

PROSPECTUS SUPPLEMENT NO. 2

**(to Prospectus dated August 12, 2021, as supplemented by
Prospectus Supplement No. 1 dated August 16, 2021)**



Sema4 Holdings Corp.

236,223,401 Shares of Common Stock

7,236,667 Warrants to Purchase Shares of Common Stock

21,995,000 Shares of Common Stock Underlying Warrants

This prospectus supplement supplements the prospectus dated August 12, 2021, as supplemented by Prospectus Supplement No. 1 dated August 16, 2021 (the "Prospectus"), which forms a part of our registration statement on Form S-1 (No. 333-258467). This prospectus supplement is being filed to update and supplement the information in the Prospectus with the information contained in our current report on Form 8-K, filed with the Securities and Exchange Commission (the "SEC") on October 14, 2021 (the "Current Report"). Accordingly, we have attached the Current Report to this prospectus supplement.

The Prospectus and this prospectus supplement relate to the offer and sale from time to time by the selling securityholders named in the Prospectus (the "Selling Securityholders") of (A) up to 236,223,401 shares of our Class A common stock, par value \$0.0001 per share ("Class A common stock" or "common stock"), consisting of (i) up to 35,000,000 shares of our Class A common stock issued in a private placement pursuant to subscription agreements each entered into on February 9, 2021; (ii) up to 11,068,750 shares of our Class A common stock issued in connection with the consummation of the Business Combination (as defined in the Prospectus), in exchange for shares of our Class B common stock originally issued in a private placement to CMLS Holdings LLC (the "Sponsor"); (iii) up to 182,917,984 shares of our Class A common stock issued or issuable to certain former stockholders and equity award holders of Sema4 (the "Sema4 equity holders") in connection with or as a result of the consummation of the Business Combination, consisting of (a) up to 149,856,840 shares of our Class A common stock; (b) up to 14,039,568 shares of our Class A common stock issuable upon the exercise or vesting of certain equity awards; and (c) up to 19,021,576 shares of Class A common stock that certain Sema4 equity holders have the contingent right to receive upon the achievement of certain vesting conditions; and (iv) up to 7,236,667 shares of our Class A common stock issuable upon the exercise of the private placement warrants (as defined below); and (B) up to 7,236,667 warrants (the "private placement warrants") originally issued in a private placement to the Sponsor and certain of the other Initial Stockholders (as defined in the Prospectus).

In addition, the Prospectus and this prospectus supplement relate to the offer and sale of: (i) up to 14,758,333 shares of our Class A common stock that are issuable by us upon the exercise of 14,758,333 warrants (the "public warrants") originally issued in our initial public offering; and (ii) up to 7,236,667 shares of our Class A common stock that are issuable by us upon the exercise of the private placement warrants following the public resale of the private placement warrants by the Selling Securityholders pursuant to the Prospectus and this prospectus supplement.

Our common stock and public warrants are listed on the Nasdaq Global Select Market (the "Nasdaq") under the symbols "SMFR" and "SMFRW," respectively. On October 12, 2021, the last reported sales price of our common stock was \$8.15 per share and the last reported sales price of our public warrants was \$2.76 per warrant.

This prospectus supplement updates and supplements the information in the Prospectus and is not complete without, and may not be delivered or utilized except in combination with, the Prospectus, including any amendments or supplements thereto. This prospectus supplement should be read in conjunction with the Prospectus and if there is

any inconsistency between the information in the Prospectus and this prospectus supplement, you should rely on the information in this prospectus supplement.

Investing in our securities involves risks. See the section entitled "Risk Factors" beginning on page 10 of the Prospectus to read about factors you should consider before buying our securities.

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

The date of this prospectus supplement is October 14, 2021

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 8-K**

CURRENT REPORT

Pursuant to Section 13 OR 15(d) of The Securities Exchange Act of 1934

Date of Report (date of earliest event reported): **October 14, 2021 (October 8, 2021)**

Sema4 Holdings Corp.

(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	001-39482 (Commission File Number)	85-1966622 (I.R.S. Employer Identification No.)
333 Ludlow Street, North Tower, 8th Floor Stamford, Connecticut (Address of Principal Executive Offices)		06902 (Zip Code)

(800) 298-6470

Registrant's telephone number, including area code
(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Class A common stock, par value \$0.0001 per share	SMFR	The Nasdaq Global Select Market
Warrants to purchase one share of Class A common stock, each at an exercise price of \$11.50 per share	SMFRW	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 5.02 Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers.

Sema4 Holdings Corp. (“Sema4 Holdings” or the “Company”) has received confirmation that James Coffin, Ph.D. the Company’s Treasurer from January 2021 to March 2021, and President and Chief Operating Officer since 2017, expects to be on short-term disability leave for medical reasons for approximately 90 days, commencing sometime in October 2021 (the “Leave”).

During the Leave, the Company’s Chief Financial Officer, Isaac Ro, and Chief Business Officer, Kareem Saad, will each perform functions previously performed by Dr. Coffin.

The Company does not anticipate that the Leave will adversely impact the Company’s financial performance and timelines for its corporate objectives, research and development progress, or strategic partnerships and collaborations.

Except for historical information, this report contains certain forward-looking statements that involve known and unknown risk and uncertainties. These forward-looking statements relate to the Company’s expectations regarding the Leave. These risks and uncertainties are further qualified by important factors that could cause actual results to differ materially from future results, performance or achievements expressed or implied by those in the forward-looking statements made in this release. These factors include, without limitation, Dr. Coffin’s medical condition, and other risks and uncertainties identified in Sema4 Holdings Corp.’s filings with the Securities and Exchange Commission.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Sema4 Holdings Corp.

Date: October 14, 2021

By: /s/ Eric Schadt

Name: Eric Schadt

Title: Chief Executive Officer