2023

- The first three cohorts of the EDP1815-207 trial failed to meet the primary endpoint which is the proportion of patients who achieve an outcome of at least a 50% improvement from baseline in Eczema Area and Severity Index (EASI) score, an EASI-50 response, compared to placebo at week 16.
- Cohorts 1-3 evaluated different concentrations, dosing regimens and manufacturing processes of EDP1815.
- In all three cohorts, EDP1815 was well-tolerated.
- EASI-50 responses or greater were achieved in 41%, 38% and 32% of patients with mild to moderate disease at week 16, in cohorts 1, 2 and 3 respectively.

- Patients on placebo had an overall EASI-50 response of 56%. Placebo responses varied significantly by geography.
- The Company is continuing to analyze the data to understand the unusually high placebo rate, particularly in specific geographies.
- The fourth cohort of the Phase 2 trial of EDP1815 in atopic dermatitis is testing a faster release capsule that potentially enables greater clinical activity.
- Data from this cohort of patients is expected in 2Q 2023 and will inform the Company's next steps in atopic dermatitis.

EDP1815 Phase 3 in Psoriasis – FDA Feedback Recently Received Provides Path to Registration Trials

- Evelo has now received feedback from the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) regarding the proposed registration trial design of EDP1815 in psoriasis, including the primary and secondary endpoints.
- Feedback from all three agencies provides a path towards registration trials in psoriasis. The Company is incorporating the comments received into its Phase 3 study designs.

EDP2939 in Psoriasis – Initiation of Dosing in First EV Product Candidate

- Dosing of healthy volunteers in Part A (Phase 1) of the trial began in January 2023 and the Company anticipates dosing of patients in Part B (Phase 2a) to commence later in 1Q 2023.
- Phase 2 data in the cohort of patients with psoriasis is still expected in the second half of 2023.

Other Business Updates

- The Company's Board of Directors has asked Simba Gill to remain in his position as CEO at this time, and the Company has halted the search for his successor.
- The Company has taken actions to implement cost reduction initiatives, including a reduction in workforce. These measures are expected to extend the Company's cash runway into 3Q 2023. The Company's core clinical priorities remain unchanged.
- Evelo is in active discussions regarding partnership opportunities across EDP1815, EDP2939, as well as the EV platform.

Conference Call

Evelo will host a conference call and webcast at 8:30 a.m. ET today. To listen to the conference call by phone, participants must pre-register here. A live webcast can be accessed under "News & Events" in the investors section of Evelo's website, https://ir.evelobio.com/news-events. The archived webcast will be available on Evelo's website for approximately 90 days following the event.

About the EDP1815-207 Trial

EDP1815-207 is a multi-center, randomized, double-blind, placebo-controlled Phase 2 trial designed to evaluate the efficacy and safety of EDP1815 in the treatment of atopic dermatitis when dosed for 16 weeks, compared to placebo. The trial enrolled patients with mild, moderate, and severe atopic dermatitis and each of the four cohorts is investigating a different aspect of the potential of EDP1815 in the treatment of atopic dermatitis.

The primary endpoint for the trial is the proportion of patients who achieve an outcome of a 50% improvement from baseline in Eczema Area and Severity Index (EASI) score (an EASI-50 response) at week 16. Secondary endpoints include several physician-reported outcomes, such as Investigator's Global Assessment ("IGA") and body surface area ("BSA"), along with patient-reported outcomes such as Dermatology Life Quality Index ("DLQI"), daily itch using the Pruritus-Numerical Rating Scale ("Pruritus-NRS"), and Patient-Oriented Eczema Measure ("POEM"). Patients are randomized into one of four cohorts. Cohorts 1-3 include approximately 100 patients per cohort randomized in a 3:1 ratio (75 to EDP1815 and 25 to placebo) for a total of approximately 300 patients. Cohorts 1-3 evaluate different concentrations, dosing regimens and manufacturing processes of EDP1815. Patients in Cohort 4, testing the faster release capsule, are randomized in a 2:1 ratio (70 to EDP1815 and 35 to placebo) for a total of approximately 105 patients.

About Evelo Biosciences
Evelo Biosciences is a clinical stage biotechnology company developing a novel platform of orally delivered medicines acting on the small intestinal axis, SINTAX, with systemic therapeutic effects. SINTAX plays a central role in governing the immune, metabolic, and neurological systems. The Company's product candidates are pharmaceutical preparations of single strains of microbes or their extracellular vesicles (EVs). Evelo's vision is to create therapies that are effective, safe, well-tolerated, and affordable to improve the lives of the billions of people living with inflammatory diseases. Evelo initially is developing EDP1815 in psoriasis and atopic dermatitis and EDP2939 in psoriasis. If shown to be effective in inflammatory disease mediated by the Th1, Th2 or Th17 inflammatory pathways, these same investigational medicines could be effective in additional inflammatory diseases, such as psoriatic and other forms of arthritis, asthma, allergy, and inflammatory bowel disease.

For more information, please visit www.evelobio.com and engage with Evelo on LinkedIn.

Forward Looking Statements
This press release contains forward-looking statements, including within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including statements concerning the expected timing of, and data results from, trials and clinical studies involving the Company's product candidates; and the expected impact, cost savings and cash runway resulting from the Company's cost saving initiatives.

These forward-looking statements are based on management's current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: we have incurred significant losses, are not currently profitable and may never become profitable; our projected cash runway; our need for additional funding; our ability to meet our debt obligations (including restrictive and operational covenants and terms of refinanced debt); our ability to cure or satisfactorily resolve any default arising from our debt agreements; our limited operating history; our unproven approach to therapeutic intervention; our ability to address regulatory questions and the likelihood of regulatory filings and approvals; the lengthy, expensive, and uncertain process of clinical drug development, including potential delays in regulatory approval; our reliance on third parties and collaborators to expand our microbial library, conduct our clinical trials, manufacture our product candidates, and develop and commercialize our product candidates, if approved; our lack of experience in manufacturing, selling, marketing, and distributing our product candidates; failure to compete successfully against other drug companies; protection of our proprietary technology and the confidentiality of our trade secrets; potential lawsuits for, or claims of, infringement of third-party intellectual property or challenges to the ownership of our intellectual property; our patents being found invalid or unenforceable; risks associated with international operations; our ability to operate with a reduced workforce, to manage potential growth and to retain key personnel, particularly following a significant downsizing; the potential volatility of our common stock; our management and principal stockholders have the ability to control or significantly influence our business; costs and resources of operating as a public company; unfavorable or no analyst research or reports; the impact of the COVID-19 pandemic on our operations, including our preclinical studies and clinical trials, and the continuity of our business; and securities class action litigation against us.

These and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the period ended September 30, 2022, and our other reports filed with the United States Securities and Exchange Commission, could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-looking statements represent management's estimates as of the date of this press release. While we may elect to update such forward-looking statements at some point in the future, except as required by law, we disclaim any obligation to do so, even if subsequent events cause our

views to change. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this press release.

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