

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549**

**Form S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

AYALA PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

82-3578375
(I.R.S. Employer
Identification Number)

Oppenheimer 4
Rehovot 7670104 Israel
+972-8-373-1541
(Address, including zip code, and telephone number, including area code, of registrant's principal executive office)

Roni Mamluk, Ph.D.
Ayala Pharmaceuticals, Inc.
1313 N. Market Street, Suite 5100
Wilmington, DE 19801
(857) 444-0553
(Address, including zip code, and telephone number, including area code, of agent for service)

Copies to:
Peter N. Handrinov
Keith L. Halverstam
Latham & Watkins LLP
200 Clarendon Street
Boston, MA 02116
(617) 948-6060

APPROXIMATE DATE OF COMMENCEMENT OF PROPOSED SALE TO THE PUBLIC: From time to time after the effective date of this registration statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective on filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	<input type="checkbox"/>		Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>		Smaller reporting company	<input checked="" type="checkbox"/>
			Emerging growth company	<input checked="" type="checkbox"/>

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for comply with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of Securities Act.

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be Registered(1)	Proposed Maximum Aggregate Offering Price(2)	Amount of registration fee
Common stock, par value \$0.01 per share	2,249,998	\$21,307,482	\$2,325(2)

- (1) Consists of (a) 333,333 outstanding shares of the registrant's common stock and (b) 1,916,665 shares of the registrant's common stock issuable upon exercise of common stock purchase warrants. Pursuant to Rule 416(a) of the Securities Act of 1933, as amended, this registration statement also covers such additional shares as may hereafter be offered or issued to prevent dilution resulting from stock splits, stock dividends, recapitalizations or certain other capital adjustments.
- (2) The registration fee has been calculated in accordance with Rule 457(c) under the Securities Act of 1933, as amended, based on the average of the high and low prices reported for the registrant's common stock on June 1, 2021.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this preliminary prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell nor does it seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion, dated June 4, 2021.

PROSPECTUS



AYALA PHARMACEUTICALS, INC.

**2,249,998 Shares
Common Stock
Offered by the Selling Securityholders**

The selling securityholders may offer and sell up to 2,249,998 shares in the aggregate of common stock identified above, of which 333,333 shares are presently issued and outstanding and 1,916,665 shares are issuable upon exercise of warrants to purchase shares of common stock. This prospectus provides you with a general description of the securities. We will not receive any proceeds from the sale of our common stock by the selling securityholders.

Each time any of the selling securityholders offers and sells securities, such selling securityholders 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.

The selling securityholders 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 Market under the symbol "AYLA." On June 1, 2021, the last reported sale price of our common stock on the Nasdaq Global Market was \$9.48 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 .

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS	1
WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE	2
THE COMPANY	4
RISK FACTORS	5
USE OF PROCEEDS	6
DESCRIPTION OF CAPITAL STOCK	7
SELLING SECURITYHOLDERS	12
PLAN OF DISTRIBUTION	14
LEGAL MATTERS	16
EXPERTS	16

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, the selling securityholders may, from time to time, sell up to 2,249,998 shares of common stock from time to time in one or more offerings as described in this prospectus. In connection with the offer and sale of securities by the selling securityholders, the selling securityholders may 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 any applicable prospectus supplement or free writing prospectuses, together with the additional information described under the heading “Where You Can Find More Information; Incorporation by Reference.”

Neither we, nor the selling securityholders, have 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 and the selling securityholders take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. The selling securityholders 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 any 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 “Ayala,” “we,” “our,” “us” and the “Company” in this prospectus, we mean Ayala Pharmaceuticals, Inc. and its consolidated subsidiary, unless otherwise specified. When we refer to “you,” we mean the potential holders of the applicable series of securities.

We use our trademarks and our logo, in this prospectus and the documents incorporated by reference. This prospectus and the documents incorporated by reference also include trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this prospectus appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

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 web site 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 <http://www.sec.gov>.

Our web site address is <https://www.ayalapharma.com>. The information on our web site, 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. 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:

- Our Annual Report on [Form 10-K](#) for the year ended December 31, 2020, filed with the SEC on March 24, 2021.
- The information specifically incorporated by reference into our Annual Report on Form 10-K from our Definitive Proxy Statement on [Schedule 14A](#), filed with the SEC on April 27, 2021.
- Our Quarterly Report on [Form 10-Q](#) for the quarter ended March 31, 2021, filed with the SEC on May 14, 2021.
- Our Current Report on [Form 8-K](#) filed with the SEC on February 22, 2021.
- The description of our common stock contained in our Registration Statement on [Form 8-A](#), filed with the SEC on May 4, 2020 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.

[Table of Contents](#)

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:

Ayala Pharmaceuticals, Inc.
Oppenheimer 4
Rehovot, Israel 7670104
(857) 444-0553

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

We are a clinical-stage oncology company focused on developing and commercializing small molecule therapeutics for patients suffering from rare and aggressive cancers, primarily in genetically defined patient populations. Our differentiated development approach is predicated on identifying and addressing tumorigenic drivers of cancer, through a combination of our bioinformatics platform and next-generation sequencing to deliver targeted therapies to underserved patient populations. Our current portfolio of product candidates, AL101 and AL102, targets the aberrant activation of the Notch pathway using gamma secretase inhibitors. Gamma secretase is the enzyme responsible for Notch activation and, when inhibited, turns off the Notch pathway activation. Aberrant activation of the Notch pathway has long been implicated in multiple solid tumor and hematological cancers and has often been associated with more aggressive cancers. In cancers, Notch is known to serve as a critical facilitator in processes such as cellular proliferation, survival, migration, invasion, drug resistance and metastatic spread, all of which contribute to a poorer patient prognosis. AL101 and AL102 are designed to address the underlying key drivers of tumor growth and our initial Phase 2 clinical data of AL101 suggest that our approach may address shortcomings of existing treatment options. We believe that our novel product candidates, if approved, have the potential to transform treatment outcomes for patients suffering from rare and aggressive cancers.

We filed our certificate of incorporation with the Secretary of State of Delaware on November 14, 2017.

Our principal executive offices are located at Oppenheimer 4, Rehovot, Israel 7670104, and our telephone number is +972-8-373-1541.

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, 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 any 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 will not receive any of the proceeds from the sale of common stock being offered by any of the selling securityholders.

DESCRIPTION OF CAPITAL STOCK

General

The following description summarizes some of the terms of our restated certificate of incorporation and restated bylaws, the amended and restated investors' rights agreement and of the General Corporation Law of the State of Delaware. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description, you should refer to our restated certificate of incorporation, restated bylaws and the amended and restated investors' rights agreement, copies of which have been filed with the Securities and Exchange Commission, as well as the relevant provisions of the General Corporation Law of the State of Delaware.

Our authorized capital stock consists of 200,000,000 shares of common stock, par value \$0.01 per share, and 10,000,000 shares of preferred stock, par value \$0.01 per share.

Common Stock

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 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. 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 any series of preferred stock that we may designate and issue in the future.

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. Holders of common stock have no preemptive, subscription, redemption or conversion rights. Our outstanding shares of common stock are 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.

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. There are no shares of preferred stock outstanding, and we have no present plans to issue any shares of preferred stock.

[Table of Contents](#)

Registration Rights

Certain of our stockholders are entitled to certain rights with respect to the registration of such shares for public resale under the Securities Act, pursuant to an amended and restated investors' rights agreement by and among us and certain of our stockholders, until the rights otherwise terminate pursuant to the terms of the investors' rights agreement. Additionally, holders of warrants to purchase our common stock are entitled to certain rights with respect to the registration for public resale under the Securities Act of shares of our common stock issued or issuable upon exercise of such warrants, pursuant to a securities purchase agreement by and among certain purchasers named therein. 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.

Piggyback Registration Rights

If 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 20% of the registrable securities then outstanding request in writing that we effect a registration with respect to all or part of such registrable securities then outstanding and having an anticipated aggregate offering amount, net of expenses, of at least \$3,000,000, we will be required to effect such registration.

Private Placement Form S-3 Registration Rights

We have also agreed to use reasonable best efforts to register certain shares of our common stock issued, or issuable upon exercise of certain warrants, for public resale pursuant to the Securities Act on a registration statement on Form S-3 promptly following the date such form is available for use by us, but in no event later than June 15, 2021.

Expenses and Indemnification

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 securityholders and blue sky fees and expenses. Additionally, we have agreed to indemnify selling stockholders for damages, and any legal or other expenses reasonably incurred, arising from or based upon any untrue statement of a material fact contained in any registration statement, an omission or alleged omission to state a material fact in any registration statement or necessary to make the statements therein not misleading, or any violation or alleged violation by the indemnifying party of securities laws, subject to certain exceptions.

Termination of Registration Rights

The registration rights terminate upon the earlier of the date that is five years after the closing of our initial public offering, such time as Rule 144 or another similar exemption under the Securities Act is available for the sale of all of such holders' shares without limitation during a three-month period without registration and the closing of a deemed liquidation event, as defined in the investors' rights agreement.

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 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 with voting or other rights or preferences as designated by our board of directors could impede the success of any attempt to change control of us. These and other provisions may have the effect of deferring hostile takeovers or delaying changes in control or management of our company.

Stockholder Meetings

Our restated certificate of incorporation 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 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.

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 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

Our restated certificate of incorporation provides that 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 stock entitled to vote in the election 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 the selection of 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 certificate of incorporation or bylaws; (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. Under our restated certificate of incorporation, this exclusive forum provision will not apply to claims which are vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery of the State of Delaware, or for which the Court of Chancery of the State of Delaware does not have subject matter jurisdiction. For instance, the provision would not apply to actions arising under federal securities laws, including suits brought to enforce any liability or duty created by the Securities Act, Exchange Act, or the rules and regulations thereunder. Our restated certificate of incorporation further provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. 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 these choice of forum provisions. It is possible that a court of law could rule that either or both of the choice of forum provisions 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 stock entitled to vote thereon.

The provisions of Delaware law, our restated certificate of incorporation and our 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

[Table of Contents](#)

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.

Stock Exchange Listing

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

SELLING SECURITYHOLDERS

This prospectus relates to the possible resale by certain of the selling securityholders from time to time of up to an aggregate of 2,249,998 shares of common stock, which consists of 333,333 shares of our common stock and warrants to purchase 1,916,665 shares of our common stock issued and sold in the private placement described below. The term “selling securityholders” includes donees, pledgees, transferees or other successors in interest selling securities received after the date of this prospectus from a selling securityholder as a gift, pledge, partnership distribution or other transfer.

On February 19, 2021, we entered into a Securities Purchase Agreement, or the Purchase Agreement, with the selling securityholders, pursuant to which we sold in a private placement (i) an aggregate of 333,333 shares of common stock, together with warrants to purchase an aggregate of 116,666 shares of common stock with an exercise price of \$18.10 per share, or the Common Warrants, for an aggregate purchase price of \$4,999,995.00 and (ii) pre-funded warrants to purchase an aggregate of 1,333,333 shares of common stock with an exercise price of \$0.01 per share, or the Pre-Funded Warrants, together with an aggregate of 466,666 Common Warrants, for an aggregate purchase price of \$19,986,661.67. Throughout this prospectus, when we refer to the “warrants,” we are referring to the Common Warrants together with the Pre-Funded Warrants.

The following table sets forth information concerning the shares of common stock that may be offered from time to time by each selling securityholder. The number of shares beneficially owned by each selling securityholder is determined under rules issued by the SEC. Under these rules, beneficial ownership includes any shares as to which the selling securityholder has sole or shared voting power or investment power. Percentage ownership is based on 13,240,961 shares of common stock outstanding as of April 30, 2021. In computing the number of shares beneficially owned by a selling securityholder and their percentage ownership, shares of common stock subject to options, warrants or other rights held by such selling securityholder that are currently exercisable or will become exercisable within 60 days of April 30, 2021 are considered outstanding, although these shares are not considered outstanding for purposes of computing the percentage ownership of any other selling securityholder. For purposes of this table, we have assumed that the selling securityholders will have sold all of the securities covered by this prospectus upon the completion of the offering (including all shares of common stock issuable upon exercise of the warrants). Each of the selling securityholders listed has sole voting and investment power with respect to the shares beneficially owned by the selling securityholder unless noted otherwise.

The information in the following table has been provided to us by or on behalf of the selling securityholders and the selling securityholders may have sold, transferred or otherwise disposed of all or a portion of their securities after the date on which they provided us with information regarding their securities. A selling securityholder may sell all, some or none of its securities in this offering. See “Plan of Distribution.”

Selling Securityholder	Common Stock Beneficially Owned Before this Offering(1)		Maximum Number of Shares of Common Stock to be Sold Pursuant to this Prospectus	Common Stock Beneficially Owned Upon Completion of this Offering	
	Number	Percentage	Number	Number	Percentage
Entities affiliated with Redmile Group, LLC(1)	1,395,464	9.9%	1,799,999	667,816	5.0%
Entities affiliated with Sio Capital Management LLC(2)	659,643	5.0%	449,999	209,664	1.6%

- (1) Consists of (i) 279,933 shares and 654,588 shares of common stock issuable upon the exercise of warrants to purchase our common stock (the “Warrants”) directly held by Redmile Capital Offshore II Master Fund, Ltd. and (ii) 387,883 shares and 1,145,411 shares of common stock issuable upon the exercise of Warrants directly held by Redmile Strategic Master Fund, LP. Redmile Group, LLC is the investment manager/adviser to each of the private investment vehicles listed in items (i) and (ii) (collectively, the

“Redmile Funds”) and, in such capacity, exercises sole voting and investment power over all of the securities held by the Redmile Funds and may be deemed to be the beneficial owner of these securities. Jeremy C. Green serves as the managing member of Redmile Group, LLC and also may be deemed to be the beneficial owner of these shares. Redmile Group, LLC and Mr. Green each disclaim beneficial ownership of these shares, except to the extent of its or his pecuniary interest in such shares, if any. Excludes an aggregate of 1,072,351 shares issuable upon the exercise of the Warrants described above, which are not exercisable within 60 days of April 30, 2021 by virtue of the Beneficial Ownership Limitation described below. Pursuant to the terms of the Warrants, a holder of a Warrant does not have the right to exercise any portion of the Warrant held by such holder, and the Company shall not effect any exercise of any Warrant, to the extent (but only to the extent) that after giving effect to such issuance after exercise, the holder (together with the holder’s affiliates, and any other persons acting as a group together with the holder or any of the holder’s affiliates), would beneficially own in excess of 9.99% (the “Beneficial Ownership Limitation”) of the number of shares of our common stock outstanding immediately after giving effect to the issuance of shares of common stock issued upon exercise of the Warrant. The Beneficial Ownership Limitation may be changed at a holder’s election upon 61 days’ notice to us. The address for the Redmile Funds is c/o Redmile Group, LLC, One Letterman Drive, Building D, Suite D3-300, San Francisco, California 94129.

- (2) Consists of 169,720 shares of common stock and warrants to purchase up to 42,407 shares of common stock held by Sio Partners LP (“Partners”), 92,884 shares of common stock and warrants to purchase up to 22,669 shares of common stock held by Sio Partners Master Fund LP (“Master Fund”), 123,185 shares of common stock and warrants to purchase up to 31,469 shares of common stock held by Compass MAV LLC (“Compass”), 78,747 shares of common stock and warrants to purchase up to 20,121 shares of common stock held by Compass Offshore MAV LTD (“Compass Offshore”), and 78,441 shares of common stock held by other investors pursuant to Investment Management Agreements with Sio Capital Management, LLC (“IMA Investors”). Pursuant to the terms of the warrants, a holder of a warrant does not have the right to exercise any portion of the warrant held by such holder, and we shall not effect any exercise of any warrant, to the extent (but only to the extent) that after giving effect to such issuance after exercise, the holder (together with the holder’s affiliates, and any other persons acting as a group together with the holder or any of the holder’s affiliates), would beneficially own in excess of 9.99% of the number of shares of our common stock outstanding immediately after giving effect to the issuance of shares of common stock upon exercise of the warrant. Each of Partners, Master Fund, Compass, Compass Offshore and IMA Investors disclaims beneficial ownership of any and all shares of common stock that are issuable upon any exercise of the warrants if such exercise would cause their aggregate beneficial ownership to exceed or remain above 9.99%, except to the extent of their interest therein. Sio Capital Management, LLC (“Sio Management”) is the investment manager of Partners, Master Fund, Compass, Compass Offshore and IMA Investors and Michael Castor is the Managing Member of Sio Management. Sio GP LLC (“Sio GP”) is the general partner of Partners and Master Fund and Mr. Castor is the sole owner of Sio GP. Sio Management and Mr. Castor may be deemed to beneficially own the securities held by Partners, Master Fund, Compass, Compass Offshore and IMA Investors. Sio GP may be deemed to beneficially own the securities held by Partners and Master Fund. Sio GP and Mr. Castor disclaim beneficial ownership over the securities held of record by Partners, Master Fund, Compass, Compass Offshore and IMA Investors, except to the extent of its or his pecuniary interest therein. The address for Sio GP, Sio Management, Mr. Castor, Partners, Master Fund, Compass, Compass Offshore and IMA Investors is 600 Third Avenue, 2nd Floor, New York, New York 10016.

PLAN OF DISTRIBUTION

The selling securityholders may from time to time offer some or all of the shares of common stock covered by this prospectus. To the extent required, this prospectus may be amended and supplemented from time to time to describe a specific plan of distribution. The selling securityholders will not pay any of the costs, expenses and fees in connection with the registration of the shares covered by this prospectus, but they will pay any and all underwriting discounts, selling commissions and similar charges attributable to sales of the shares. We will not receive any proceeds from the sale of the shares of our common stock covered hereby. The selling securityholders may sell some or all of the shares of common stock covered by this prospectus from time to time or may decide not to sell any of the shares of common stock covered by this prospectus. The selling securityholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on one or more exchanges or in the over-the-counter market or otherwise, at prices and under terms then prevailing or at prices related to the then-current market price or in negotiated transactions. The selling securityholders may dispose of their shares by one or more of, or a combination of, the following methods:

- distributions to members, partners, stockholders or other equityholders of the selling securityholders;
- purchases by a broker-dealer as principal and resale by such broker-dealer for its own account pursuant to this prospectus;
- ordinary brokerage transactions and transactions in which the broker solicits purchasers;
- block trades in which the broker-dealer so engaged will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- an over-the-counter distribution in accordance with the rules of Nasdaq;
- through trading plans entered into by a selling securityholder pursuant to Rule 10b5-1 under the Exchange Act, that are in place at the time of an offering pursuant to this prospectus and any applicable prospectus supplement hereto that provide for periodic sales of their securities on the basis of parameters described in such trading plans;
- to or through underwriters or broker-dealers;
- in “at the market” offerings, as defined in Rule 415 under the Securities Act, at negotiated prices, at prices prevailing at the time of sale or at prices related to such prevailing market prices, including sales made directly on a national securities exchange or sales made through a market maker other than on an exchange or other similar offerings through sales agents;
- in privately negotiated transactions;
- in options transactions;
- through a combination of any of the above methods of sale; or
- any other method permitted pursuant to applicable law.

In addition, any shares that qualify for sale pursuant to Rule 144 promulgated under the Securities Act, or Rule 144, may be sold under Rule 144 rather than pursuant to this prospectus. A selling securityholder that is an entity may elect to make an in-kind distribution of common stock to its members, partners, stockholders or other equityholders pursuant to the registration statement of which this prospectus forms a part by delivering a prospectus. To the extent that such members, partners, stockholders or other equityholders are not affiliates of ours, such members, partners, stockholders or other equityholders would thereby receive freely tradable shares of common stock pursuant to a distribution pursuant to the registration statement of which this prospectus forms a part.

To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution. In connection with distributions of the shares or otherwise, the selling

[Table of Contents](#)

securityholders may enter into hedging transactions with broker-dealers or other financial institutions. In connection with such transactions, broker-dealers or other financial institutions may engage in short sales of shares of common stock in the course of hedging the positions they assume with selling securityholders. The selling securityholders may also sell shares of common stock short and redeliver the shares to close out such short positions. The selling securityholders may also enter into option or other transactions with broker-dealers or other financial institutions that require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). The selling securityholders may also pledge shares to a broker-dealer or other financial institution, and, upon a default, such broker-dealer or other financial institution, may effect sales of the pledged shares pursuant to this prospectus (as supplemented or amended to reflect such transaction).

A selling securityholder 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 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 any selling securityholder or borrowed from any selling securityholder or others to settle those sales or to close out any related open borrowings of stock, and may use securities received from any selling securityholder 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 will be identified in the applicable prospectus supplement (or a post-effective amendment). In addition, any selling securityholder 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. 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.

In effecting sales, broker-dealers or agents engaged by the selling securityholders may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the selling securityholders in amounts to be negotiated immediately prior to the sale.

In offering the shares covered by this prospectus, the selling securityholders and any broker-dealers who execute sales for the selling securityholders may be deemed to be “underwriters” within the meaning of the Securities Act in connection with such sales. Any profits realized by the selling securityholders and the compensation of any broker-dealer may be deemed to be underwriting discounts and commissions.

In order to comply with the securities laws of certain states, if applicable, the shares must be sold in such jurisdictions only through registered or licensed brokers or dealers. In addition, in certain states the shares may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

We have advised the selling securityholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling securityholders and their affiliates. In addition, we will make copies of this prospectus available to the selling securityholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling securityholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

At the time a particular offer of shares is made, if required, a prospectus supplement will be distributed that will set forth the number of shares being offered and the terms of the offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallocated or paid to any dealer, and the proposed selling price to the public.

LEGAL MATTERS

The validity of the common stock being offered by this prospectus has been passed upon for us by Latham & Watkins LLP.

EXPERTS

The consolidated financial statements of Ayala Pharmaceuticals, Inc. at December 31, 2019 and 2020, and for the years then ended, incorporated by reference in this prospectus and registration statement have been audited by Kost Forer Gabbay & Kasierer, a member of Ernst & Young Global, independent registered public accounting firm, as set forth in their report thereon appearing in Ayala Pharmaceuticals, Inc.'s Annual Report on Form 10-K, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following is an estimate of the expenses (all of which are to be paid by the registrant) that we may incur in connection with the securities being registered hereby.

SEC registration fee	\$ 2,325
Printing expenses	10,000
Legal fees and expenses	25,000
Accounting fees and expenses	10,000
Miscellaneous	2,675
Total	<u>\$ 50,000</u>

Item 15. Indemnification of Directors and Officers

Subsection (a) of Section 145 of the General Corporation Law of the State of Delaware, or the DGCL, empowers a corporation to indemnify any person who was or is a party or who is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of the corporation) by reason of the fact that the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with such action, suit or proceeding if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe the person's conduct was unlawful.

Subsection (b) of Section 145 empowers a corporation to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor by reason of the fact that the person acted in any of the capacities set forth above, against expenses (including attorneys' fees) actually and reasonably incurred by the person in connection with the defense or settlement of such action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

Section 145 further provides that to the extent a director or officer of a corporation has been successful on the merits or otherwise in the defense of any action, suit or proceeding referred to in subsections (a) and (b) of Section 145, or in defense of any claim, issue or matter therein, such person shall be indemnified against expenses (including attorneys' fees) actually and reasonably incurred by such person in connection therewith; that indemnification provided for by Section 145 shall not be deemed exclusive of any other rights to which the indemnified party may be entitled; and the indemnification provided for by Section 145 shall, unless otherwise provided when authorized or ratified, continue as to a person who has ceased to be a director, officer, employee or agent and shall inure to the benefit of such person's heirs, executors and administrators. Section 145 also empowers the corporation to purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise against any

[Table of Contents](#)

liability asserted against such person and incurred by such person in any such capacity, or arising out of his status as such, whether or not the corporation would have the power to indemnify such person against such liabilities under Section 145.

Section 102(b)(7) of the DGCL provides that a corporation's certificate of incorporation may contain a provision eliminating or limiting the personal liability of a director to the corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, provided that such provision shall not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the DGCL, or (iv) for any transaction from which the director derived an improper personal benefit.

Any underwriting agreement or distribution agreement that the registrant enters into with any underwriters or agents involved in the offering or sale of any securities registered hereby may require such underwriters or dealers to indemnify the registrant, some or all of its directors and officers and its controlling persons, if any, for specified liabilities, which may include liabilities under the Securities Act of 1933, as amended.

Our restated certificate of incorporation provides that we will indemnify each person who was or is a party or threatened to be made a party to any threatened, pending or completed action, suit or proceeding (other than an action by or in the right of us) by reason of the fact that he or she is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an "Indemnitee"), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful. Our restated certificate of incorporation provides that we will indemnify any Indemnitee who was or is a party to an action or suit by or in the right of us to procure a judgment in our favour by reason of the fact that the Indemnitee is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees) and, to the extent permitted by law, amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding, and any appeal therefrom, if the Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, except that no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to us, unless a court determines that, despite such adjudication but in view of all of the circumstances, he or she is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that any Indemnitee has been successful, on the merits or otherwise, he or she will be indemnified by us against all expenses (including attorneys' fees) actually and reasonably incurred in connection therewith. Expenses must be advanced to an Indemnitee under certain circumstances.

We have entered into indemnification agreements with each of our directors and officers. These indemnification agreements may require us, among other things, to indemnify our directors and officers for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or officer in any action or proceeding arising out of his or her service as one of our directors or officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request.

We maintain a general liability insurance policy that covers certain liabilities of directors and officers of our corporation arising out of claims based on acts or omissions in their capacities as directors or officers.

Table of Contents

Item 16. Exhibits

<u>Exhibit Number</u>	<u>Description</u>
3.1	Restated Certificate of Incorporation of Ayala Pharmaceuticals, Inc. (incorporated by reference to Exhibit 3.1 of the Company's Current Report on Form 8-K filed with the SEC on May 12, 2020).
3.2	Amended and Restated Bylaws of Ayala Pharmaceuticals, Inc. (incorporated by reference to Exhibit 3.2 of the Company's Current Report on Form 8-K filed with the SEC on May 12, 2020).
4.1	Specimen Stock Certificate Evidencing the Shares of Common Stock (incorporated by reference to the Amendment to the Company's Registration Statement on Form S-1, filed with the SEC on May 4, 2020).
4.2	Form of Common Stock Warrant (incorporated by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K, filed with the SEC on February 22, 2021).
4.3	Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.2 to the Company's Current Report on Form 8-K, filed with the SEC on February 22, 2021).
4.4	Securities Purchase Agreement, dated February 19, 2021, by and among Ayala Pharmaceuticals, Inc. and the Investors named therein (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, filed with the SEC on February 22, 2021).
5.1	Opinion of Latham & Watkins LLP.
23.1	Consent of Latham & Watkins LLP (included in Exhibit 5.1).
23.2	Consent of Ernst & Young LLP.
24.1	Powers of Attorney (incorporated by reference to the signature page hereto).

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that paragraphs (a)(1)(i), (a)(1)(ii), and (a)(1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to section 13 or section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is a part of the registration statement.

Table of Contents

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(5) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. *Provided, however,* that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(6) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities:

The undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communications that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the

[Table of Contents](#)

registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(h) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Rehovot, Israel, on June 4, 2021.

AYALA PHARMACEUTICALS, INC.

By: /s/ Roni Mamluk
Roni Mamluk, Ph.D.
Chief Executive Officer

POWER OF ATTORNEY

Each of the undersigned officers and directors of the registrant hereby severally constitutes and appoints Roni Mamluk and Yossi Maimon, or either of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, and in any and all capacities, to file and sign any and all amendments, including post-effective amendments, to this registration statement and any other registration statement for the same offering that is to be effective under Rule 462(b) of the Securities Act of 1933, and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith and about the premises as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their substitute or substitutes, may lawfully do or cause to be done by virtue hereof. This power of attorney shall be governed by and construed with the laws of the State of Delaware and applicable federal securities laws.

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement has been signed below by the following persons on behalf of the registrant in the capacities and on the dates indicated.

<u>SIGNATURE</u>	<u>TITLE</u>	<u>DATE</u>
<u>/s/ Roni Mamluk</u> Roni Mamluk, Ph.D.	Chief Executive Officer and Director <i>(principal executive officer)</i>	June 4, 2021
<u>/s/ Yossi Maimon</u> Yossi Maimon	Chief Financial Officer <i>(principal financial officer and principal accounting officer)</i>	June 4, 2021
<u>/s/ David Sidransky</u> David Sidransky, M.D.	Chairman of the Board of Directors	June 4, 2021
<u>/s/ Vered Bisker-Leib</u> Vered Bisker-Leib, Ph.D.	Director	June 4, 2021
<u>/s/ Murray A. Goldberg</u> Murray A. Goldberg	Director	June 4, 2021
<u>/s/ Todd Sone</u> Todd Sone	Director	June 4, 2021
<u>/s/ Robert Spiegel</u> Robert Spiegel, M.D.	Director	June 4, 2021

200 Clarendon Street
 Boston, Massachusetts 02116
 Tel: +1.617.948.6000 Fax: +1.617.948.6001
 www.lw.com

LATHAM & WATKINS LLP

FIRM / AFFILIATE OFFICES
 Beijing Moscow
 Boston Munich
 Brussels New York
 Century City Orange County
 Chicago Paris
 Dubai Riyadh
 Düsseldorf San Diego
 Frankfurt San Francisco
 Hamburg Seoul
 Hong Kong Shanghai
 Houston Silicon Valley
 London Singapore
 Los Angeles Tokyo
 Madrid Washington, D.C.
 Milan

June 4, 2021

Ayala Pharmaceuticals, Inc.
 Oppenheimer 4
 Rehovot Israel 7670104

Re: Registration Statement on Form S-3; 2,249,998 shares of common stock, par value \$0.01 per share

Ladies and Gentlemen:

We have acted as special counsel to Ayala Pharmaceuticals, Inc., a Delaware corporation (the “**Company**”), in connection with the resale from time to time by the selling stockholders (the “**Selling Stockholders**”) named in the Registration Statement (as defined below) of 2,249,998 shares (the “**Shares**”) of the Company’s common stock, par value \$0.01 per share (the “**Common Stock**”). The Shares include (i) 333,333 outstanding shares of Common Stock issued by the Company to the Selling Stockholders on February 23, 2021 (the “**Common Shares**”) and (ii) 1,916,665 shares of Common Stock issuable upon exercise of Common Stock purchase warrants issued by the Company to the Selling Stockholders (the “**Warrant Holders**”) on February 23, 2021 (the “**Warrants**,” and the shares of Common Stock issuable upon exercise of the Warrants, the “**Warrant Shares**”). The Shares are included in a registration statement on Form S-3 under the Securities Act of 1933, as amended (the “**Act**”), filed with the Securities and Exchange Commission on June 4, 2021 (the “**Registration Statement**”). This opinion is being furnished in connection with the requirements of Item 601(b)(5) of Regulation S-K under the Act, and no opinion is expressed herein as to any matter pertaining to the contents of the Registration Statement or the prospectus contained therein, other than as expressly stated herein with respect to the issue of the Shares.

As such counsel, we have examined such matters of fact and questions of law as we have considered appropriate for purposes of this letter. With your consent, we have relied upon certificates and other assurances of officers of the Company and others as to factual matters without having independently verified such factual matters. We are opining herein as to General Corporation Law of the State of Delaware, and we express no opinion with respect to any other laws.

Subject to the foregoing and the other matters set forth herein, it is our opinion that, as of the date hereof:

1. The issue and sale of the Common Shares have been duly authorized by all necessary corporate action of the Company, and the Common Shares are validly issued, fully paid and non-assessable.

2. The issue of the Warrant Shares has been duly authorized by all necessary corporate action of the Company, and when the Warrant Shares have been duly registered on the books of the transfer agent and registrar therefor in the name or on behalf of the Warrant Holders, and have been issued by the Company upon exercise of the Warrants, the Warrant Shares will be validly issued, fully paid and nonassessable.

In rendering the foregoing opinion 2, we have assumed that the Company will comply with all applicable notice requirements regarding uncertificated shares provided in the General Corporation Law of the State of Delaware.

This opinion is for your benefit in connection with the Registration Statement and may be relied upon by you and by persons entitled to rely upon it pursuant to the applicable provisions of the Act. We consent to your filing this opinion as an exhibit to the Registration Statement and to the reference to our firm in the prospectus contained therein under the heading "Legal Matters." In giving such consent, we do not thereby admit that we are in the category of persons whose consent is required under Section 7 of the Act or the rules and regulations of the Commission thereunder.

Very truly yours,

/s/ Latham & Watkins LLP

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption “Experts” in the Registration Statement (Form S-3) and related Prospectus of Ayala Pharmaceuticals, Inc and to the incorporation by reference therein of our report dated March 24, 2021, with respect to the consolidated financial statements of Ayala Pharmaceuticals, Inc included in its Annual Report (Form 10-K) for the year ended December 31, 2020, filed with the Securities and Exchange Commission.

/s/ Kost Forer Gabbay & Kasierer
A Member of Ernst & Young Global

Tel-Aviv, Israel
June 4, 2021