

PROSPECTUS SUPPLEMENT
(to Prospectus dated June 6, 2019)

4,500,000 Shares



Common Stock

We are offering 4,500,000 shares of our common stock.

Our shares trade on The Nasdaq Global Select Market under the symbol “EVLO.” On January 28, 2021, the last sale price of our shares as reported on The Nasdaq Global Select Market was \$18.60 per share.

We are an “emerging growth company” under the federal securities laws and are subject to reduced public company disclosure standards. See “Prospectus Supplement Summary—Implications of Being an Emerging Growth Company.”

On January 28, 2021, we entered into a stock purchase agreement with ALJ Health Care & Life Sciences Company Limited, or ALJ, pursuant to which ALJ agreed to purchase, subject to certain conditions, up to \$7.5 million of our common stock in a private placement concurrent, or the concurrent private placement, with, and subject to, the completion of this offering, at a purchase price of \$15.00 per share, equal to the public offering price per share at which our common stock is sold to the public in this offering. The sale of such shares will not be registered under the Securities Act of 1933, as amended, or the Act. The closing of this offering is not conditioned upon the closing of the concurrent private placement.

Investing in our common stock involves risks that are described in the “[Risk Factors](#)” beginning on page S-7 of this prospectus supplement, page 5 of the accompanying prospectus and under similar headings in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

	<u>Per Share</u>	<u>Total</u>
Public Offering Price	\$ 15.00	\$ 67,500,000
Underwriting Discounts and commissions ⁽¹⁾	\$ 0.90	\$ 4,050,000
Proceeds, before expenses, to us	\$ 14.10	\$ 63,450,000

⁽¹⁾ See the section entitled “Underwriting” for additional disclosure regarding underwriter compensation and estimated offering expenses.

The underwriters may also exercise their option to purchase up to an additional 675,000 of shares from us, at the public offering price, less the underwriting discount, for 30 days after the date of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The shares will be ready for delivery on or about February 2, 2021.

Joint Book-Running Managers

Morgan Stanley

Cowen

BMO Capital Markets

The date of this prospectus supplement is January 28, 2021

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We have proprietary rights to trademarks, trade names and service marks appearing in this prospectus supplement that are important to our business. Solely for convenience, the trademarks, trade names and service marks may appear in this prospectus supplement without the ® and TM symbols, but any such references are not intended to indicate, in any way, that we forgo or will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensors to these trademarks, trade names and service marks. All trademarks, trade names and service marks appearing in this prospectus supplement are the property of their respective owners.

ABOUT THIS PROSPECTUS SUPPLEMENT

On June 3, 2019, we filed with the Securities and Exchange Commission, or SEC, a registration statement on Form S-3 (File No. 333-231911) utilizing a shelf registration process relating to the securities described in this prospectus supplement, which registration statement was declared effective on June 6, 2019. Under this shelf registration process, we may, from time to time, sell up to \$200 million in the aggregate of common stock, preferred stock, warrants and/or units in any combination.

This prospectus supplement describes the specific terms of this offering of shares of our common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein and into the accompanying prospectus. The second part, the accompanying prospectus, provides more general information. If the information in this prospectus supplement is inconsistent with the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement.

We and the underwriters have not authorized anyone to provide you with any information or to make any representations other than those included or incorporated by reference in this prospectus supplement and the accompanying prospectus and any relevant free writing prospectus. If you receive any information not authorized by us, we and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, such information. We are not making an offer to sell the shares of common stock in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus or any relevant free writing prospectus is accurate as of any date other than its respective date, regardless of its time of delivery or any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

It is important for you to read and consider all of the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus in making your investment decision. We include cross-references in this prospectus supplement and the accompanying prospectus to captions in these materials where you can find additional related discussions. The table of contents in this prospectus supplement provides the pages on which these captions are located. You should read both this prospectus supplement and the accompanying prospectus, together with the additional information described in the sections entitled “Where You Can Find More Information” on page S-27 and “Incorporation by Reference” on page S-28 of this prospectus supplement, before investing in our common stock.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless the context otherwise requires, “Evelo Biosciences,” the “company,” “we,” “us,” “our” and similar names refer to Evelo Biosciences, Inc. and its consolidated subsidiaries.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering may contain forward-looking statements. All statements other than statements of historical facts contained in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, including statements regarding our future results of operations and financial position, anticipated use of cash, business strategy, prospective products, product approvals, manufacturing development activities, research and development costs, anticipated timing and likelihood of success of clinical trials, expected timing of the release of clinical trial data, the plans and objectives of management for future operations and future results of anticipated products, are forward-looking statements. These statements 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. This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus may also contain estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other similar expressions. The forward-looking statements in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the respective dates of this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, as applicable, and are subject to a number of risks, uncertainties and assumptions, including those described under “Risk Factors” and elsewhere in this prospectus supplement. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, whether as a result of any new information, future events, changed circumstances or otherwise.

PROSPECTUS SUPPLEMENT SUMMARY

The following summary is qualified in its entirety by, and should be read together with, the more detailed information and financial statements and related notes thereto appearing elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. Before you decide to invest in our securities, you should read the entire prospectus supplement and the accompanying prospectus carefully, including the risk factors and the financial statements and related notes included or incorporated by reference in this prospectus supplement and the accompanying prospectus.

Our Company

Overview

Evelo Biosciences is discovering and developing a new class of orally delivered investigational medicines that are intended to act on cells in the small intestine to produce systemic therapeutic effects throughout the body. The target cells in the small intestine play a central role in governing the immune, metabolic and neurological systems throughout the body. We refer to this biology as the small intestinal axis, or SINTAX™. We have built a platform to discover and develop novel oral medicines which target SINTAX. By harnessing SINTAX, we believe we can transform healthcare via medicines that have the potential to be effective, safe, convenient and affordable and be able to treat patients at all stages of disease and to treat patients globally.

Our first product candidates are orally delivered pharmaceutical preparations derived from naturally occurring, specific single strains of microbes. In preclinical models, our product candidates have engaged immune cells in the small intestine and driven changes in systemic biology without systemic exposure and without colonizing the gut. We have observed in early clinical trials and in preclinical studies that specific product candidates modulated immune responses throughout the body by acting on SINTAX. We currently have one product candidate in multiple clinical trials, EDP1815 for the treatment of inflammatory diseases and the treatment of hyperinflammation caused by SARs-CoV-2. We have two additional product candidates for the treatment of inflammatory diseases: EDP1867 and EDP2939, and one additional product candidate for the treatment of cancer: EDP1908.

We believe that orally delivered SINTAX medicines have the potential to address patient needs at all stages of disease due to their potentially superior characteristics over current therapies:

- Each of our product candidates has been observed to act through multiple clinically relevant and validated biological pathways in preclinical models. By acting on multiple pathways simultaneously, we believe our product candidates could impact disease in ways that are not possible with current single-target or dual-target therapies.
- Our data suggest that our product candidates for inflammatory diseases have the potential to resolve disease causing inflammation while preserving immunity, a significant potential benefit compared to other anti-inflammatory therapies that often cause significant immunosuppression.
- We believe our product candidates are likely to be well-tolerated given that they are derived from naturally occurring, specific single strains of human commensal microbes that engage immune cells in the small intestine and drive changes in systemic biology without systemic exposure and without colonizing the gut. Our initial clinical data support this potential and, if we are able to validate this profile in future clinical trials, we believe our product candidates have the potential to be used at all stages of disease and in many more patients than current immunomodulatory drugs.
- Our discovery and development of oral SINTAX product candidates has the potential to be more efficient than other product classes such as cell therapy, monoclonal antibodies and small molecules.

We believe our product candidates do not require the lengthy target validation and compound discovery requirements of conventional drug discovery.

Recent Developments

EDP1815

In December 2020, we announced positive topline clinical data from our Phase 1b clinical trial of EDP1815 in 23 evaluable subjects with mild to moderate atopic dermatitis, also known as eczema. The primary endpoint of the Phase 1b trial was safety and tolerability. EDP1815 was observed to be well tolerated with no serious adverse events. Secondary endpoints included a range of established markers of clinical efficacy in atopic dermatitis, such as the percentage change in Eczema Area and Severity Index, or EASI, score, which is the most common tool used to measure extent and severity of atopic eczema, and the percentage change in Investigator’s Global Assessment and Body Surface Area (IGA*BSA). Clinical differences were observed in evaluable subjects at day 56 between those receiving EDP1815 and placebo, in both the percentage change in EASI (62% difference, p=0.034) and the percentage change in IGA*BSA (71% difference, p=0.019). Improvements in these measures were observed as early as day 14. At day 56, 10 out of 16 patients in the active group showed improvements in EASI score, with four out of 16 patients having achieved an EASI50 clinical response, three of which achieved at least an EASI75, compared to zero out of seven of patients in the placebo group. EASI50 and EASI75 represent 50% and 75% improvements, respectively, as compared to the patient’s baseline EASI score. These results provide further evidence that modulating SINTAX can drive significant clinical benefit without the need for systemic exposure.

On January 20, 2021, we announced additional clinical data following completion of the mild and moderate atopic dermatitis cohort in the Phase 1b clinical trial. These new results included patient-reported outcomes, as well as all of the physician-reported outcomes for all 24 patients in the cohort. EDP1815 was well tolerated in this cohort with no treatment-related adverse events of moderate or severe intensity, and no serious adverse events.

Treatment with EDP1815 resulted in clinically meaningful improvement in the Dermatology Life Quality Index, or DLQI, and Patient-Oriented Eczema Measure, or POEM. These patient-reported outcomes capture the important impact of the disease on patients, including the domains of itch and sleep, both of which saw improvements in patients receiving EDP1815. All five measures of itch within the Pruritus-Numerical Rating Scale (Pruritus-NRS), SCORing Atopic Dermatitis, or SCORAD, POEM, and DLQI showed greater improvements in the treated group at day 56 compared with placebo.

The full results reinforced the positive interim data released in December 2020. Additional physician- reported outcomes of Investigator’s Global Assessment, or IGA, and SCORAD were consistent with the previously reported EASI and IGA*BSA measures. Table 1 shows the treatment difference between patients receiving EDP1815 and placebo as measured by percentage change of these well-established efficacy endpoints at day 56.

Table 1

<u>Clinical Measure</u>	<u>Treatment Difference between EDP1815 and Placebo Percentage Change at Day 56*</u>
EASI	52% (p=0.062)
IGA*BSA	65% (p=0.022)
SCORAD	55% (p=0.043)

* Least Squares Mean Percentage Change From Baseline

Although the Phase 1b study was not powered to evaluate statistical significance on efficacy measures, the data showed consistent improvements in percentage change from baseline compared to placebo for all three clinical scores: EASI, IGA*BSA, and SCORAD. In addition, 7 out of 16 (44%) patients treated with EDP1815 achieved an outcome of a 50% improvement from baseline in EASI score (EASI50) by day 70, compared with 0% in the placebo group, showing sustained improvement in those patients responding to EDP1815.

We expect to report additional biomarker data from this Phase 1b trial at a future medical conference. We are planning to initiate a Phase 2 dose-ranging study of EDP1815 in atopic dermatitis in Q3 2021.

EDP 1908 and EDP 1503

In December 2020, we announced that we are prioritizing EDP1908 as our lead clinical candidate in oncology given its superior preclinical activity over EDP1503. We have halted patient recruitment in the Phase 1/2 clinical trial of EDP1503 and intend to wind down the study. Interim clinical data from our Phase 1/2 open-label study evaluating EDP1503 in combination with pembrolizumab in patients with triple-negative breast cancer showed that as of a cutoff date of October 30, 2020, EDP1503 was well-tolerated, with an overall response rate of 17% and a disease control rate, or DCR, of 25% in the 12 patients who received the higher dose of EDP1503. These results suggest that SINTAX has the potential to be targeted with oral, well tolerated, gut-restricted medicines.

Concurrent Private Placement

On January 28, 2021, we entered into a stock purchase agreement with ALJ Health Care & Life Sciences Company Limited, or ALJ, pursuant to which ALJ agreed to purchase, subject to certain conditions, \$7.5 million of our common stock in a private placement concurrent with, and subject to, the completion of this offering, at a purchase price of \$15.00 per share, equal to the public offering price per share at which our common stock is sold to the public in this offering. The sale of such shares will not be registered under the Act. The closing of this offering is not conditioned upon the closing of the concurrent private placement.

Company Information

We were incorporated under the laws of the State of Delaware in 2014. Our executive offices are located at 620 Memorial Drive, Massachusetts 02139, and our telephone number is (617) 577-0300. Our website address is www.evelobio.com. We do not incorporate the information on or accessible through our website into this prospectus supplement, and you should not consider any information on, or that can be accessed through, our website as part of this prospectus supplement.

Implications of Being an Emerging Growth Company

We qualify as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, as amended, or the JOBS Act. As an emerging growth company, we may take advantage of reduced reporting requirements that are otherwise applicable generally to public companies. These provisions include, but are not limited to:

- the option to present only two years of audited financial statements in addition to any required unaudited interim financial statements and only two years of related “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure;
- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements;
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved;

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- exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting; and
- an exemption from new or revised financial accounting standards until they would apply to private companies and from compliance with any new requirements adopted by the Public Company Accounting Oversight Board requiring mandatory audit firm rotation.

We may take advantage of these exemptions for up to five years or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of \$1.07 billion or more; (ii) December 31, 2023; (iii) the date on which we have issued more than \$1 billion in non-convertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. We have elected to take advantage of this extended transition period.

THE OFFERING

Common stock offered by us	4,500,000 shares of common stock.
Option to purchase additional shares	We have granted the underwriters an option for a period of 30 days after the date of this prospectus supplement to purchase up to an additional 675,000 shares of common stock at the public offering price, less the underwriting discount.
Common stock to be outstanding immediately after this offering	52,470,119 shares of common stock (or 53,145,119 shares of common stock if the underwriters exercise their option to purchase additional shares in full).
Concurrent private placement	ALJ has agreed to purchase \$7.5 million of our common stock in a private placement concurrent with, and subject to, the completion of this offering at a purchase price of \$15.00 per share, equal to the initial public offering price per share at which our common stock is sold to the public in this offering. The sale of such shares will not be registered under the Act. The closing of this offering is not conditioned upon the closing of the concurrent private placement.
Use of proceeds	We intend to use the net proceeds from the offering and the concurrent private placement, in addition to our existing cash resources, for the following purposes: (i) continue the development of EDP1815 in a Phase 2 trial in psoriasis and initiate a Phase 2 trial of EDP1815 in atopic dermatitis; (ii) prepare to advance EDP1815 in multiple Phase 3 trials in psoriasis and atopic dermatitis, upon receipt of positive Phase 2 data; (iii) continue the Phase 2 and Phase 2/3 clinical trials of EDP1815 for the treatment of hyperinflammation caused by SARs-CoV-2; (iv) advance EDP1867 in a Phase 1b trial in atopic dermatitis; (v) progress our first bacterial extracellular vesicle product candidates into the clinic, including EDP2939 for inflammation and EDP1908 for oncology; (vi) other research and development activities for additional product candidates, including advancing additional oral product candidates through preclinical development across therapeutic areas; and (vii) the remainder, if any, for working capital and other general corporate purposes. See “Use of Proceeds.”

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Risk factors

This investment involves a high degree of risk. You should read the description of risks set forth under “Risk Factors” beginning on page S-7 of this prospectus supplement or otherwise incorporated by reference in this prospectus supplement for a discussion of factors to consider before deciding to purchase our securities.

Nasdaq Global Select Market symbol

“EVLO”

The number of shares of our common stock to be outstanding immediately after this offering and the concurrent private placement is based on 47,470,119 shares outstanding as of December 31, 2020 and gives effect to the sale of 4,500,000 shares of common stock in this offering and 500,000 shares of common stock in the concurrent private placement, and excludes:

- 3,114,275 shares of common stock issuable upon exercise of stock options outstanding under our 2015 Stock Incentive Plan, or 2015 Plan, at a weighted-average exercise price of \$4.05 per share, as of December 31, 2020;
- 3,496,387 shares of common stock issuable upon the exercise of stock options outstanding under our 2018 Incentive Award Plan, or the 2018 Plan, at a weighted-average exercise price of \$8.77 per share, as of December 31, 2020;
- 951,621 shares of our common stock available for future issuance under our 2018 Plan, as of December 31, 2020, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under our 2018 Plan;
- 18,386 shares of restricted common stock as of December 31, 2020 resulting from the early exercise of stock options issued under our 2015 Plan and that remain subject to vesting of the underlying stock options; and
- 284,000 shares of restricted stock units issuable upon vesting under our 2018 Plan, as of December 31, 2020; and
- 307,753 shares of common stock available for future issuance under our 2018 Employee Stock Purchase Plan, or ESPP, as of December 31, 2020, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under our ESPP.

RISK FACTORS

Investing in our common stock involves risk. Before deciding whether to invest in our common stock, you should consider carefully the risks and uncertainties described below. You should also consider the risks, uncertainties and assumptions discussed under the heading “Risk Factors” in the accompanying prospectus, our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2020 incorporated by reference in this prospectus supplement, any amendment or update thereto reflected in subsequent filings with the SEC, including in our annual reports on Form 10-K and quarterly reports on Form 10-Q, and all other information contained or incorporated by reference in this prospectus supplement, as updated by our subsequent filings under the Exchange Act. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. If any of these risks actually occurs, our business, business prospects, financial condition or results of operations could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. Please also read carefully the section above entitled “Cautionary Statement Regarding Forward-Looking Statements.”

Risks Related to this Offering

A significant portion of our total outstanding shares is restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to decline significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock. As of September 30, 2020, we had 46,184,087 shares of outstanding common stock, of which approximately 23,066,685 shares are subject to restrictions on transfer under 90-day lock-up arrangements with the underwriters of this offering. These restrictions are due to expire on April 28, 2021, resulting in a substantial number of these shares becoming eligible for public sale at that time if they are registered under the Securities Act or if they qualify for an exemption from registration under the Securities Act including under Rules 144 or 701.

Moreover, based on filings with the SEC as of September 30, 2020, holders of an aggregate of approximately 18.4 million shares of our common stock have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We have also registered shares of our common stock issued and available for issuance under our equity compensation plans, which can be freely sold in the public market, subject to vesting requirements, volume limitations applicable to affiliates and lock-up agreements. If these additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

We have broad discretion in the use of the net proceeds from this offering and our existing cash and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled “Use of Proceeds,” as well as our existing cash and cash equivalents, and you will be relying on the judgment of our management regarding such application. You will not have the opportunity, as part of your investment decision, to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply the net proceeds or our existing cash in ways that ultimately increase the value of your investment. If we do not invest or apply the net proceeds from this offering or our existing cash and cash equivalents in ways that enhance stockholder value, we may fail to achieve expected business and financial

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results, which could cause our stock price to decline. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders.

You will experience immediate dilution in the book value per share of the securities you purchase in this offering.

Because the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on a net tangible book value per share of our common stock of \$1.09 as of September 30, 2020, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$12.64 per share in the net tangible book value of the common stock you purchase. Any exercise of outstanding stock options, warrants or other equity awards will result in further dilution. See “Dilution” for a more detailed discussion of the dilution you will incur if you purchase our securities in this offering.

Our pursuit of a potential therapeutic treatment for COVID-19 is highly uncertain and at an early stage. We may be unable to produce a therapeutic that successfully treats COVID-19 in a timely manner, if at all, and the therapeutic may never be approved.

We had to adjust certain aspects of our clinical trial for EDP1815, and we may experience difficulties or delays in enrolling patients in a clinical trial for EDP1815 due to the impact of the global COVID-19 pandemic in the geographic regions where we choose to conduct our trials or other reasons. We may be unable to produce an efficacious and/or approved product for the treatment of patients with early COVID-19 in a timely manner, if at all. If the outbreak is effectively contained or the risk of SARS-CoV-2 infection is diminished or eliminated before we can successfully develop and manufacture our product candidate, if ever, the commercial viability of such product candidate may be diminished or eliminated. We are also committing financial resources and personnel to the development of this product candidate which may cause delays in or otherwise negatively impact our other development programs, despite uncertainties surrounding the longevity and extent of SARS-CoV-2 as a global health concern. Our business could be materially and negatively impacted by our allocation of significant resources to a global health threat that is unpredictable and could rapidly dissipate or against which our treatment, if developed, may not be effective. Other parties are currently producing therapeutic candidates for early COVID-19 treatment, which may be more efficacious or may be approved prior to EDP1815. If we are unable to produce a therapeutic that successfully treats COVID-19 in a timely manner, if at all, or the therapeutic is never approved, our business, results of operations and financial performance, as well as trading price of our common stock or other securities, will be materially and adversely affected.

Interim, “topline” and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or top-line data from our preclinical studies and clinical trials. Preliminary and top-line data readouts are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the top-line or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, top-line data should be viewed with caution until the final data are available.

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From time to time, we may also disclose interim data from our preclinical studies and clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If the interim, top-line, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of the shares of common stock we are offering will be \$63.1 million after deducting the estimated underwriting discounts and commissions and estimated offering costs payable by us. If the underwriters exercise in full their option to purchase additional shares, we estimate that our net proceeds from this offering will be approximately \$72.6 million.

We estimate that the net proceeds from the concurrent private placement will be \$7.5 million.

The principal purpose of this offering and the concurrent private placement is to obtain additional capital to support our operations. We expect to use the net proceeds of this offering and the concurrent private placement, in addition to our existing cash resources, for the following purposes:

- continue the development of EDP1815 in a Phase 2 trial in psoriasis and initiate a Phase 2 trial of EDP1815 in atopic dermatitis;
- prepare to advance EDP1815 in multiple Phase 3 trials in both psoriasis and atopic dermatitis, upon receipt of positive Phase 2 data;
- continue the Phase 2 and Phase 2/3 clinical trials of EDP1815 for the treatment of hyperinflammation caused by SARs-CoV-2;
- advance EDP1867 in a Phase 1b trial in atopic dermatitis;
- progress our first bacterial extracellular vesicle (EV) product candidates into the clinic, including EDP2939 for inflammation and EDP1908 for oncology;
- other research and development activities for additional product candidates, including advancing additional oral product candidates through preclinical development across therapeutic areas; and
- the remainder, if any, for working capital and other general corporate purposes.

This expected use of the net proceeds from this offering and the concurrent private placement represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our use of the net proceeds from this offering and the concurrent private placement will depend on a number of factors, such as the timing and progress of our research and development efforts, the timing and progress of any collaborative or strategic partnering efforts, and the competitive environment for our planned products. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds from this offering and the concurrent private placement. The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our clinical trials and other development efforts and other factors described under “Risk Factors” in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein, as well as the amount of cash used in our operations. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of the net proceeds. Pending the use of the net proceeds described above, we plan to invest the net proceeds from this offering and the concurrent private placement in a variety of capital preservation investments, including short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

Based on the planned use of proceeds described above, we believe that the net proceeds from this offering and the concurrent private placement and our existing cash and cash equivalents will be sufficient to enable us to fund our operating expenses and capital expenditure requirements to at least the end of the first quarter of 2022. We have based this estimate on assumptions that may prove to be incorrect, and we could use our available capital resources sooner than we currently expect. We may satisfy our future cash needs through the sale of equity securities, debt financings, working capital lines of credit, corporate collaborations or license agreements, grant funding, interest income earned on invested cash balances or a combination of one or more of these sources.

MARKET FOR COMMON STOCK

The principal market on which our common stock is being traded is The Nasdaq Global Select Market under the symbol “EVLO.” As of September 30, 2020, there were 46,184,087 shares of our common stock outstanding, held of record by 31 stockholders, which excludes stockholders whose shares were held in nominee or street name by brokers. On January 28, 2021, the closing price for the common stock as reported on The Nasdaq Global Select Market was \$18.60.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our common stock. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends on our common stock in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any current or future financing instruments.

DILUTION

If you purchase shares of our common stock in this offering, your interest will be immediately diluted to the extent of the difference between the public offering price per share of our common stock and the net tangible book value per share of our common stock immediately after this offering and the concurrent private placement. Our net tangible book value as of September 30, 2020 was \$50.4 million, or \$1.09 per share of common stock. “Net tangible book value” is total assets minus the sum of liabilities and intangible assets. “Net tangible book value per share” is net tangible book value divided by the total number of shares of common stock outstanding.

After giving effect to the sale by us of 4,500,000 shares of common stock in this offering and of 500,000 shares of common stock in the concurrent private placement, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses that we will pay, our as adjusted net tangible book value as of September 30, 2020, would have been approximately \$121.0 million, or \$2.36 per share of common stock. This amount represents an immediate increase in net tangible book value of \$1.27 per share to existing stockholders and an immediate dilution in tangible book value of \$12.64 per share to purchasers of our common stock in this offering.

The following table illustrates the dilution:

Public offering price per share of common stock		\$15.00
Historical net tangible book value per share as of September 30, 2020	\$1.09	
Increase in net tangible book value per share attributable to this offering and the concurrent private placement	<u>1.27</u>	
As adjusted net tangible book value per share after this offering and the concurrent private placement		<u>2.36</u>
Dilution per share to investors in this offering		<u>\$12.64</u>

If the underwriters exercise their option to purchase 675,000 additional shares in full at the public offering price of \$15.00 per share, the as adjusted net tangible book value will increase to \$2.52 per share, representing an immediate increase in net tangible book value of \$1.43 per share of our common stock to existing stockholders and an immediate dilution of \$12.48 per share to purchasers of our common stock in this offering.

The above discussion and table are based on 46,184,087 shares of our common stock outstanding as of September 30, 2020. The number of shares outstanding as of September 30, 2020 excludes:

- 3,152,147 shares of common stock issuable upon exercise of stock options outstanding under our 2015 Plan, at a weighted-average exercise price of \$4.05 per share, as of September 30, 2020;
- 3,425,460 shares of common stock issuable upon the exercise of stock options outstanding under our 2018 Plan, at a weighted-average exercise price of \$8.89 per share, as of September 30, 2020;
- 1,304,183 shares of our common stock available for future issuance under our 2018 Plan, as of September 30, 2020, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under our 2018 Plan;

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- 36,772 shares of restricted common stock as of September 30, 2020 resulting from the early exercise of stock options issued under our 2015 Plan and that remain subject to vesting of the underlying stock options; and
- 307,753 shares of common stock available for future issuance under our ESPP, as of September 30, 2020, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under our ESPP.

The foregoing table does not give effect to the exercise of any outstanding options. To the extent options are exercised or restricted shares vest, there may be further dilution to new investors.

UNDERWRITING

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC and Cowen and Company, LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

<u>Name</u>	<u>Number of Shares</u>
Morgan Stanley & Co. LLC	2,025,000
Cowen and Company, LLC	1,350,000
BMO Capital Markets Corp	1,125,000
Total	<u>4,500,000</u>

The underwriters and the representatives are collectively referred to as the “underwriters” and the “representatives,” respectively. The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters’ option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of \$0.54 per share under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 675,000 additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter’s name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters’ option to purchase up to an additional 675,000 additional shares of common stock.

	<u>Per Share</u>	<u>Total</u>	
		<u>No Exercise</u>	<u>Full Exercise</u>
Public offering price	\$ 15.00	\$ 67,500,000	\$ 77,625,000
Underwriting discounts and commissions to be paid by us:	\$ 0.90	\$ 4,050,000	\$ 4,657,500
Proceeds, before expenses, to us	\$ 14.10	\$ 63,450,000	\$ 72,967,500

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$0.3 million. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority, Inc. up to \$30,000.

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Our common stock is listed on The Nasdaq Global Select Market under the trading symbol “EVLO.”

Except for the concurrent private placement, we and all directors and officers and certain affiliates have agreed that, without the prior written consent of Morgan Stanley & Co. LLC and Cowen and Company, LLC, on behalf of the underwriters, we and they will not, during the period until and including the 90th day after the date of this prospectus supplement (the “restricted period”), directly or indirectly, offer, sell, pledge, contract to sell (including any short sale), grant any option to purchase or otherwise transfer or dispose of any shares of our common stock (including, without limitation, shares of common stock which may be deemed to be beneficially owned currently or hereafter in accordance with the rules and regulations of the SEC, shares of common stock which may be issued upon exercise of a stock option or warrant and any other security convertible into or exchangeable for common stock), enter into any short sale or any purchase, sale or grant of any right (including, without limitation, any put or call option) with respect to any security (other than a broad-based market basket or index) that includes, relates to or derives any significant part of its value from our common stock, or publicly announce any intention to do so.

The restrictions described in the immediately preceding paragraph do not apply to us (i) to the extent that any such actions give effect to the transactions contemplated by the underwriting agreement for this offering, (ii) if we issue shares pursuant to the exercise of an option or warrant or the conversion of a security outstanding as of the date of this prospectus supplement and described in the registration statement and prospectus supplement, (iii) the establishment or amendment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that such plan does not provide for the transfer of common stock during the restricted period and to the extent a public announcement or filing under the Exchange Act, if any, is required of or voluntarily made by us regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period, (iv) the grant or issuance by us, or exercise or settlement (in cash, shares of common stock or otherwise), of options, restricted stock awards, restricted stock units or any other type of equity award to our employees, officers, directors, advisors or consultants pursuant to employee benefit plans described in the registration statement and prospectus supplement, (v) the filing of a registration statement with the Commission on Form S-8 with respect to employee benefit plans in described in the registration statement and prospectus supplement, or (vi) the sale or issuance of or entry into an agreement to sell or issue shares of common stock or securities convertible into or exercisable for common stock in connection with any merger, acquisition of securities, businesses, property or any other assets, joint ventures, strategic alliances, equipment leasing arrangements or debt financing, provided that the aggregate number of shares of Common Stock or securities convertible into or exercisable for common stock that we may sell or issue or agree to sell or issue pursuant to this clause (vi) shall not exceed 5% of the total number of shares of our common stock issued and outstanding, and provided further, that each recipient of shares of Common Stock or securities convertible into or exercisable for Common Stock pursuant to clauses (iv) and (vi) shall agree to be bound by the terms of the lock-up agreement.

The restrictions described in the second preceding paragraph do not apply, in the case of our directors, officers and shareholders, to:

- (a) transactions relating to shares of common stock or other securities acquired in this offering or in open market transactions after the pricing of this offering; provided that no filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made in connection with subsequent sales of common stock or other securities acquired in such open market transactions;
- (b) transfers of shares of common stock or any security convertible into common stock as a bona fide gift, or to a charitable organization or educational institution in a transaction not involving a disposition for value;
- (c) transfers or dispositions of shares of common stock or other securities to any member of the immediate family of the security holder or any trust for the direct or indirect benefit of the security holder or the immediate family of the security holder in a transaction not involving a disposition for value;

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- (d) transfers or dispositions of shares of common stock or other securities to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held by the security holder or the immediate family the security holder in a transaction not involving a disposition for value;
- (e) transfers or dispositions of shares of common stock or other securities (i) by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the security holder upon the death of the security holder, or (ii) by operation of law pursuant to orders of a court or regulatory agency, a domestic order or negotiated divorce settlement; or
- (f) if the security holder is an entity, (i) transfers or dispositions of shares of common stock or other securities to another corporation, member, partnership, limited liability company, trust or other entity that is a direct or indirect affiliate (as defined under Rule 12b-2 of the Exchange Act) of the security holder, or to an investment fund or other entity that controls or manages, or is under common control with, the security holder, or (ii) distributions of shares of common stock or any security convertible into common stock to partners, members, stockholders, beneficiaries or other equity holders of the security holder;

provided that in the case of any transfer, disposition or distribution pursuant to clause (b), (c), (d), (e) or (f), (i) each transferee, donee or distributee shall sign and deliver a lock-up agreement and (ii) no filing under Section 16(a) of the Exchange Act, reporting a reduction in beneficial ownership of shares of common stock, shall be required or shall be voluntarily made during the restricted period (other than, in the case of a transfer or other disposition pursuant to clause (e) above, any Form 4 or Form 5 required to be filed under the Exchange Act if the undersigned is subject to Section 16 reporting with respect to us under the Exchange Act and indicating by footnote disclosure or otherwise the nature of the transfer or disposition);

- (g) transfers or dispositions of common stock or any security convertible into or exercisable or exchangeable for common stock to us pursuant to any contractual arrangement in effect as of the date of this prospectus supplement that provides for the repurchase of the security holder's common stock or other securities by us or in connection with the termination of the security holder's employment with or service to us, provided that no filing under Section 16(a) of the Exchange Act, reporting a reduction in beneficial ownership of shares of common stock, shall be required or shall be voluntarily made during the restricted period in connection with any such transfers or dispositions (other than any Form 4 or Form 5 required to be filed under the Exchange Act if the undersigned is subject to Section 16 reporting with respect to us under the Exchange Act and indicating by footnote disclosure or otherwise the nature of the transfer or disposition);
- (h) transfers or dispositions of shares of common stock or other securities to us in connection with the conversion of any convertible security into, or the exercise of any option or warrant for, shares of common stock; provided that (i) any such shares of common stock received by the security holder shall be subject to the terms of the lock-up agreement and (ii) no filing under Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of shares of common stock shall be required or shall be voluntarily made during the restricted period;
- (i) transfers or dispositions of shares of common stock or other securities to a nominee or custodian of a person or entity to whom a disposition or transfer would be permissible under clauses (a) through (h) above;
- (j) the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (i) such plan does not provide for the transfer of common stock during the restricted period and (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required of or voluntarily made by or on behalf of the security holder or us regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of common stock may be made under such plan during the restricted period; or

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- (k) transfers or dispositions of shares of common stock or such other securities pursuant to a bona fide tender offer for shares of the our capital stock, merger, consolidation or other similar transaction made to all holders of our securities involving a change of control that has been approved by our board of directors; provided that, in the event that such change of control transaction is not consummated, this clause (k) shall not be applicable and the security holder's shares and other securities shall remain subject to the restrictions contained in the lock-up agreement.

Morgan Stanley & Co. LLC and Cowen and Company, LLC, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

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We are party to a sales agreement with Cowen and Company, LLC, pursuant to which we may sell up to \$50.0 million of our common stock from time to time through an “at-the-market offering” program. As of December 31, 2020, we have sold 1,232,131 shares of our common stock pursuant to the sales agreement.

Selling Restrictions

Canada

Shares of our common stock may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of shares of our common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser’s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser’s province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

European Economic Area and United Kingdom

In relation to each Member State of the European Economic Area and the United Kingdom (each, a “Relevant State”), no securities have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the securities which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of securities may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

- (a) to any legal entity which is a qualified investor as defined under the Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the representatives; or
- (c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation, provided that no such offer of shares shall require us or any of our representatives to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, the expression an “offer to the public” in relation to any shares in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase any shares, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129 (as amended).

United Kingdom

Each underwriter has represented and agreed that:

- (a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000 (“FSMA”) received by it in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and
- (b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS OF OUR COMMON STOCK

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership and disposition of the shares of common stock to be issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or foreign tax laws are not discussed. This discussion is based on the United States Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service, or IRS, in effect as of the date of this offering. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a holder of our common stock. We have not sought and do not currently intend to seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that hold our common stock as a “capital asset” within the meaning of Section 1221 of the Code (property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a Non-U.S. Holder’s particular circumstances, including the impact of the alternative minimum tax or the Medicare contribution tax on net investment income. In addition, it does not address consequences relevant to Non-U.S. Holders subject to particular rules, including, without limitation:

- U.S. expatriates and certain former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies, and other financial institutions;
- brokers, dealers or traders in securities or currencies;
- “controlled foreign corporations,” “passive foreign investment companies,” and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- persons for whom our common stock constitutes “qualified small business stock” within the meaning of Section 1202 of the Code;
- persons subject to special tax accounting rules as a result of any item of gross income with respect to our common stock being taken into account in an “applicable financial statement” (as defined in the Code);
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and
- tax-qualified retirement plans.

If a partnership (or other entity treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS FOR INFORMATION PURPOSES ONLY AND IS NOT INTENDED AS LEGAL OR TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of a Non-U.S. Holder

For purposes of this discussion, a “Non-U.S. Holder” is a beneficial owner of our common stock that is neither a “U.S. person” nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is:

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and the control of one or more United States persons (within the meaning of Section 7701(a)(30) of the Code), or (2) has made a valid election under applicable Treasury Regulations to continue to be treated as a United States person.

Distributions

As described in the section entitled “Dividend Policy,” we do not anticipate declaring or paying dividends to holders of our common stock in the foreseeable future. However, if we do make distributions on our common stock, such distributions of cash or property on our common stock will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a Non-U.S. Holder’s adjusted tax basis in our common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below in the section relating to the sale or disposition of our common stock. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of the withholding rules discussed below we, or the applicable withholding agent, may treat the entire distribution as a dividend.

Subject to the discussion below on backup withholding and foreign accounts, dividends paid to a Non-U.S. Holder of our common stock that are not effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty).

Non-U.S. Holders will be entitled to a reduction in or an exemption from withholding on dividends as a result of either (a) an applicable income tax treaty or (b) the Non-U.S. Holder holding our common stock in connection with the conduct of a trade or business within the United States and dividends being effectively connected with that trade or business. To claim such a reduction in or exemption from withholding, the Non-U.S. Holder must provide the applicable withholding agent with a properly executed (a) IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) claiming an exemption from or reduction of the withholding tax under the benefit of an income tax treaty between the United States and the country in which the Non-U.S. Holder resides or is established, or (b) IRS Form W-8ECI stating that the dividends are not subject to withholding tax because they are effectively connected with the conduct by the Non-U.S. Holder of a trade or business within the United States, as may be applicable. These certifications must be provided to the applicable

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withholding agent prior to the payment of dividends and must be updated periodically. Non-U.S. Holders that do not timely provide the applicable withholding agent with the required certification, but that qualify for a reduced rate under an applicable income tax treaty, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

If dividends paid to a Non-U.S. Holder are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such dividends are attributable), then, although exempt from U.S. federal withholding tax (provided the Non-U.S. Holder provides appropriate certification, as described above), the Non-U.S. Holder will be subject to U.S. federal income tax on such dividends on a net income basis at the regular graduated U.S. federal income tax rates. In addition, a Non-U.S. Holder that is a corporation may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on its effectively connected earnings and profits for the taxable year that are attributable to such dividends, as adjusted for certain items. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

Sale or Other Disposition of Common Stock

Subject to the discussions below on backup withholding and foreign accounts, a Non-U.S. Holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other disposition of our common stock unless:

- the gain is effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such gain is attributable);
- the Non-U.S. Holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes U.S. real property interests, or USRPIs, by reason of our status as a U.S. real property holding corporation, or USRPHC, for U.S. federal income tax purposes.

Gain described in the first bullet point above will generally be subject to U.S. federal income tax on a net income basis at the regular graduated U.S. federal income tax rates. A Non-U.S. Holder that is a foreign corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A Non-U.S. Holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on any gain derived from the disposition, which may be offset by certain U.S. source capital losses of the Non-U.S. Holder (even though the individual is not considered a resident of the United States) provided the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we are not currently and do not anticipate becoming a USRPHC. Because the determination of whether we are a USRPHC depends on the fair market value of our USRPIs relative to the fair market value of our other business assets and our non-U.S. real property interests, however, there can be no assurance we are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition by a Non-U.S. Holder of our common stock will not be subject to U.S. federal income tax if our common stock is "regularly traded," as defined by applicable Treasury Regulations, on an established securities market, and such Non-U.S. Holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the Non-U.S. Holder's holding period.

Non-U.S. Holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Subject to the discussion below on foreign accounts, a Non-U.S. Holder will not be subject to backup withholding with respect to distributions on our common stock we make to the Non-U.S. Holder, provided the applicable withholding agent does not have actual knowledge or reason to know such holder is a United States person and the holder certifies its non-U.S. status, such as by providing a valid IRS Form W-8BEN, W-8BEN-E or W-8ECI, or other applicable certification. However, information returns generally will be filed with the IRS in connection with any distributions (including deemed distributions) made on our common stock to the Non-U.S. Holder, regardless of whether any tax was actually withheld. Copies of these information returns may also be made available under the provisions of a specific treaty or agreement to the tax authorities of the country in which the Non-U.S. Holder resides or is established.

Information reporting and backup withholding may apply to the proceeds of a sale or other taxable disposition of our common stock within the United States, and information reporting may (although backup withholding generally will not) apply to the proceeds of a sale or other taxable disposition of our common stock outside the United States conducted through certain U.S.-related financial intermediaries, in each case, unless the beneficial owner certifies under penalty of perjury that it is a Non-U.S. Holder on IRS Form W-8BEN or W-8BEN-E, or other applicable form (and the payor does not have actual knowledge or reason to know that the beneficial owner is a U.S. person) or such owner otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a Non-U.S. Holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under the Foreign Account Tax Compliance Act, or FATCA, on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends (including deemed dividends) paid on our common stock, or (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends (including deemed dividends) paid on our common stock. While withholding under FATCA would have applied also to payments of gross proceeds from the sale or other disposition of common stock on or after January 1, 2019, recently proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of these withholding rules we or the applicable withholding agent may treat the entire distribution as a dividend. Prospective investors should consult their tax advisors regarding the potential application of these withholding provisions.

LEGAL MATTERS

The validity of the common stock being offered hereby will be passed upon for us by Latham & Watkins LLP. Goodwin Procter LLP is acting as counsel for the underwriters in connection with certain legal matters related to this offering.

EXPERTS

The consolidated financial statements of Evelo Biosciences, Inc. appearing in Evelo Biosciences, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2019 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon (which contains an explanatory paragraph describing conditions that raise substantial doubt about the Company's ability to continue as a going concern as described in Note 1 to the consolidated financial statements) included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated by reference herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the information requirements of the Exchange Act and, in accordance therewith, file annual, quarterly and special reports, proxy statements and other information with the SEC. These documents may be accessed through the SEC's electronic data gathering, analysis and retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (www.sec.gov).

We have the authority to designate and issue more than one class or series of stock having various preferences, conversion and other rights, voting powers, restrictions, limitations as to dividends, qualifications, and terms and conditions of redemption. See "Description of Capital Stock" in the accompanying prospectus. We will furnish a full statement of the relative rights and preferences of each class or series of our stock which has been so designated and any restrictions on the ownership or transfer of our stock to any shareholder upon request and without charge. Written requests for such copies should be directed to Evelo Biosciences, Inc., 620 Memorial Drive, Cambridge, Massachusetts 02139, or by telephone request to (617) 577-0300. Our website is located at www.evelobio.com. Information contained on or accessible through our website is not incorporated by reference into this prospectus supplement and, therefore, is not part of this prospectus supplement or the accompanying prospectus.

INCORPORATION BY REFERENCE

The SEC's rules allow us to "incorporate by reference" information in this prospectus supplement, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or a subsequently filed document incorporated by reference modifies or replaces that statement.

This prospectus supplement incorporates by reference the documents set forth below that have previously been filed with the SEC:

- our Annual Report on [Form 10-K](#) for the year ended December 31, 2019, filed with the SEC on February 14, 2020;
- our Quarterly Reports on Form 10-Q for the quarters ended [March 31, 2020](#), [June 30, 2020](#) and [September 30, 2020](#) filed with the SEC on May 11, 2020, July 31, 2020 and October 30, 2020, respectively;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2019 from our [definitive proxy statement](#) on Schedule 14A (other than information furnished rather than filed), which was filed with the SEC on April 27, 2020;
- our Current Reports on Form 8-K, filed with the SEC on [February 28, 2020](#), [May 18, 2020](#), [June 18, 2020](#), [June 29, 2020](#), [December 9, 2020](#), [December 17, 2020](#), [January 20, 2021](#) and [January 28, 2021](#); and
- The description of our Common Stock contained in our Registration Statement on [Form 8-A](#), filed with the SEC on April 30, 2018, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed in such forms that are related to such items unless such Form 8-K expressly provides to the contrary) we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act in this prospectus supplement, prior to the termination of this offering, including all such documents we may file with the SEC after the date of the initial registration statement and prior to the effectiveness of the registration statement, will also be incorporated by reference in this prospectus supplement and deemed to be part of this prospectus supplement from the date of the filing of such reports and documents. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed above or filed in the future, that are not deemed "filed" with the SEC, including our performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

You may request a free copy of any of the documents incorporated by reference in this prospectus supplement by writing or telephoning us at the following address:

Evelo Biosciences, Inc.
620 Memorial Drive
Cambridge, Massachusetts 02139
(617) 577-0300

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement.

PROSPECTUS



\$200,000,000

**Common Stock
Preferred Stock
Warrants
Units**

We may offer and sell up to \$200,000,000 in the aggregate of the securities identified above from time to time in one or more offerings. This prospectus provides you with a general description of the securities.

Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in any of our securities.

We may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled "About this Prospectus" and "Plan of Distribution" for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE "[RISK FACTORS](#)" ON PAGE 5 OF THIS PROSPECTUS AND ANY SIMILAR SECTION CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "EVLO." On May 31, 2019, the last reported sale price of our common stock on The Nasdaq Global Select Market was \$7.48 per share.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is June 6, 2019.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the U.S. Securities and Exchange Commission, or the SEC, using a “shelf” registration process. By using a shelf registration statement, we may sell securities from time to time and in one or more offerings up to a total dollar amount of \$200,000,000 as described in this prospectus. Each time that we offer and sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and sold and the specific terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement or free writing prospectus may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement or free writing prospectus, you should rely on the prospectus supplement or free writing prospectus, as applicable. Before purchasing any securities, you should carefully read both this prospectus and the applicable prospectus supplement (and any applicable free writing prospectuses), together with the additional information described under the heading “Where You Can Find More Information; Incorporation by Reference.”

We have not authorized anyone to provide you with any information or to make any representations other than those contained in this prospectus, any applicable prospectus supplement or any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate only as of the date on its respective cover, that the information appearing in any applicable free writing prospectus is accurate only as of the date of that free writing prospectus, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates. This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. In addition, the market and industry data and forecasts that may be included or incorporated by reference in this prospectus, any prospectus supplement or any applicable free writing prospectus may involve estimates, assumptions and other risks and uncertainties and are subject to change based on various factors, including those discussed under the heading “Risk Factors” contained in this prospectus, the applicable prospectus supplement and any applicable free writing prospectus, and under similar headings in other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

When we refer to “Evelo Biosciences,” “we,” “our company,” “our,” “us” and the “Company” in this prospectus, we mean Evelo Biosciences, Inc. and its consolidated subsidiaries, unless otherwise specified. When we refer to “you,” we mean the potential holders of the applicable series of securities.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is www.sec.gov.

Our website address is www.evelobio.com. The information on our website, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement or documents incorporated by reference in the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to "incorporate by reference" information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in this prospectus or a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or a subsequently filed document incorporated by reference modifies or replaces that statement.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC (other than those documents or the portions of those documents not deemed to be filed):

- Our Annual Report on [Form 10-K](#) for the year ended December 31, 2018, filed with the SEC on February 15, 2019.
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2018 from our definitive proxy statement on [Schedule 14A](#) (other than information furnished rather than filed), which was filed with the SEC on April 25, 2019.
- Our Quarterly Report on [Form 10-Q](#) for the quarter ended March 31, 2019, filed with the SEC on May 3, 2019.
- Our Current Reports on Form 8-K, filed with the SEC on [April 25, 2019](#) and [June 3, 2019](#).
- The description of our Common Stock contained in our Registration Statement on [Form 8-A](#), filed with the SEC on April 30, 2018, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the "Exchange Act" in this prospectus, prior to the termination of this offering, including all such documents we may file with the SEC after the date of the initial registration statement and prior to the effectiveness of the registration statement, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

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You may request a free copy of any of the documents incorporated by reference in this prospectus by writing or telephoning us at the following address:

Evelo Biosciences, Inc.
620 Memorial Drive
Cambridge, Massachusetts 02139
(617) 577-0300

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus or any accompanying prospectus supplement.

THE COMPANY

Evelo Biosciences is discovering and developing oral biologics that act on cells in the small intestine with therapeutic effects throughout the body. These cells in the small intestine play a central role in governing immune, metabolic and neurological systems. We believe that we have the potential to use these cells in the small intestine as therapeutic targets of novel oral biologic therapies that could transform the treatment of many chronic diseases and cancer.

Our first oral biologic product candidates are monoclonal microbials, single strains of microbes selected for defined pharmacological properties. They have been observed in preclinical models to have systemic dose-dependent effects, modulating multiple clinically-validated pathways. We believe that monoclonal microbials exert their activity by engaging with specialized immune and other cells as they pass through the small intestine. These conditioned cells then circulate via the lymphatic system and impact disease and health at all sites of the body. We believe our monoclonal microbials are likely to be well tolerated in clinical trials, given that they are single strains of naturally-evolved human commensal microbes that act on cells in the small intestine without significant risk of systemic exposure. We believe their potential to exert integrated effects on multiple pathways drives the potential to impact diseases in ways not addressed by single-target therapies, and that these properties could present significant advantages over existing therapies. Based on our preclinical studies, we believe that our product candidates, if successfully developed and approved, have the potential to improve the lives of people with chronic diseases and cancer.

We were incorporated under the laws of the State of Delaware in 2014. Our principal executive offices are located at 620 Memorial Drive, Cambridge, Massachusetts 02139, and our telephone number is (617) 577-0300. Our website address is www.evelobio.com. The information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our securities. Our common stock is listed on The Nasdaq Global Select Market under the symbol "EVLO."

RISK FACTORS

Investment in any securities offered pursuant to this prospectus and the applicable prospectus supplement involves risks. You should carefully consider the risk factors incorporated by reference to our most recent annual report on Form 10-K and any subsequent quarterly reports on Form 10-Q or current reports on Form 8-K we file after the date of this prospectus, and all other information contained or incorporated by reference into this prospectus, as updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in the applicable prospectus supplement and any applicable free writing prospectus before acquiring any of such securities. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of the securities as set forth in the applicable prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is not complete and may not contain all the information you should consider before investing in our capital stock. This description is summarized from, and qualified in its entirety by reference to, our restated certificate of incorporation, which has been publicly filed with the SEC. See “Where You Can Find More Information; Incorporation by Reference.”

Our authorized capital stock consists of:

- 200,000,000 shares of common stock, par value \$0.001 per share; and
- 10,000,000 shares of preferred stock, par value \$0.001 per share.

Common Stock

Our common stock is listed on The Nasdaq Global Select Market under the symbol “EVLO.”

Voting Rights. Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Subject to the supermajority votes for some matters, other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter. Our restated certificate of incorporation and amended and restated bylaws also provide that our directors may be removed only for cause and only by the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon. In addition, the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon is required to amend or repeal, or to adopt any provision inconsistent with, several of the provisions of our restated certificate of incorporation. See below under “-Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws-Amendment of Charter Provisions.”

Rights Upon Liquidation. In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately our net assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock.

Other Rights. Holders of common stock have no preemptive, subscription, redemption or conversion rights. Our outstanding shares of common stock are, and the shares offered by us under this prospectus will be, when issued and paid for, validly issued, fully paid and nonassessable. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Transfer Agent

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

Dividend

Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock. We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

Preferred Stock

Under the terms of our restated certificate of incorporation, our board of directors is authorized to direct us to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock.

Options

As of March 31, 2019, options to purchase an aggregate of 3,980,111 shares of our common stock were outstanding under our 2015 Stock Incentive Plan and options to purchase an aggregate of 1,705,151 shares of our common stock were outstanding under our 2018 Incentive Award Plan.

Registration Rights

Certain holders of our common stock are entitled to rights with respect to the registration of such shares for public resale under the Securities Act of 1933, as amended, or the Securities Act, pursuant to an amended and restated investors' rights agreement by and among us and certain of our stockholders, until such shares can otherwise be sold without restriction under Rule 144, or until the rights otherwise terminate pursuant to the terms of the investors' rights agreement. The registration of shares of common stock as a result of the following rights being exercised would enable holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective.

Form S-1 Registration Rights

If the holders of a majority of the registrable securities request in writing that we effect a registration with respect to all or part of such registrable securities then outstanding, we may be required to register their shares. We are obligated to effect at most two registrations in response to these demand registration rights. If the holders requesting registration intend to distribute their shares by means of an underwriting, the managing underwriter of such offering will have the right to limit the numbers of shares to be underwritten for reasons related to the marketing of the shares.

Piggyback Registration Rights

If at any time we propose to register any shares of our common stock under the Securities Act, subject to certain exceptions, the holders of registrable securities will be entitled to notice of the registration and to include their shares of registrable securities in the registration. If our proposed registration involves an underwriting, the managing underwriter of such offering will have the right to limit the number of shares to be underwritten for reasons related to the marketing of the shares.

Form S-3 Registration Rights

If, at any time after we become entitled under the Securities Act to register our shares on a registration statement on Form S-3, the holders of at least 30% of the registrable securities then outstanding request in writing that we effect a registration with respect to registrable securities at an aggregate price to the public in the offering of at least \$5,000,000, we will be required to effect such registration; provided, however, that we will not be required to effect such a registration if, within the 12-month period preceding such request, we have already effected two registrations on Form S-3 for the holders of registrable securities.

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Expenses

Ordinarily, other than underwriting discounts and commissions, we will be required to pay all expenses incurred by us related to any registration effected pursuant to the exercise of these registration rights. These expenses may include all registration and filing fees, printing expenses, fees and disbursements of our counsel, reasonable fees and disbursements of a counsel for the selling security holders and blue sky fees and expenses.

Termination of Registration Rights

The registration rights terminate upon the earlier of May 8, 2025 and the closing of a deemed liquidation event, as defined in the investors' rights agreement, or, with respect to the registration rights of an individual holder, when the holder can sell all of such holder's registrable securities in a three-month period without restriction under Rule 144 under the Securities Act.

Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws

Some provisions of Delaware law, our restated certificate of incorporation and our amended and restated bylaws could make the following transactions more difficult: an acquisition of us by means of a tender offer; an acquisition of us by means of a proxy contest or otherwise; or the removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions which provide for payment of a premium over the market price for our shares.

These provisions, summarized below, are intended to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of the increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Undesignated Preferred Stock

The ability of our board of directors, without action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock, which may include voting or other rights, dividend rights and preferences, rights to convert to common stock or other securities, and liquidation rights and preferences. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render it more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.

Stockholder Meetings

Our amended and restated bylaws provide that a special meeting of stockholders may be called only by our chairman of the board, chief executive officer or president (in the absence of a chief executive officer), or by a resolution adopted by a majority of our board of directors.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Our amended and restated bylaws establish advance notice procedures with respect to stockholder proposals to be brought before a stockholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors. The notice must contain certain information specified in our amended and restated bylaws. These procedures may have the effect of precluding the conduct of certain business at a meeting or the nomination of candidates for election as directors by stockholders if the proper procedures are not followed.

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Elimination of Stockholder Action by Written Consent

Our restated certificate of incorporation eliminates the right of stockholders to act by written consent without a meeting.

Staggered Board

Our board of directors is divided into three classes. The directors in each class will serve for a three-year term, one class being elected each year by our stockholders. This system of electing and removing directors may tend to discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors.

Removal of Directors and Vacancies

Our restated certificate of incorporation and amended and restated bylaws provide that, subject to the rights of holders of any series of preferred stock, no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote in the election of directors. Subject to the rights of holders of any series of preferred stock, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office, unless our board of directors determines by resolution that any such vacancy or newly created directorship shall be filled by our stockholders. Our amended and restated bylaws give our board of directors the exclusive right to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from filling vacancies on our board of directors.

Stockholders Not Entitled to Cumulative Voting

Our restated certificate of incorporation does not permit stockholders to cumulate their votes in the election of directors. Accordingly, the holders of a majority of the outstanding shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they choose, other than any directors that holders of our preferred stock may be entitled to elect.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the General Corporation Law of the State of Delaware, which prohibits persons deemed to be “interested stockholders” from engaging in a “business combination” with a publicly held Delaware corporation for three years following the date these persons become interested stockholders unless the business combination is, or the transaction in which the person became an interested stockholder was, approved in a prescribed manner or another prescribed exception applies. Generally, an “interested stockholder” is a person who, together with affiliates and associates, owns, or within three years prior to the determination of interested stockholder status did own, 15% or more of a corporation’s voting stock. Generally, a “business combination” includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. The existence of this provision may have an anti-takeover effect with respect to transactions not approved in advance by the board of directors.

Choice of Forum

Our restated certificate of incorporation provides that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our restated certificate of incorporation or

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amended and restated bylaws; (4) any action to interpret, apply, enforce or determine the validity of our restated certificate of incorporation or amended and restated bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. Our restated certificate of incorporation also provides that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision. It is possible that a court of law could rule that the choice of forum provision contained in our restated certificate of incorporation is inapplicable or unenforceable if it is challenged in a proceeding or otherwise.

Amendment of Charter Provisions

The amendment of any of the above provisions, except for the provision making it possible for our board of directors to issue preferred stock and the provision prohibiting cumulative voting, would require approval by holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon.

The provisions of Delaware law, our restated certificate of incorporation and our amended and restated bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in the composition of our board and management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock or preferred stock. We may issue warrants independently or together with other securities, and the warrants may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and the investors or a warrant agent. The following summary of material provisions of the warrants and warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and warrant certificate applicable to a particular series of warrants. The terms of any warrants offered under a prospectus supplement may differ from the terms described below. We urge you to read the applicable prospectus supplement and any related free writing prospectus, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants.

The particular terms of any issue of warrants will be described in the prospectus supplement relating to the issue. Those terms may include:

- the number of shares of common stock or preferred stock purchasable upon the exercise of warrants to purchase such shares and the price at which such number of shares may be purchased upon such exercise;
- the designation, stated value and terms (including, without limitation, liquidation, dividend, conversion and voting rights) of the series of preferred stock purchasable upon exercise of warrants to purchase preferred stock;
- the date, if any, on and after which the warrants and the related preferred stock or common stock will be separately transferable;
- the terms of any rights to redeem or call the warrants;
- the date on which the right to exercise the warrants will commence and the date on which the right will expire;
- United States federal income tax consequences applicable to the warrants; and
- any additional terms of the warrants, including terms, procedures, and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled to:

- vote, consent or receive dividends;
- receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
- exercise any rights as stockholders of Evelo Biosciences.

Each warrant will entitle its holder to purchase the number of shares of preferred stock or common stock at the exercise price set forth in, or calculable as set forth in, the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

A holder of warrant certificates may exchange them for new warrant certificates of different denominations, present them for registration of transfer and exercise them at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Until any warrants to purchase common stock or preferred stock are exercised, the holders of the warrants will not have any rights of holders of the underlying common stock or preferred stock, including any rights to receive dividends or payments upon any liquidation, dissolution or winding up on the common stock or preferred stock, if any.

DESCRIPTION OF UNITS

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units.

The following description, together with the additional information included in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

- the title of the series of units;
- identification and description of the separate constituent securities comprising the units;
- the price or prices at which the units will be issued;
- the date, if any, on and after which the constituent securities comprising the units will be separately transferable;
- a discussion of certain United States federal income tax considerations applicable to the units; and
- any other terms of the units and their constituent securities.

GLOBAL SECURITIES

Book-Entry, Delivery and Form

Unless we indicate differently in any applicable prospectus supplement or free writing prospectus, the securities initially will be issued in book-entry form and represented by one or more global securities. The global securities will be deposited with, or on behalf of, The Depository Trust Company, New York, New York, as depositary, or DTC, and registered in the name of Cede & Co., the nominee of DTC. Unless and until it is exchanged for individual certificates evidencing securities under the limited circumstances described below, a global security may not be transferred except as a whole by the depositary to its nominee or by the nominee to the depositary, or by the depositary or its nominee to a successor depositary or to a nominee of the successor depositary.

DTC has advised us that it is:

- a limited-purpose trust company organized under the New York Banking Law;
- a “banking organization” within the meaning of the New York Banking Law;
- a member of the Federal Reserve System;
- a “clearing corporation” within the meaning of the New York Uniform Commercial Code; and
- a “clearing agency” registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC holds securities that its participants deposit with DTC. DTC also facilitates the settlement among its participants of securities transactions, such as transfers and pledges, in deposited securities through electronic computerized book-entry changes in participants' accounts, thereby eliminating the need for physical movement of securities certificates. “Direct participants” in DTC include securities brokers and dealers, including underwriters, banks, trust companies, clearing corporations and other organizations. DTC is a wholly-owned subsidiary of The Depository Trust & Clearing Corporation, or DTCC. DTCC is the holding company for DTC, National Securities Clearing Corporation and Fixed Income Clearing Corporation, all of which are registered clearing agencies. DTCC is owned by the users of its regulated subsidiaries. Access to the DTC system is also available to others, which we sometimes refer to as indirect participants, that clear through or maintain a custodial relationship with a direct participant, either directly or indirectly. The rules applicable to DTC and its participants are on file with the SEC.

Purchases of securities under the DTC system must be made by or through direct participants, which will receive a credit for the securities on DTC's records. The ownership interest of the actual purchaser of a security, which we sometimes refer to as a beneficial owner, is in turn recorded on the direct and indirect participants' records. Beneficial owners of securities will not receive written confirmation from DTC of their purchases. However, beneficial owners are expected to receive written confirmations providing details of their transactions, as well as periodic statements of their holdings, from the direct or indirect participants through which they purchased securities. Transfers of ownership interests in global securities are to be accomplished by entries made on the books of participants acting on behalf of beneficial owners. Beneficial owners will not receive certificates representing their ownership interests in the global securities, except under the limited circumstances described below.

To facilitate subsequent transfers, all global securities deposited by direct participants with DTC will be registered in the name of DTC's partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other nominee will not change the beneficial ownership of the securities. DTC has no knowledge of the actual beneficial owners of the securities. DTC's records reflect only the identity of the direct participants to whose accounts the securities are credited, which may or may not be the beneficial owners. The participants are responsible for keeping account of their holdings on behalf of their customers.

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So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depositary and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

Conveyance of notices and other communications by DTC to direct participants, by direct participants to indirect participants and by direct participants and indirect participants to beneficial owners will be governed by arrangements among them, subject to any legal requirements in effect from time to time.

Redemption notices will be sent to DTC. If less than all of the securities of a particular series are being redeemed, DTC's practice is to determine by lot the amount of the interest of each direct participant in the securities of such series to be redeemed.

Neither DTC nor Cede & Co. (or such other DTC nominee) will consent or vote with respect to the securities. Under its usual procedures, DTC will mail an omnibus proxy to us as soon as possible after the record date. The omnibus proxy assigns the consenting or voting rights of Cede & Co. to those direct participants to whose accounts the securities of such series are credited on the record date, identified in a listing attached to the omnibus proxy.

So long as securities are in book-entry form, we will make payments on those securities to the depositary or its nominee, as the registered owner of such securities, by wire transfer of immediately available funds. If securities are issued in definitive certificated form under the limited circumstances described below and unless if otherwise provided in the description of the applicable securities herein or in the applicable prospectus supplement, we will have the option of making payments by check mailed to the addresses of the persons entitled to payment or by wire transfer to bank accounts in the United States designated in writing to the applicable trustee or other designated party at least 15 days before the applicable payment date by the persons entitled to payment, unless a shorter period is satisfactory to the applicable trustee or other designated party.

Redemption proceeds, distributions and dividend payments on the securities will be made to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC. DTC's practice is to credit direct participants' accounts upon DTC's receipt of funds and corresponding detail information from us on the payment date in accordance with their respective holdings shown on DTC records. Payments by participants to beneficial owners will be governed by standing instructions and customary practices, as is the case with securities held for the account of customers in bearer form or registered in "street name." Those payments will be the responsibility of participants and not of DTC or us, subject to any statutory or regulatory requirements in effect from time to time. Payment of redemption proceeds, distributions and dividend payments to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC, is our responsibility, disbursement of payments to direct participants is the responsibility of DTC, and disbursement of payments to the beneficial owners is the responsibility of direct and indirect participants.

Except under the limited circumstances described below, purchasers of securities will not be entitled to have securities registered in their names and will not receive physical delivery of securities. Accordingly, each beneficial owner must rely on the procedures of DTC and its participants to exercise any rights under the securities and the indenture.

The laws of some jurisdictions may require that some purchasers of securities take physical delivery of securities in definitive form. Those laws may impair the ability to transfer or pledge beneficial interests in securities.

DTC may discontinue providing its services as securities depositary with respect to the securities at any time by giving reasonable notice to us. Under such circumstances, in the event that a successor depositary is not obtained, securities certificates are required to be printed and delivered.

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As noted above, beneficial owners of a particular series of securities generally will not receive certificates representing their ownership interests in those securities. However, if:

- DTC notifies us that it is unwilling or unable to continue as a depository for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depository is not appointed within 90 days of the notification to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be; or
- we determine, in our sole discretion, not to have such securities represented by one or more global securities,

we will prepare and deliver certificates for such securities in exchange for beneficial interests in the global securities. Any beneficial interest in a global security that is exchangeable under the circumstances described in the preceding sentence will be exchangeable for securities in definitive certificated form registered in the names that the depository directs. It is expected that these directions will be based upon directions received by the depository from its participants with respect to ownership of beneficial interests in the global securities.

Euroclear and Clearstream

If so provided in the applicable prospectus supplement, you may hold interests in a global security through Clearstream Banking S.A., which we refer to as Clearstream, or Euroclear Bank S.A./N.V., as operator of the Euroclear System, which we refer to as Euroclear, either directly if you are a participant in Clearstream or Euroclear or indirectly through organizations that are participants in Clearstream or Euroclear. Clearstream and Euroclear will hold interests on behalf of their respective participants through customers' securities accounts in the names of Clearstream and Euroclear, respectively, on the books of their respective U.S. depositories, which in turn will hold such interests in customers' securities accounts in such depositories' names on DTC's books.

Clearstream and Euroclear are securities clearance systems in Europe. Clearstream and Euroclear hold securities for their respective participating organizations and facilitate the clearance and settlement of securities transactions between those participants through electronic book-entry changes in their accounts, thereby eliminating the need for physical movement of certificates.

Payments, deliveries, transfers, exchanges, notices and other matters relating to beneficial interests in global securities owned through Euroclear or Clearstream must comply with the rules and procedures of those systems. Transactions between participants in Euroclear or Clearstream, on the one hand, and other participants in DTC, on the other hand, are also subject to DTC's rules and procedures.

Investors will be able to make and receive through Euroclear and Clearstream payments, deliveries, transfers and other transactions involving any beneficial interests in global securities held through those systems only on days when those systems are open for business. Those systems may not be open for business on days when banks, brokers and other institutions are open for business in the United States.

Cross-market transfers between participants in DTC, on the one hand, and participants in Euroclear or Clearstream, on the other hand, will be effected through DTC in accordance with the DTC's rules on behalf of Euroclear or Clearstream, as the case may be, by their respective U.S. depositories; however, such cross-market transactions will require delivery of instructions to Euroclear or Clearstream, as the case may be, by the counterparty in such system in accordance with the rules and procedures and within the established deadlines (European time) of such system. Euroclear or Clearstream, as the case may be, will, if the transaction meets its settlement requirements, deliver instructions to its U.S. depository to take action to effect final settlement on its behalf by delivering or receiving interests in the global securities through DTC, and making or receiving payment in

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accordance with normal procedures for same-day fund settlement. Participants in Euroclear or Clearstream may not deliver instructions directly to their respective U.S. depositaries.

Due to time zone differences, the securities accounts of a participant in Euroclear or Clearstream purchasing an interest in a global security from a direct participant in DTC will be credited, and any such crediting will be reported to the relevant participant in Euroclear or Clearstream, during the securities settlement processing day (which must be a business day for Euroclear or Clearstream) immediately following the settlement date of DTC. Cash received in Euroclear or Clearstream as a result of sales of interests in a global security by or through a participant in Euroclear or Clearstream to a direct participant in DTC will be received with value on the settlement date of DTC but will be available in the relevant Euroclear or Clearstream cash account only as of the business day for Euroclear or Clearstream following DTC's settlement date.

Other

The information in this section of this prospectus concerning DTC, Clearstream, Euroclear and their respective book-entry systems has been obtained from sources that we believe to be reliable, but we do not take responsibility for this information. This information has been provided solely as a matter of convenience. The rules and procedures of DTC, Clearstream and Euroclear are solely within the control of those organizations and could change at any time. Neither we nor the trustee nor any agent of ours or of the trustee has any control over those entities and none of us takes any responsibility for their activities. You are urged to contact DTC, Clearstream and Euroclear or their respective participants directly to discuss those matters. In addition, although we expect that DTC, Clearstream and Euroclear will perform the foregoing procedures, none of them is under any obligation to perform or continue to perform such procedures and such procedures may be discontinued at any time. Neither we nor any agent of ours will have any responsibility for the performance or nonperformance by DTC, Clearstream and Euroclear or their respective participants of these or any other rules or procedures governing their respective operations.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods or through underwriters or dealers, through agents and/or directly to one or more purchasers. The securities may be distributed from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each time that we sell securities covered by this prospectus, we will provide a prospectus supplement or supplements that will describe the method of distribution and set forth the terms and conditions of the offering of such securities, including the offering price of the securities and the proceeds to us, if applicable.

Offers to purchase the securities being offered by this prospectus may be solicited directly. Agents may also be designated to solicit offers to purchase the securities from time to time. Any agent involved in the offer or sale of our securities will be identified in a prospectus supplement.

If a dealer is utilized in the sale of the securities being offered by this prospectus, the securities will be sold to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If an underwriter is utilized in the sale of the securities being offered by this prospectus, an underwriting agreement will be executed with the underwriter at the time of sale and the name of any underwriter will be provided in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we or the purchasers of securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for which they may act as agent. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis and a dealer will purchase securities as a principal, and may then resell the securities at varying prices to be determined by the dealer.

Any compensation paid to underwriters, dealers or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers will be provided in the applicable prospectus supplement. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof and to reimburse those persons for certain expenses.

Any common stock will be listed on The Nasdaq Global Select Market, but any other securities may or may not be listed on a national securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than were sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option, if any. In addition,

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these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement so indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in such sale transactions will be an underwriter and, if not identified in this prospectus, will be named in the applicable prospectus supplement (or a post-effective amendment). In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus and an applicable prospectus supplement. Such financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

The specific terms of any lock-up provisions in respect of any given offering will be described in the applicable prospectus supplement.

The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business for which they receive compensation.

LEGAL MATTERS

Latham & Watkins LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Evelo Biosciences, Inc. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Evelo Biosciences, Inc. appearing in Evelo Biosciences, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2018, have been audited by Ernst & Young LLP, an independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

4,500,000 Shares



Common Stock

PROSPECTUS SUPPLEMENT

Morgan Stanley

Cowen

BMO Capital Markets

January 28, 2021
