

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

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

ORCHARD THERAPEUTICS PLC
(Exact name of registrant as specified in its charter)

England and Wales
(State or other jurisdiction of
incorporation or organization)

Not Applicable
(I.R.S. Employer
Identification Number)

**108 Cannon Street
London EC4N 6EU
United Kingdom
Tel: +44 (0) 20 3808 8286**
(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

**Cogency Global Inc.
10 East 40th Street 10th Floor
New York, New York 10016
+1 212 947 7200**
(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent for Service)

Copies of all communications, including communications sent to agent for service, should be sent to:

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Approximate date of commencement of proposed sale to the public: From time to time after this registration statement becomes effective.

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 upon 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, a 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 type="checkbox"/>

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 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered(1)	Amount to be Registered(1)	Proposed Maximum Offering Price Per Share(2)	Proposed Maximum Aggregate Offering Price(2)	Amount of Registration Fee
Ordinary Shares, nominal value £0.10 per share	24,115,755	\$7.28	\$175,562,696.40	\$19,153.89

- (1) Consists of (a) 20,900,321 ordinary shares represented by American Depositary Shares, or ADSs, each representing one ordinary share, and (b) 3,215,434 ordinary shares issuable upon the redesignation of 3,215,434 Non-Voting Ordinary Shares, nominal value £0.10 per share, and represented by ADSs. Pursuant to Rule 416(a) of the Securities Act of 1933, as amended, this Registration Statement shall also cover any additional ordinary shares of the Registrant that become issuable by reason of any stock dividend, stock split, recapitalization or other similar transaction effected without receipt of consideration that increases the number of the Registrant's outstanding ordinary shares. The ADSs issuable upon deposit of the ordinary shares registered hereby have been registered under a separate registration statement on Form F-6 (File No. 333-227905).
- (2) Estimated in accordance with Rule 457(c) solely for purposes of calculating the registration fee on the basis of the average of the high and low prices of the Registrant's ADSs as reported on the Nasdaq Global Select Market on April 1, 2021.

PROSPECTUS



**24,115,755 American Depositary Shares
Representing 24,115,755 Ordinary Shares
Offered by the Selling Securityholders**

This prospectus relates to the proposed resale or other disposition by the selling securityholders identified herein of up to 24,115,755 of our ordinary shares, nominal value £0.10 per share, represented by American Depositary Shares, or ADSs, of which 20,900,321 ordinary shares are presently issued and 3,215,434 are issuable upon the redesignation of 3,215,434 of our Non-Voting Ordinary Shares, nominal value £0.10 per share, or Non-Voting Ordinary Shares.

The ordinary shares represented by ADSs being offered were issued and sold to qualified institutional buyers or accredited investors in a private placement, or the Private Placement, which closed on February 9, 2021. We are not selling any ADSs under this prospectus and will not receive any of the proceeds from the sale or other disposition of ADSs by the selling securityholders.

The selling securityholders may sell the ADSs on Nasdaq or any other national securities exchange or quotation service on which the ADSs may be listed at the time of sale, in the over-the-counter market, through ordinary brokerage trades, pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods or through underwriters or broker-dealers, through agents and/or directly to one or more purchasers, or by any other legally available means. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, or at negotiated prices. See "Plan of Distribution" beginning on page 20 for more information about how the selling securityholders may sell or dispose of their ADSs.

The selling securityholders (which term as used herein includes their respective donees, pledgees, transferees or other successors in interest) may offer and sell or otherwise dispose of any or all of the ADSs described in this prospectus from time to time. The selling securityholders may sell any, all or none of the securities offered by this prospectus and we do not know when or in what amount the selling securityholders may sell their ADSs hereunder.

All expenses of registration incurred in connection with this offering are being borne by us. All selling and other expenses incurred by the selling securityholders will be borne by the selling securityholders.

Our ADSs trade on the Nasdaq Global Select Market under the symbol "ORTX". On April 7, 2021, the last reported sale price for our ADSs on the Nasdaq Global Select Market was \$6.88 per share.

INVESTING IN THESE SECURITIES INVOLVES CERTAIN RISKS. PLEASE READ THE INFORMATION UNDER THE HEADING "[RISK FACTORS](#)" ON PAGE 3 OF THIS PROSPECTUS AND IN THE DOCUMENTS INCORPORATED BY REFERENCE IN THIS PROSPECTUS FOR A DISCUSSION OF THE FACTORS YOU SHOULD CAREFULLY CONSIDER BEFORE DECIDING TO PURCHASE THESE SECURITIES.

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 April 8, 2021

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, utilizing a “shelf” registration process. Under this shelf registration process, certain selling securityholders may from time to time sell any combination of the securities described in this prospectus in one or more offerings.

Neither we nor the selling securityholders have authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus. Neither we nor the selling securityholders take responsibility for, and can provide no assurance as to the reliability of, any other information others may give you. The selling securityholders are offering to sell, and seeking offers to buy, our securities only in jurisdictions where it is lawful to do so. This prospectus does not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor does this prospectus constitute an offer to sell or the solicitation of an offer to buy shares in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus is delivered or shares are sold on a later date. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless the context otherwise indicates, references in this prospectus to “Orchard,” “we,” “our,” “us” and “the Company” refer, collectively, to Orchard Therapeutics plc, a public limited company registered under the laws of England and Wales, and its consolidated subsidiaries.

We own various trademark registrations and applications, and unregistered trademarks, including Orchard Therapeutics plc and our corporate logo. All other trade names, trademarks and service marks of other companies appearing in this prospectus are the property of their respective holders. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend to use or display other companies’ trademarks and trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

ABOUT ORCHARD THERAPEUTICS PLC

Company Overview

We are a global gene therapy company dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous hematopoietic stem cell, or HSC, gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. We seek to achieve this outcome by utilizing a lentiviral vector to introduce a functional copy of a missing or faulty gene into the patient's own, or autologous, HSCs through an *ex vivo* process, resulting in a gene-modified cellular drug product that can then be administered to the patient at the bedside.

To date, over 160 patients have been treated with our product candidates across seven different diseases, with follow-up periods of more than 10 years following a single administration. We believe the data observed across these development programs, in combination with our expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide potentially curative therapies to people suffering from a broad range of diseases.

We are currently focusing our *ex vivo* autologous HSC gene therapy approach on three therapeutic disease areas: neurodegenerative, immunological and blood disorders. Our portfolio includes two commercial-stage products approved in Europe, seven lentiviral-based product candidates in clinical-stage development and several other product candidates in preclinical development. Our two lead programs are OTL-200, which was approved in the European Union, or EU, United Kingdom, or UK, Iceland, Liechtenstein and Norway under the brand name Libmeldy for eligible patients with early-onset metachromatic leukodystrophy, or MLD, and OTL-103, which is being investigated for the treatment of Wiskott Aldrich syndrome, or WAS. For each of our lead product candidates, we are in ongoing discussions with regulatory authorities with respect to the clinical and other data required for future regulatory submissions. In late 2020, for instance, the U.S. Food & Drug Administration, or FDA, cleared our investigational new drug, or IND, application for OTL-200, and we plan to complete interactions with the FDA to determine the path to file a biologics license application, or BLA, by mid-2021. We plan to file a marketing authorization application, or MAA, for OTL-103 in Europe by year-end 2021 and a BLA for OTL-103 in the U.S. in 2022.

Company Information

We were originally incorporated under the laws of England and Wales in August 2018 as Orchard Rx Limited (now known as Orchard Therapeutics plc) to become a holding company for Orchard Therapeutics (Europe) Limited (previously known as Orchard Therapeutics Limited). Orchard Rx Limited subsequently re-registered as a public limited company and its name was changed from Orchard Rx Limited to Orchard Therapeutics plc in October 2018. Orchard Therapeutics (Europe) Limited was originally incorporated under the laws of England and Wales in September 2015 as Newincco 1387 Limited and subsequently changed its name to Orchard Therapeutics Limited in November 2015 and to Orchard Therapeutics (Europe) Limited in October 2018.

Our registered office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom, and our telephone number is +44 (0) 203 808 8286. Our website address is www.orchard-tx.com. We do not incorporate the information on or accessible through our website into this prospectus, and you should not consider any information on, or that can be accessed through, our website as part of this prospectus.

RISK FACTORS

Investment in any securities offered pursuant to this prospectus involves risks. You should carefully consider the risk factors incorporated by reference to our most recent Annual Report on Form 10-K, 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 Securities Exchange Act of 1934, as amended, or the Exchange Act, and the risk factors and other information contained in the applicable prospectus supplement 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.

FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference into it contain “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Exchange Act. Forward-looking statements relate to future events or our future financial performance. Without limiting the foregoing, we generally identify forward-looking statements by terminology such as “may,” “would,” “should,” “expects,” “plans,” “anticipates,” “could,” “intends,” “target,” “projects,” “contemplates,” “believes,” “estimates,” “predicts,” “assume,” “intend,” “potential,” “continue” or other similar words or the negative of these terms. These statements 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. The outcome of the events described in these forward-looking statements is subject to risks, uncertainties and other factors, including those contained in or incorporated by reference into this prospectus and in the sections entitled “Risk Factors” in our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q or Current Reports on Form 8-K. Accordingly, you should not place undue reliance upon these forward-looking statements. We cannot assure you that the events and circumstances reflected in the forward-looking statements will be achieved or occur, the timing of events and circumstances and actual results could differ materially from those projected in the forward looking statements. Forward-looking statements contained in this prospectus include, but are not limited to, statements about:

- the timing, progress and results of clinical trials and preclinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the timing, scope or likelihood of regulatory submissions, filings, and approvals;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the market opportunity for and size of the patient populations for Libmeldy (OTL-200) and our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial products, product candidates and technology;
- our plans and ability to build out our commercial infrastructure and successfully identify eligible patients, launch, market, and sell Libmeldy in Europe and any current and future product candidates for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of Libmeldy, Strimvelis, and any of our product candidates, if approved, including reimbursement for patients treated in a country where they are not resident;
- the adequacy, scalability and commercial viability of our manufacturing capacity, methods and processes, including those of our manufacturing partners, and plans for future development;
- the rate and degree of market acceptance and clinical utility of our commercial products and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- the impact of the COVID-19 global pandemic on our business operations, including clinical trials, regulatory strategy, and the operations of our third-party manufacturers, suppliers, and partners;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our commercial products and product candidates;

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- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our ability to attract and retain qualified employees and key personnel;
- our ability to contract with third party suppliers, clinical sites and manufacturers and their ability to perform adequately;
- our projected financial condition, including the sufficiency of our cash, cash equivalents and investments to fund operations in future periods and future liquidity, working capital and capital requirements; and
- other risks and uncertainties, including those listed under the caption “Item 1A. Risk Factors” of our most recent Annual Report on Form 10-K.

The forward-looking statements made or incorporated by reference in this prospectus relate only to events as of the date on which the statements are made. We have included important factors in the cautionary statements included in this prospectus and incorporated herein by reference, including under the caption entitled “Risk Factors,” that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. Except as required by law, we do not assume any intent to update any forward-looking statements after the date on which the statement is made, whether as a result of new information, future events or circumstances or otherwise.

USE OF PROCEEDS

We are registering these securities pursuant to registration rights granted to the selling securityholders. We are not selling any securities under this prospectus and will not receive any of the proceeds from the sale of the ADSs in this offering. The selling securityholders will receive all of the proceeds from this offering.

SELLING SECURITYHOLDERS

On February 4, 2021, we entered into a Securities Purchase Agreement with the selling securityholders, or the SPA, pursuant to which we sold to the selling securityholders (i) 20,900,321 ordinary shares and (ii) 3,215,434 Non-Voting Ordinary Shares. Pursuant to the SPA, we agreed to file a registration statement to register the ADSs representing the ordinary shares sold to the selling securityholders, including the ordinary shares issuable upon redesignation of the Non-Voting Ordinary Shares. We also agreed, among other things, to indemnify the selling securityholders, their partners, members, officers and directors, and each person who controls such securityholders, from certain liabilities and to pay certain expenses incurred by us in connection with the registration of the ADSs.

This prospectus covers the sale or other disposition from time to time by the selling securityholders identified in the table below of ADSs representing up to the total number of ordinary shares held by the selling securityholders subject to the SPA, including ordinary shares issuable upon the redesignation of Non-Voting Ordinary Shares.

We are registering the above-referenced ADSs to permit each of the selling securityholders and their pledgees, donees, transferees or other successors-in-interest that receive their shares after the date of this prospectus to resell or otherwise dispose of the ADSs representing the ordinary shares in the manner contemplated under “Plan of Distribution” below.

None of the selling securityholders has, or within the past three years has had, any position, office or other material relationship with us.

The following table sets forth the name of each selling securityholder, the number of ordinary shares owned by each of the respective selling securityholders (which ordinary shares may be represented by ADSs), the number of ADSs that may be offered under this prospectus and the number of our ordinary shares owned by the selling securityholders (which ordinary shares may be represented by ADSs) assuming all of the ADSs covered hereby are sold. The number of ADSs in the column “Maximum Number of ADSs that may be Offered Pursuant to this Prospectus” represents all of the ADSs that a selling securityholder may offer under this prospectus. The selling securityholders may sell some, all or none of their ADSs. We do not know how long the selling securityholders will hold the shares before selling them, and we currently have no agreements, arrangements or understandings with the selling securityholders regarding the sale or other disposition of any of the shares. The ADSs covered hereby may be offered from time to time by the selling securityholders.

The information set forth below is based upon information obtained from the selling securityholders and upon information in our possession regarding the issuance of ordinary shares and Non-Voting Ordinary Shares to the selling securityholders in connection with the Private Placement. The percentages of shares owned after the offering are based on 123,754,597 our ordinary shares outstanding as of March 31, 2021, including the ADSs covered hereby and assuming the redesignation of the Non-Voting Ordinary Shares.

Name of Selling Securityholders	Ordinary Shares Beneficially Owned Prior to Offering(1)	Maximum Number of ADSs that may be Offered Pursuant to this Prospectus	Ordinary Shares Beneficially Owned After Offering(1)(2)	
			Number	Percent
Artisan International Small-Mid Fund, a mutual fund series of Artisan Partners Funds, Inc.(3)	4,391,363	3,496,783	894,580	*
Casdin Partners Master Fund, L.P.(4)	3,215,434	3,215,434	—	—
Entities associated with RA Capital Healthcare Fund, L.P.(5)	15,530,647	3,215,434	12,315,213	9.95%
Avidity Master Fund LP(6)	2,855,772	2,855,772	—	—
Avidity Capital Fund II LP(7)	359,662	359,662	—	—

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Name of Selling Securityholders	Ordinary Shares Beneficially Owned Prior to Offering(1)	Maximum Number of ADSs that may be Offered Pursuant to this Prospectus	Ordinary Shares Beneficially Owned After Offering(1)(2)	
			Number	Percent
Farallon Capital Partners, L.P.(8)	558,800	558,800	—	—
Farallon Capital Institutional Partners, L.P.(8)	949,200	949,200	—	—
Farallon Capital Institutional Partners II, L.P.(8)	186,200	186,200	—	—
Farallon Capital Institutional Partners III, L.P.(8)	95,800	95,800	—	—
Four Crossings Institutional Partners V, L.P.(8)	122,200	122,200	—	—
Farallon Capital Offshore Investors II, L.P.(8)	1,089,134	1,089,134	—	—
Farallon Capital F5 Master I, L.P.(8)	172,000	172,000	—	—
Farallon Capital (AM) Investors, L.P.(8)	42,100	42,100	—	—
Citadel Multi-Strategy Equities Master Fund Ltd.(9)	2,697,012	2,411,575	285,437	*
Sphera Global Healthcare Master Fund(10)	803,540	803,540	—	—
Sphera Biotech Master Fund, LP(11)	563,024	563,024	—	—
Federated Hermes Kaufmann Fund, a portfolio of Federated Hermes Equity Funds(12)	530,000	530,000	—	—
Federated Hermes Kaufmann Small Cap Fund, a portfolio of Federated Hermes Equity Funds(12)	660,900	660,900	—	—
Federated Hermes Kaufmann Fund II, a Portfolio of Federated Hermes Insurance Series(12)	14,887	14,887	—	—
Cowen Investments LLC(13)	1,320,787	1,205,787	115,000	*
Invus Public Equities, L.P.(14)	1,803,858	803,858	1,000,000	*
Entities associated with Baker Bros. Advisors LP(15)	401,929	401,929	—	—
Woodline Master Fund LP(16)	415,487	361,736	53,751	*

* Less than one percent

- (1) “Beneficial ownership” is a term broadly defined by the SEC in Rule 13d-3 under the Exchange Act, and includes more than the typical form of share ownership, that is, shares held in the person’s name. The term also includes what is referred to as “indirect ownership,” meaning ownership of shares as to which a person has or shares investment power. For purposes of this table, a person or group of persons is deemed to have “beneficial ownership” of any shares underlying options and other purchase rights that are currently exercisable or exercisable within 60 days of March 31, 2021.
- (2) Assumes that all ADSs being registered in this prospectus are resold to third parties and that with respect to a particular selling securityholder, such selling securityholder sells all securities registered under this prospectus held by such selling securityholder.
- (3) Artisan International Small-Mid Fund, a mutual fund series of Artisan Partners Funds, Inc’s address is c/o Artisan Partners Limited Partnership 875 East Wisconsin Avenue, Suite 800, Milwaukee, WI 53202, Attention: Legal Department.
- (4) The shares reflected as beneficially owned by Casdin Partners Master Fund, LP in the table above consist of 3,215,434 shares. Such securities are owned directly by Casdin Partners Master Fund, LP and may be deemed to be indirectly beneficially owned by (i) Casdin Capital, LLC, the investment adviser to Casdin Partners Master Fund, LP, (ii) Casdin Partners GP, LLC, the general partner of Casdin Partners Master Fund LP, and (iii) Eli Casdin, the managing member of Casdin Capital, LLC and Casdin Partners GP, LLC. Each of Casdin Capital, LLC, Casdin Partners GP, LLC and Eli Casdin disclaims beneficial ownership of such securities except to the extent of their respective pecuniary interest therein. Casdin Partners Master Fund, L.P.’s address is 1350 Avenue of the Americas, Suite 2600, New York, NY 10019.
- (5) Consists of (i) 12,315,213 shares and (ii) 3,215,434 Non-Voting Ordinary Shares held by RA Capital Healthcare Fund, L.P. (the “Fund”). RA Capital Healthcare Fund GP, LLC is the general partner of the Fund. The general partner of RA Capital Management, L.P. (“RA Capital”) is RA Capital Management GP, LLC, of which Dr. Kolchinsky and Mr. Shah are the controlling persons. RA Capital serves as investment adviser for the Fund and may be deemed a beneficial owner, for purposes of Section 13(d) of the Securities Exchange Act of 1934 (the “Act”), of any securities of the Issuer held by the Fund. The Fund has delegated

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to RA Capital the sole power to vote and the sole power to dispose of all securities held in the Fund's portfolio, including the shares of the Issuer reported herein. Because the Fund has divested voting and investment power over the reported securities it holds and may not revoke that delegation on less than 61 days' notice, the Fund disclaims beneficial ownership of the securities it holds for purposes of Section 13(d) of the Act and therefore disclaim any obligation to report ownership of the reported securities under Section 13(d) of the Act. As managers of RA Capital, Dr. Kolchinsky and Mr. Shah may be deemed beneficial owners, for purposes of Section 13(d) of the Act, of any securities of the Issuer beneficially owned by RA Capital. RA Capital, Dr. Kolchinsky, and Mr. Shah disclaim beneficial ownership of the securities reported in this Resale Registration Statement (the "Statement") other than for the purpose of determining their obligations under Section 13(d) of the Act, and the filing of the Statement shall not be deemed an admission that either RA Capital, Dr. Kolchinsky, or Mr. Shah is the beneficial owner of such securities for any other purpose. The Fund's address is 200 Berkeley Street, 18th Floor, Boston, MA 02116.

- (6) Avidity Master Fund LP's address is 2828 N. Harwood St. Suite 1220, Dallas, TX 75201.
- (7) Avidity Capital Fund II LP's address is 2828 N. Harwood St. Suite 1220, Dallas, TX 75201.
- (8) Farallon Partners, L.L.C. ("FPLLC"), as the general partner of each of Farallon Capital Partners, L.P., Farallon Capital Institutional Partners, L.P., Farallon Capital Institutional Partners II, L.P., Farallon Capital Institutional Partners III, L.P., Farallon Capital Offshore Investors II, L.P. and Farallon Capital (AM) Investors, L.P., (collectively, the "FPLLC Entities"), may be deemed to beneficially own such shares held by or issuable to each of the FPLLC Entities. Farallon F5 (GP), L.L.C. ("F5MI GP"), as the general partner of Farallon Capital F5 Master I, L.P. ("F5MI"), may be deemed to beneficially own such shares held by or issuable to F5MI. Farallon Institutional (GP) V, L.L.C. ("FCIP V GP"), as the general partner of Four Crossings Institutional Partners V, L.P. ("FCIP V"), may be deemed to beneficially own such shares held by or issuable to FCIP V. Each of Philip D. Dreyfuss, Michael B. Fisch, Richard B. Fried, David T. Kim, Michael G. Linn, Rajiv A. Patel, Thomas G. Roberts, Jr., William Seybold, Andrew J. M. Spokes, John R. Warren and Mark C. Wehrly (collectively, the "Farallon Managing Members"), as a (i) managing member or senior managing member, as the case may be, of FPLLC or (ii) manager or senior manager, as the case may be, of F5MI GP and FCIP V GP, in each case with the power to exercise investment discretion, may be deemed to beneficially own such shares held by or issuable to the FCPLLC Entities, F5MI or FCIP V. Each of FPLLC, F5MI GP, FCIP V GP and the Farallon Managing Members disclaims beneficial ownership of any such shares. The address of each of the entities and individuals referenced in this footnote is c/o Farallon Capital Management, L.L.C., One Maritime Plaza, Suite 2100, San Francisco, CA 94111.
- (9) Citadel Advisors LLC ("Citadel Advisors") is the portfolio manager of Citadel Multi-Strategy Equities Master Fund Ltd. ("CEMF"). Citadel Advisors Holdings LP ("CAH") is the sole member of Citadel Advisors. Citadel GP LLC ("CGP") is the general partner of CAH. Kenneth Griffin owns a controlling interest in CGP. Mr. Griffin, as the owner of a controlling interest in CGP, may be deemed to have shared power to vote and/or shared power to dispose of the securities held by CEMF. This disclosure shall not be construed as an admission that Mr. Griffin or any of the Citadel related entities listed above is the beneficial owner of any securities of the Company other than the securities actually owned by such person (if any). The address of CEMF is c/o Citadel Advisors LLC, 601 Lexington Avenue, New York, NY 10022.
- (10) Sphera Global Healthcare Master Fund's address is c/o Maples Corporate Services, Limited P.O. Box 309, Uglund House, Grand Cayman, KY1-1104, Cayman Islands.
- (11) Sphera Biotech Master Fund, LP's address is c/o Maples Corporate Services, Limited P.O. Box 309, Uglund House, Grand Cayman, KY1-1104, Cayman Islands.
- (12) Beneficial ownership consists of (i) 660,900 shares held by Federated Hermes Kaufmann Small Cap Fund, a portfolio of Federated Hermes Equity Funds, (ii) 530,000 shares held by Federated Hermes Kaufmann Fund, a portfolio of Federated Hermes Equity Funds, and (iii) 14,887 shares held by Federated Hermes Kaufmann Fund II, a portfolio of Federated Hermes Insurance Series (collectively, the "Federated Funds"). The address of the Federated Funds is 4000 Ericsson Drive, Warrendale, Pennsylvania 15086-7561. The Federated Funds are managed by Federated Equity Management Company of Pennsylvania and subadvised by Federated Global Investment Management Corp., which are wholly owned subsidiaries of FII Holdings, Inc., which is a wholly owned subsidiary of Federated Hermes, Inc., or the Federated Parent. All of the Federated Parent's outstanding voting stock is held in the Voting Shares Irrevocable Trust, or the Federated

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Trust, for which Thomas R. Donahue, Rhodora J. Donahue and J. Christopher Donahue, who are collectively referred to as Federated Trustees, act as trustees. The Federated Parent's subsidiaries have the power to direct the vote and disposition of the securities held by the Federated Funds. Each of the Federated Parent, its subsidiaries, the Federated Trust, and each of the Federated Trustees expressly disclaim beneficial ownership of such securities.

- (13) CHI Advisors LLC is the investment manager of Cowen Investments LLC and has voting and investment power with respect to the securities held by Cowen Investments LLC. The business address for Cowen Investments LLC is c/o CHI Advisors LLC, 599 Lexington Avenue, 19th Floor, New York, New York 10022.
- (14) Invus Public Equities, L.P.'s address is 750 Lexington Ave. 30th Fl., New York, NY 10022.
- (15) Consists of (i) 372,413 ordinary shares held by Baker Brothers Life Sciences, L.P. and (ii) 29,516 ordinary shares held by 667, L.P. (together with Baker Brothers Life Sciences, L.P., the "BBA Funds"). Baker Bros. Advisors LP ("BBA") is the management company and investment adviser to the BBA Funds and has the sole voting and investment power with respect to the shares held by the BBA Funds. Baker Bros. Advisors (GP) LLC ("BBA-GP") is the sole general partner of BBA. The managing members of BBA-GP are Julian C. Baker and Felix J. Baker. The address for the BBA Funds is 860 Washington St. 3rd Fl., New York, NY 10014.
- (16) Woodline Master Fund LP's address is 4 Embarcadero Center, Suite 3450, San Francisco CA 94111.

MATERIAL INCOME TAX CONSIDERATIONS

The following summary contains a description of material U.K. and U.S. federal income tax consequences of the acquisition, ownership and disposition of our ordinary shares or ADSs. This summary should not be considered a comprehensive description of all the tax considerations that may be relevant to the decision to acquire ordinary shares or ADSs in this offering.

Material U.S. federal income tax considerations for U.S. holders

The following is a description of the material U.S. federal income tax consequences to the U.S. Holders described below of owning and disposing of our ordinary shares or ADSs. It is not a comprehensive description of all tax considerations that may be relevant to a particular person's decision to acquire securities. This discussion applies only to a U.S. Holder that is an initial purchaser of the ordinary shares or ADSs pursuant to the offering and that holds our ordinary shares or ADSs as a capital asset for tax purposes (generally, property held for investment). In addition, it does not describe all of the tax consequences that may be relevant in light of a U.S. Holder's particular circumstances, including state and local tax consequences, estate tax consequences, alternative minimum tax consequences, the potential application of the Medicare contribution tax, and tax consequences applicable to U.S. Holders subject to special rules, such as:

- banks, insurance companies, and certain other financial institutions;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- dealers or traders in securities who use a mark-to-market method of tax accounting;
- persons holding ordinary shares or ADSs as part of a hedging transaction, "straddle," wash sale, conversion transaction or integrated transaction or persons entering into a constructive sale with respect to ordinary shares or ADSs;
- persons whose "functional currency" for U.S. federal income tax purposes is not the U.S. dollar;
- brokers, dealers or traders in securities, commodities or currencies;
- tax-exempt entities or government organizations;
- S corporations, partnerships, or other entities or arrangements classified as partnerships for U.S. federal income tax purposes;
- regulated investment companies or real estate investment trusts;
- persons who acquired our ordinary shares or ADSs pursuant to the exercise of any employee stock option or otherwise as compensation; and
- persons holding our ordinary shares or ADSs in connection with a trade or business, permanent establishment, or fixed base outside the United States.

If an entity that is classified as a partnership for U.S. federal income tax purposes holds ordinary shares or ADSs, the U.S. federal income tax treatment of a partner will generally depend on the status of the partner and the activities of the partnership. Partnerships holding ordinary shares or ADSs and partners in such partnerships are encouraged to consult their tax advisers as to the particular U.S. federal income tax consequences of holding and disposing of ordinary shares or ADSs.

The discussion is based on Internal Revenue Code of 1986, as amended, or the Code, administrative pronouncements, judicial decisions, final, temporary and proposed Treasury Regulations, and the income tax treaty between the United Kingdom and the United States, or the Treaty, all as of the date hereof, changes to any of which may affect the tax consequences described herein—possibly with retroactive effect.

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A “U.S. Holder” is a holder who, for U.S. federal income tax purposes, is a beneficial owner of ordinary shares or ADSs and is:

- (i) An individual who is a citizen or individual resident of the United States;
- (ii) a corporation, or other entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia;
- (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- (iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

Passive Foreign Investment Company Rules

If we are classified as a passive foreign investment company, or PFIC, in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or
- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

We do not believe that we were a PFIC in the 2020 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for

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purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a “controlled foreign corporation” for any taxable year (see discussion below in “Controlled foreign corporation considerations”), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future.

If we are classified as a PFIC in any year with respect to which a U.S. Holder owns the ordinary shares or ADSs, we will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding years during which the U.S. Holder owns the ordinary shares or ADSs, regardless of whether we continue to meet the tests described above unless (i) we cease to be a PFIC and the U.S. Holder has made a “deemed sale” election under the PFIC rules, or (ii) the U.S. Holder makes a Qualified Electing Fund Election, or QEF Election, with respect to all taxable years during such U.S. Holders holding period in which we are a PFIC. If the “deemed sale” election is made, a U.S. Holder will be deemed to have sold the ordinary shares or ADSs the U.S. Holder holds at their fair market value and any gain from such deemed sale would be subject to the rules described below. After the deemed sale election, so long as we do not become a PFIC in a subsequent taxable year, the U.S. Holder’s ordinary shares or ADSs with respect to which such election was made will not be treated as shares in a PFIC and the U.S. Holder will not be subject to the rules described below with respect to any “excess distribution” the U.S. Holder receives from us or any gain from an actual sale or other disposition of the ordinary shares or ADSs. U.S. Holders should consult their tax advisors as to the possibility and consequences of making a deemed sale election if we cease to be a PFIC and such election becomes available.

For each taxable year we are treated as a PFIC with respect to U.S. Holders, U.S. Holders will be subject to special tax rules with respect to any “excess distribution” such U.S. Holder receives and any gain such U.S. Holder recognizes from a sale or other disposition (including, under certain circumstances, a pledge) of ordinary shares or ADSs, unless (i) such U.S. Holder makes a QEF Election or (ii) our ordinary shares or ADSs constitute “marketable” securities, and such U.S. Holder makes a mark-to-market election as discussed below. Distributions a U.S. Holder receives in a taxable year that are greater than 125% of the average annual distributions a U.S. Holder received during the shorter of the three preceding taxable years or the U.S. Holder’s holding period for the ordinary shares or ADSs will be treated as an excess distribution. Under these special tax rules:

- the excess distribution or gain will be allocated ratably over a U.S. Holder’s holding period for the ordinary shares or ADSs;
- the amount allocated to the current taxable year, and any taxable year prior to the first taxable year in which we became a PFIC, will be treated as ordinary income; and
- the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years prior to the year of disposition or “excess distribution” cannot be offset by any net operating losses for such years, and gains (but not losses) realized on the sale of the ordinary shares or ADSs cannot be treated as capital, even if a U.S. Holder holds the ordinary shares or ADSs as capital assets.

If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF Election. In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

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U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are “marketable.” Ordinary shares or ADSs will be marketable if they are “regularly traded” on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, and you are a holder of ADSs, we expect the mark-to-market election would be available to U.S. Holders if we are a PFIC. Each U.S. Holder should consult its tax advisor as to the whether a mark-to-market election is available or advisable with respect to the ordinary shares or ADSs.

A U.S. Holder that makes a mark-to-market election must include in ordinary income for each year an amount equal to the excess, if any, of the fair market value of the ordinary shares or ADSs at the close of the taxable year over the U.S. Holder’s adjusted tax basis in the ordinary shares or ADSs. An electing holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder’s adjusted basis in the ordinary shares or ADSs over the fair market value of the ordinary shares or ADSs at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains for prior years. Gains from an actual sale or other disposition of the ordinary shares or ADSs will be treated as ordinary income, and any losses incurred on a sale or other disposition of the shares will be treated as an ordinary loss to the extent of any net mark-to-market gains for prior years. Once made, the election cannot be revoked without the consent of the Internal Revenue Service, or the IRS, unless the ordinary shares or ADSs cease to be marketable.

However, a mark-to-market election generally cannot be made for equity interests in any lower-tier PFICs that we own, unless shares of such lower-tier PFIC are themselves “marketable.” As a result, even if a U.S. Holder validly makes a mark-to-market election with respect to our ordinary shares or ADSs, the U.S. Holder may continue to be subject to the PFIC rules (described above) with respect to its indirect interest in any of our investments that are treated as an equity interest in a PFIC for U.S. federal income tax purposes. U.S. Holders should consult their tax advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an annual report containing such information as the U.S. Treasury may require. A U.S. Holder’s failure to file the annual report will cause the statute of limitations for such U.S. Holder’s U.S. federal income tax return to remain open with regard to the items required to be included in such report until three years after the U.S. Holder files the annual report, and, unless such failure is due to reasonable cause and not willful neglect, the statute of limitations for the U.S. Holder’s entire U.S. federal income tax return will remain open during such period. U.S. Holders should consult their tax advisors regarding the requirements of filing such information returns under these rules.

WE STRONGLY URGE YOU TO CONSULT YOUR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs.

Controlled foreign corporation considerations

Each “Ten Percent Shareholder” (as defined below) in a non-U.S. corporation that is classified as a “controlled foreign corporation,” or a CFC, for U.S. federal income tax purposes generally is required to include in income each year for U.S. federal tax purposes such Ten Percent Shareholder’s pro rata share of certain types of income earned by the CFC, including “Subpart F income,” “global intangible low-taxed income” and certain other income generated by the CFC, even if the CFC has made no distributions to its shareholders. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in the CFC may be required to classify a portion of such gain as dividend income rather than capital gain (see discussion below in “Taxation of

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distributions” regarding the tax treatment of dividend income). A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A “Ten Percent Shareholder” is a United States person (as defined by the Code) who owns or is considered to own 10% or more of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation.

We believe that we were not a CFC in the 2020 taxable year, though we have not made a determination regarding our CFC status in the current taxable year, and we may become a CFC in a subsequent taxable year. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. In addition, recent changes to the attribution rules relating to the determination of CFC status may make it difficult to determine our CFC status for any taxable year. It is possible that, following this offering, a shareholder treated as a U.S. person for U.S. federal income tax purposes will acquire, directly or indirectly, enough shares to be treated as a Ten Percent Shareholder. We also believe that immediately following this offering we may have certain shareholders that are Ten Percent Shareholders for U.S. federal income tax purposes. U.S. Holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a PFIC, we generally will not be treated as a PFIC with respect to those U.S. Holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Taxation of distributions

Subject to the discussion above under “Passive Foreign Investment Company Rules,” distributions paid on ordinary shares or ADSs, other than certain pro rata distributions of ordinary shares or ADSs, will generally be treated as dividends to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Because we may not calculate our earnings and profits under U.S. federal income tax principles, we expect that distributions generally will be reported to U.S. Holders as dividends. Subject to applicable limitations and the discussions above regarding concerns expressed by the U.S. Treasury, dividends paid to certain non-corporate U.S. Holders may be taxable at preferential rates applicable to “qualified dividend income” if we are a “qualified foreign corporation” and certain other requirements are met. However, the qualified dividend income treatment may not apply if we are treated as a PFIC with respect to the U.S. Holder. The amount of the dividend will be treated as foreign-source dividend income to U.S. Holders and will not be eligible for the dividends-received deduction generally available to U.S. corporations under the Code. Dividends will generally be included in a U.S. Holder’s income on the date of the U.S. Holder’s receipt of the dividend. The amount of any dividend income paid in foreign currency will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of actual or constructive receipt, regardless of whether the payment is in fact converted into U.S. dollars. If the dividend is converted into U.S. dollars on the date of receipt, a U.S. Holder should not be required to recognize foreign currency gain or loss in respect of the dividend income. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt. Such gain or loss would generally be treated as U.S.-source ordinary income or loss. The amount of any distribution of property other than cash (and other than certain pro rata distributions of ordinary shares or ADSs or rights to acquire ordinary shares or ADSs) will be the fair market value of such property on the date of distribution.

For foreign tax credit limitation purposes, our dividends will generally be treated as passive category income. Because no U.K. income taxes will be withheld from dividends on ordinary shares or ADSs, there will be no creditable foreign taxes associated with any dividends that a U.S. Holder will receive. The rules governing foreign tax credits are complex and U.S. Holders should therefore consult their tax advisers regarding the effect of the receipt of dividends for foreign tax credit limitation purposes.

Sale or other taxable disposition of ordinary shares and ADSs

Subject to the discussion above under “Passive Foreign Investment Company Rules,” gain or loss realized on the sale or other taxable disposition of ordinary shares or ADSs will be capital gain or loss, and will be long-term capital gain or loss if the U.S. Holder held the ordinary shares or ADSs for more than one year. The amount of the gain or loss will equal the difference between the U.S. Holder’s tax basis in the ordinary shares or ADSs disposed of and the amount realized on the disposition, in each case as determined in U.S. dollars. This gain or loss will generally be U.S.-source gain or loss for foreign tax credit purposes. The deductibility of capital losses is subject to limitations.

If the consideration received by a U.S. Holder is not paid in U.S. dollars, the amount realized will be the U.S. dollar value of the payment received determined by reference to the spot rate of exchange on the date of the sale or other disposition. However, if the ordinary shares or ADSs are treated as traded on an “established securities market” and you are either a cash basis taxpayer or an accrual basis taxpayer that has made a special election (which must be applied consistently from year to year and cannot be changed without the consent of the IRS), you will determine the U.S. dollar value of the amount realized in a non-U.S. dollar currency by translating the amount received at the spot rate of exchange on the settlement date of the sale. If you are an accrual basis taxpayer that is not eligible to or does not elect to determine the amount realized using the spot rate on the settlement date, you will recognize foreign currency gain or loss to the extent of any difference between the U.S. dollar amount realized on the date of sale or disposition and the U.S. dollar value of the currency received at the spot rate on the settlement date.

Information reporting and backup withholding

Payments of dividends and sales proceeds that are made within the United States or through certain U.S.-related financial intermediaries generally are subject to information reporting, and may be subject to backup withholding, unless (i) the U.S. Holder is a corporation or other exempt recipient or (ii) in the case of backup withholding, the U.S. Holder provides a correct taxpayer identification number and certifies that it is not subject to backup withholding on a duly executed Form W-9 or otherwise establishes an exemption.

Backup withholding is not an additional tax. The amount of any backup withholding from a payment to a U.S. Holder will be allowed as a credit against the U.S. Holder’s U.S. federal income tax liability and may entitle the U.S. Holder to a refund, provided that the required information is timely furnished to the IRS.

Information with respect to foreign financial assets

Certain U.S. Holders who are individuals (and, under regulations, certain entities) may be required to report information relating to the ordinary shares or ADSs, subject to certain exceptions (including an exception for ordinary shares or ADSs held in accounts maintained by certain U.S. financial institutions), by filing IRS Form 8938 (Statement of Specified Foreign Financial Assets) with their federal income tax return. Such U.S. Holders who fail to timely furnish the required information may be subject to a penalty. Additionally, if a U.S. Holder does not file the required information, the statute of limitations with respect to tax returns of the U.S. Holder to which the information relates may not close until three years after such information is filed. U.S. Holders should consult their tax advisers regarding their reporting obligations with respect to their ownership and disposition of the ordinary shares or ADSs.

U.K. Taxation

The following is intended as a general guide to current U.K. tax law and HM Revenue and Customs, or HMRC, published practice (which is not binding) applying as at the date of this prospectus (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs. It does not constitute legal or tax advice and does not purport to be a complete analysis of all U.K. tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief

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from U.K. taxation. It is written on the basis that the company is not (and will not) directly or indirectly at any time derive 75% or more of our qualifying asset value from U.K. land, and that it is and remains solely resident in the U.K. for tax purposes and will therefore be subject to the U.K. tax regime and not the U.S. tax regime save as set out above under “Material U.S. federal income tax considerations for U.S. Holders.”

Except to the extent that the position of non-U.K. resident persons is expressly referred to, this guide relates only to persons who are resident (and in the case of individuals, domiciled or deemed domiciled) for tax purposes solely in the U.K. and do not have a permanent establishment, branch or agency (or equivalent) in any other jurisdiction with which the holding of the ADSs is connected, or U.K. Holders, who are absolute beneficial owners of the ADSs (and do not hold the ADSs through an Individual Savings Account or a Self-Invested Personal Pension) and any dividends paid in respect of the ADSs or underlying ordinary shares (where the dividends are regarded for U.K. tax purposes as that person’s own income). It is assumed that for the purposes of this guide that a holder of an ADS is the beneficial owner of the underlying ordinary share and any dividend income for U.K. direct tax purposes.

This guide may not relate to certain classes of U.K. Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- brokers or dealers in securities or persons who hold ADSs otherwise than as an investment;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to U.K. taxation on a remittance basis or to whom split year treatment applies.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN PARTICULAR CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-U.K. RESIDENT OR DOMICILED PERSONS OR PERSONS SUBJECT TO TAXATION IN ANY JURISDICTION OTHER THAN THE UK ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of U.K. tax.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade, profession or vocation in the U.K. through a permanent establishment, branch or agency to which the ADSs are attributable. There are certain exceptions for trading in the U.K. through independent agent, such as some brokers and investment managers.

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Dividend income is treated as the top slice of the total income chargeable to U.K. income tax for an individual U.K. Holder. An individual U.K. Holder who receives a dividend in the 2021/2022 tax year will be entitled to a tax-free allowance of £2,000. Income within the dividend allowance counts towards an individual's basic or higher rate limits and may, therefore, affect the level of personal allowance to which they are entitled. Dividend income in excess of this tax-free allowance will (subject to the availability of any income tax personal allowance) be charged at 7.5% (for the tax year 2021/2022) to the extent the excess amount falls within the basic rate band, 32.5% (for the tax year 2021/2022) to the extent the excess amount falls within the higher rate band, and 38.1% (for the tax year 2021/2022) to the extent the excess amount falls within additional rate band.

Corporation tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. corporation tax on dividends received from the company unless it carries on (whether solely or in partnership) a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable.

Corporate U.K. Holders should not be subject to U.K. corporation tax on any dividend received from the company so long as the dividends qualify for exemption, which should be the case, although certain conditions must be met. It should be noted that the exemptions, whilst of wide application, are not comprehensive and are subject to anti-avoidance rules in relation to a dividend. If the conditions for the exemption are not satisfied or such anti-avoidance provisions apply, or such U.K. Holder elects for an otherwise exempt dividend to be taxable, U.K. corporation tax will be chargeable on the amount of any dividends (at the current rate of 19% for the tax year 2021/2022 rising to 25% in the tax year 2023/2024 for companies with profits of more than £50,000 whilst the rate of 19% should apply to companies with profits not exceeding £50,000 with a tapered rate applying to profits between £50,000 and £250,000).

Chargeable gains

A disposal or deemed disposal of ADSs by a U.K. Holder may, depending on the U.K. Holder's circumstances and subject to any available exemptions or reliefs (such as the annual exemption), give rise to a chargeable gain or an allowable loss for the purposes of U.K. capital gains tax and corporation tax on chargeable gains.

If an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate is liable to U.K. capital gains tax on the disposal of ADSs, the applicable rate will be 20% (for the tax year 2021/2022). For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and liable to U.K. capital gains tax on such disposal, the applicable rate would be 10% (for the tax year 2021/2022), save to the extent that any capital gains when aggregated with the U.K. Holder's other taxable income and gains in the relevant tax year exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (for the tax year 2021/2022).

If a corporate U.K. Holder becomes liable to U.K. corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of U.K. corporation tax would apply (at the current rate of 19% for the tax year 2021/2022 rising to 25% in the tax year 2023/2024 for companies with profits of more than £50,000 whilst the rate of 19% should apply to companies with profits not exceeding £50,000 with a tapered rate applying to profits between £50,000 and £250,000).

A holder of ADSs which is not resident for tax purposes in the U.K. should not normally be liable to U.K. capital gains tax or corporation tax on chargeable gains on a disposal (or deemed disposal) of ADSs, unless the person is carrying on (whether solely or in partnership) a trade, profession or vocation in the U.K. through a branch or agency (or, in the case of a corporate holder of ADSs, through a permanent establishment) to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the U.K. or is treated as resident outside the U.K. for the purposes of a double taxation treaty for a period of less than five

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years and who disposes of ADSs during that period of temporary non-residence may be liable on his or her return to the U.K. (or upon ceasing to be regarded as resident outside the U.K. for the purposes of double taxation treaty) to U.K. tax on any capital gain realized (subject to any available exemption or relief).

Stamp duty and stamp duty reserve tax

The discussion below relates to the holders of our ordinary shares or ADSs wherever resident, however it should be noted that special rules may apply to certain persons such as market makers, brokers, dealers or intermediaries.

Issue of Ordinary Shares

As a general rule, no U.K. stamp duty or stamp duty reserve tax (or SDRT) is payable on the issue of underlying ordinary shares in the company.

Transfers of Ordinary Shares

An unconditional agreement to transfer ordinary shares will normally give rise to a charge to SDRT at the rate of 0.5% of the amount or value of the consideration payable for the transfer. The purchaser of the shares is liable for the SDRT. Transfers of ordinary shares in certificated form are generally also subject to stamp duty at the rate of 0.5% of the amount or value of the consideration given for the transfer (rounded up to the next £5.00). Stamp duty is normally paid by the purchaser. The charge to SDRT will be cancelled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

Clearance Services and Depositary Receipts

Under current U.K. tax law and published HMRC practice, no SDRT (and, where the transfer is effected by a written instrument, stamp duty) is generally payable where an issue or transfer of ordinary shares (including an unconditional agreement to transfer ordinary shares to a clearance service or a depositary receipt system (including to a nominee or agent for, a person whose business is or includes the issue of depositary receipts or the provision of clearance services)) is an integral part of an issue of share capital unless the clearance service has made and maintained an election under section 97A of the U.K. Finance Act 1986, or a section 97A election. It is understood that HMRC regards the facilities of DTC as a clearance service for these purposes and we are not aware of any section 97A election having been made by the DTC.

Issue or Transfers of ADSs

No U.K. SDRT or stamp duty is required to be paid in respect of the issue of or an agreement to transfer ADSs (including by way of a paperless transfer of ADSs through the facilities of DTC).

PLAN OF DISTRIBUTION

The selling securityholders and their pledgees, donees, transferees or other successors in interest may offer and sell the ordinary shares represented by ADSs from time to time on Nasdaq or any other national securities exchange or quotation service on which the ADSs may be listed at the time of sale, in the over-the-counter market, through ordinary brokerage trades, pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods or through underwriters or broker-dealers, through agents and/or directly to one or more purchasers, or by any other legally available means. The ADSs 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.

The selling securityholders may also sell shares under Rule 144 under the Securities Act, if available, or Section 4(a)(1) under the Securities Act rather than under this prospectus, provided that they meet the criteria and conform to the requirements of those provisions.

If the selling securityholders effect such transactions by selling shares to or through underwriters, broker-dealers or agents, such underwriters, broker-dealers or agents engaged by the selling securityholders may arrange for other broker-dealers to participate in sales. Broker-dealers may receive commissions or discounts from the selling securityholders (or, if any broker-dealer acts as agent for the purchaser of shares, from the purchaser) in amounts to be negotiated.

The selling securityholders may, from time to time, pledge or grant a security interest in some or all of the shares owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares from time to time under this prospectus, or under a supplement or amendment to this prospectus amending, if necessary, the list of selling securityholders to include the pledgee, transferee or other successors in interest as selling securityholders under this prospectus.

The selling securityholders have informed us that, except as set forth below, none of them has any agreement or understanding, directly or indirectly, with any person to distribute the ordinary shares. If any selling securityholder notifies us that a material arrangement has been entered into with a broker-dealer for the sale of shares through a block trade, special offering or secondary distribution or a purchase by a broker or dealer, we may be required to file a prospectus supplement pursuant to the applicable rules promulgated under the Securities Act. Certain selling securityholders who are entities rather than natural persons may distribute shares to their partners, shareholders or other owners in normal course, who may in turn sell the shares in the manner listed above. The selling securityholders also may transfer the ordinary shares in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

In connection with the sale of the ordinary shares or interests in ordinary shares, the selling securityholders may enter into hedging transactions after the effective date of the registration statement of which this prospectus is a part with broker-dealers or other financial institutions, which may in turn engage in short sales of the shares in the course of hedging the positions they assume. The selling securityholders may also sell shares short after the effective date of the registration statement of which this prospectus is a part and deliver these shares to close out their short positions, or loan or pledge the shares to broker-dealers that in turn may sell these shares. The selling securityholders may also enter into option or other transactions after the effective date of the registration statement of which this prospectus is a part with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of

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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 and any broker-dealers or agents that are involved in selling the shares may be deemed to be “underwriters” within the meaning of the Securities Act in connection with such sales. In such event, any commissions received by such broker-dealers or agents and any profit on the resale of the shares purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act. Any selling securityholder who is an “underwriter” within the meaning of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act and the provisions of the Exchange Act and the rules thereunder relating to stock manipulation. We have advised the selling securityholders that they are required to comply with Regulation M promulgated under the Exchange Act during such time as they may be engaged in a distribution of the shares. The foregoing may affect the marketability of the shares.

The aggregate proceeds to the selling securityholders from the sale of the ADSs offered by them will be the purchase price of the shares less discounts or commissions, if any. Each of the selling securityholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of shares to be made directly or through agents. We will not receive any of the proceeds from this offering.

We will pay all expenses of the registration of the ADSs representing the ordinary shares, including, without limitation, SEC filing fees. We have agreed with the selling securityholders to keep the registration statement of which this prospectus supplement constitutes a part effective until such time as the ADSs offered by the selling securityholders have been disposed of in accordance with such registration statement, the ADSs offered by the selling securityholders have been disposed of pursuant to Rule 144 under the Securities Act or the ADSs offered by the selling securityholders may be resold pursuant to Rule 144 without restriction or limitation (including without any limitation as to volume of sales and without the selling securityholder complying with any method of sale requirements or notice requirements under Rule 144).

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. Copies of certain information filed by us with the SEC are also available on our website at www.orchard-tx.com. The information on our website is not incorporated by reference into this prospectus and should not be considered to be a part of this prospectus. Our website address is included in this prospectus as an inactive technical reference only.

This prospectus is part of a registration statement we filed with the SEC. The registration statement contains more information than this prospectus regarding us and our securities, including certain exhibits and schedules. With respect to the statements contained in this prospectus regarding the contents of any agreement or any other document, in each instance, the statement is qualified in all respects by the complete text of the agreement or document, a copy of which has been filed as an exhibit to the registration statement. You can obtain a copy of the registration statement from the SEC's website.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded.

This prospectus incorporates by reference the documents listed below (File No. 001-38722) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until the offering of the securities under the registration statement is terminated or completed:

- Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2020, filed with the SEC on March 2, 2021;
- 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 29, 2020; and
- The description of our ordinary shares and ADSs contained in our Registration Statement on [Form 8-A](#), as filed with the SEC under Section 12(b) of the Exchange Act on October 29, 2018, including any amendment or report filed for the purpose of updating such description (File No. 001-38722).

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address and phone number:

Orchard Therapeutics plc
Attention: Investor Relations
108 Cannon Street
London EC4N 6EU
United Kingdom
+44 (0) 20 3808 8286

LEGAL MATTERS

Certain legal matters of English law and U.S. federal law will be passed upon for us by Goodwin Procter (UK) LLP and Goodwin Procter LLP, respectively.

EXPERTS

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2020 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.



**24,115,755 American Depositary Shares
Representing 24,115,755 Ordinary Shares
Offered by the Selling Securityholders**

PROSPECTUS

April 8, 2021

PART II.
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

Set forth below is an estimate (except in the case of the registration fee) of the amount of fees and expenses to be incurred in connection with the issuance and distribution of the offered securities, other than underwriting discounts and commissions. All fees and expenses including the amounts set forth below, other than underwriting discounts and commissions and the legal fees of counsel for any party other than us, incurred in connection with the sale of the offered securities will be borne by us.

SEC registration fee	\$ 19,153.89
Legal fees and expenses	\$ 250,000
Accounting fees and expenses	\$ 20,000
Total	<u>\$ 289,153.89</u>

Item 15. Indemnification of Directors and Officers.

Subject to the U.K. Companies Act 2006, members of the Registrant's board of directors and its officers have the benefit of the following indemnification provisions in the registrant's Articles of Association:

Current and former members of the Registrant's board of directors or officers shall be reimbursed for:

- (i) all costs, charges, losses, expenses and liabilities sustained or incurred in relation to his or her actual or purported execution of his or her duties in relation to the Registrant, including any liability incurred in defending any criminal or civil proceedings; and
- (ii) expenses incurred or to be incurred in defending any criminal or civil proceedings, in an investigation by a regulatory authority or against a proposed action to be taken by a regulatory authority, or in connection with any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the Registrant as a company (collectively, the "Statutes") arising in relation to the Registrant or an associated company, by virtue of the actual or purposed execution of the duties of his or her office or the exercise of his or her powers.

In the case of current or former members of the Registrant's board of directors, there shall be no entitlement to reimbursement as referred to above for (i) any liability incurred to the Registrant or any associated company, (ii) the payment of a fine imposed in any criminal proceeding or a penalty imposed by a regulatory authority for non-compliance with any requirement of a regulatory nature, (iii) the defense of any criminal proceeding if the member of the Registrant's board of directors is convicted, (iv) the defense of any civil proceeding brought by the Registrant or an associated company in which judgment is given against the director, and (v) any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the Registrant as a company in which the court refuses to grant relief to the director.

In addition, members of the Registrant's board of directors and its officers who have received payment from the Registrant under these indemnification provisions must repay the amount they received in accordance with the Statutes or in any other circumstances that the Registrant may prescribe or where the Registrant has reserved the right to require repayment.

In addition, the Registrant has entered or intends to enter into a deed of indemnity with each of its directors and officers. In addition to such indemnification, the Registrant provides its directors and officers with directors' and officers' liability insurance.

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Item 16. Exhibits.

Exhibit No.	Description
3.1	<u>Articles of Association of Orchard Therapeutics plc (filed as Exhibit 3.1 to Registrant's Current Report on Form 8-K (File No. 001-38722), filed with the Securities and Exchange Commission (the "Commission") on June 19, 2020 and incorporated herein by reference)</u>
4.1	<u>Deposit Agreement (filed as Exhibit 2.1 to the Registrant's Annual Report on Form 20-F (File No. 001-38722), filed with the Commission on March 22, 2019 and incorporated herein by reference)</u>
4.2	<u>Form of American Depositary Receipt (filed as Exhibit 2.2 to the Registrant's Annual Report on Form 20-F (File No. 001-38722), filed with the Commission on March 22, 2019 and incorporated herein by reference)</u>
4.3	<u>Investment and shareholders' agreement by and between the registrant and the shareholders named therein, dated August 2, 2018, as amended (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form F-1 (File No. 333-231916), filed with the Commission on June 3, 2019 and incorporated herein by reference)</u>
4.4	<u>Securities Purchase Agreement, by and among the Registrant and the investors listed in Exhibit A thereto, dated February 4, 2021 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38722), filed with the Commission on February 9, 2021 and incorporated herein by reference)</u>
5.1#	<u>Opinion of Goodwin Procter (UK) LLP</u>
23.1#	<u>Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm</u>
23.2#	<u>Consent of Goodwin Procter (UK) LLP (included in Exhibit 5.1)</u>
24.1#	<u>Powers of Attorney (included in the signature pages to the Registration Statement)</u>

Filed herewith.

Item 17. Undertakings.

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, as amended, or the Securities Act of 1933;
 - (ii) to reflect in the prospectus any facts or events arising after the effective date of this 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 this 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 a 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 this registration statement or any material change to such information in this registration statement; *provided, however*, that paragraphs (1)(i), (1)(ii) and (1)(iii) do not apply if the information required to

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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, as amended (the "Exchange Act"), that are incorporated by reference in this registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of this registration statement.

- (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 the 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.
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:
 - (i) 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
 - (ii) 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.

- (5) 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 such 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, such 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 such 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 such undersigned Registrant or used or referred to by such undersigned Registrant;
 - (iii) the portion of any other free writing prospectus relating to the offering containing material information about such undersigned Registrant or its securities provided by or on behalf of such undersigned Registrant; and
 - (iv) any other communication that is an offer in the offering made by such undersigned Registrant to the purchaser.

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- (6) 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 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in this 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.

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 indemnification provisions described herein, or otherwise, the Registrant has been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Securities Act of 1933 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 of 1933 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 London, United Kingdom, on this 8th day of April, 2021.

ORCHARD THERAPEUTICS PLC

By: /s/ Bobby Gaspar

Name: Bobby Gaspar

Title: Chief Executive Officer

SIGNATURES AND POWER OF ATTORNEY

We, the undersigned officers and directors of Orchard Therapeutics plc, hereby severally constitute and Bobby Gaspar and Frank E. Thomas, and each of them singly, our true and lawful attorneys with full power to any of them, and to each of them singly, to sign for us and in our names in the capacities indicated below the Registration Statement on Form S-3 filed herewith and any and all amendments (including post-effective amendments) to said Registration Statement (or any other registration statement for the same offering that is to be effective upon filing pursuant to Rule 462 under the Securities Act of 1933, as amended) and generally to do all such things in our name and behalf in our capacities as officers and directors to enable Orchard Therapeutics plc to comply with the provisions of the Securities Act of 1933, as amended, and all requirements of the Securities and Exchange Commission, hereby ratifying and confirming our signatures as they may be signed by our said attorneys, or any of them, to said Registration Statement and any and all amendments (including post-effective amendments) thereto.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
<u>/s/ Bobby Gaspar</u> Bobby Gaspar	Chief Executive Officer and Director (Principal Executive Officer)	April 8, 2021
<u>/s/ Frank E. Thomas</u> Frank E. Thomas	President and Chief Operating Officer (Principal Financial and Accounting Officer)	April 8, 2021
<u>/s/ James A. Geraghty</u> James A. Geraghty	Chairman of the Board of Directors	April 8, 2021
<u>/s/ Steven M. Altschuler</u> Steven M. Altschuler, M.D.	Director	April 8, 2021
<u>/s/ Joanne T. Beck</u> Joanne T. Beck, Ph.D.	Director	April 8, 2021
<u>/s/ John Curnutte</u> John Curnutte, M.D., Ph.D.	Director	April 8, 2021

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Signature	Title	Date
<u>/s/ Marc Dunoyer</u> Marc Dunoyer	Director	April 8, 2021
<u>Jon Ellis, Ph.D.</u>	Director	
<u>/s/ Charles A. Rowland, Jr.</u> Charles A. Rowland, Jr.	Director	April 8, 2021
<u>/s/ Alicia Secor</u> Alicia Secor	Director	April 8, 2021
Cogency Global Inc.		
By: <u>/s/ Colleen A. De Vries</u> Name: Colleen A. De Vries Title: Senior Vice President on behalf of Cogency Global Inc.	Authorized Representative in the United States	April 8, 2021



Goodwin Procter (UK) LLP
100 Cheapside
London EC2V 6DY

goodwinlaw.com
+44 (0) 20 7447 4200

8 April 2021

Orchard Therapeutics plc
108 Cannon Street
London, EC4N 6EU

Ladies and Gentlemen:

Orchard Therapeutics plc – Registration Statement on Form S-3 – Exhibit 5.1

We have acted as English legal advisers to Orchard Therapeutics plc, a public limited company incorporated in England and Wales (the “**Company**”) in connection with the preparation and filing on the date hereof with the U.S. Securities and Exchange Commission (the “**SEC**”) of a registration statement on Form S-3 to which this letter is attached as an exhibit (the “**Registration Statement**”) including a prospectus (the “**Prospectus**”) pursuant to the U.S. Securities Act of 1933, as amended (the “**Securities Act**”).

The filing of the Registration Statement is in connection with the private placement of 20,900,321 American Depositary Shares (the “**ADSs**”) each representing one ordinary share of £0.10 each in the capital of the Company the (the “**Ordinary Shares**”) and 3,215,434 non-voting ordinary shares of £0.10 each that may be redesignated as ordinary shares, nominal value of £0.10 per share and represented by ADSs (the “**Non-Voting Ordinary Shares**”), together with the Ordinary Shares allotted and issued in connection with the private placement therewith, the “**Shares**”) issued pursuant to a securities purchase agreement dated 4 February 2021 (the “**Purchase Agreement**”) by and among the Company and the Purchasers (as defined in the Purchase Agreement) set out therein. The Purchase Agreement provides for the registration of the Shares and, in particular, includes the terms of issue attaching to the Non-Voting Ordinary Shares attached thereto at exhibit B (the “**Terms of Issue**”).

Company’s ADSs are listed on The Nasdaq Global Select Market under the symbol “ORTX”.

We understand that the existing issued Ordinary Shares are not, and are not intended to be, admitted to trading on any market or exchange, or otherwise listed, in the United Kingdom.

1. INTRODUCTION

1.1 Purpose

In connection with the preparation and filing of a registration statement on Form S-3, we have been asked to provide opinions on certain matters, as set out below. We have taken instruction in this regard solely from the Company.

1.2 Defined terms and headings

In this letter:

Goodwin Procter (UK) LLP is a limited liability partnership registered in England and Wales with registered number OC362294. Its registered office is at 100 Cheapside, London, EC2V 6DY. A list of the names of the members of Goodwin Procter (UK) LLP is available for inspection at the registered office. Goodwin Procter (UK) LLP is authorised and regulated by the Solicitors Regulation Authority. Goodwin Procter (UK) LLP is affiliated with Goodwin Procter LLP, which operates in the United States of America.

- (a) capitalised terms used without definition in this letter or the schedules hereto have the meanings assigned to them in the Registration Statement unless a contrary indication appears; and
- (b) headings are for ease of reference only and shall not affect interpretation.

1.3 Legal review

For the purpose of issuing this letter, we have examined such questions of law as we have considered appropriate. We have reviewed the following documents and conducted only the following enquiries and searches:

- (a) an online search at Companies House in respect of information available for inspection on the Company's file conducted on 8 April 2021 at 10.30 a.m. (London time);
- (b) an enquiry of the Central Index of Winding Up Petitions, London on 8 April 2021 at 10.30 a.m. (London time) ((a) and (b) together, the "**Searches**");
- (c) a certificate dated 8 April 2021 signed by the President and Chief Operating Officer of the Company (the "**Certificate**") relating to certain factual matters as at the date of the Certificate and having annexed thereto copies (certified by the President and Chief Operating Officer of the Company as being true, complete, accurate and up-to-date in each case) of the following documents:
 - i. a PDF copy of the minutes containing the resolutions of the board of directors of the Company (the "**Board**") dated 27 January 2021 and the pricing committee constituted by the Board (the "**Pricing Committee**") dated 4 February 2021 authorising the Company, inter alia, to issue for sale the Shares in accordance with the offer terms set out in the Purchase Agreement;
 - ii. a PDF executed copy of the resolutions passed by the shareholders of the Company at the general meeting of the Company held on 17 June 2020 at which it was resolved, inter alia, to grant authorities to the Board for the purposes of sections 551 and 570 of the Companies Act 2006, as amended to allot shares or grant rights to subscribe for shares;
 - iii. a PDF copy of the current articles of association of the Company adopted on 17 June 2020 (the "**Articles**");
 - iv. PDF copies of (a) the certificate of incorporation of the Company dated 1 August 2018 and (b) the certificate of incorporation on re-registration of the Company as a public limited company dated 29 October 2018; and
 - v. a PDF copy of the Terms of Issue in relation to the Non-Voting Ordinary Shares issued pursuant to the Purchase Agreement,
- (d) a PDF copy of the duly executed Purchase Agreement dated 4 February 2021 which for the avoidance of doubt includes the Terms of Issue (referred to above); and

- (e) a draft copy of the Registration Statement (which for the avoidance of doubt includes the Prospectus) to be filed with the SEC on 8 April 2021.

1.4 **Applicable law**

This letter, the opinions given in it, and any non-contractual obligations arising out of or in connection with this letter and/or the opinions given in it, are governed by, and to be construed in accordance with, English law and relate only to English law as applied by the English courts, including the laws of the European Union to the extent having the force of law in England, as at today's date. In particular:

- (a) we have not investigated the laws of any country other than England and we express no opinion in this letter on the laws of any jurisdiction other than England and we assume that no foreign law affects any of the opinions given below. It is assumed that no foreign law which may apply to the matters contemplated by the Prospectus Supplement, the Company, any document or any other matter contemplated by any document would or might affect this letter and/or the opinions given in it;
- (b) we do not undertake or accept any obligation to update this letter and/or the opinions given in it to reflect subsequent changes in English law or factual matters; and
- (c) we express no opinion in this letter on the laws of any jurisdiction other than England. It is assumed that no foreign law which may apply to the matters contemplated by the Registration Statement, the Company, any document or any other matter contemplated by any document would or might affect this letter and/or the opinions given in it.

1.5 **Assumptions and reservations**

The opinions given in this letter are given on the basis of each of the assumptions set out in schedule 1 (*Assumptions*) and are subject to each of the reservations set out in schedule 2 (*Reservations*) to this letter. The opinions given in this letter are strictly limited to the matters stated in paragraph 2 (*Opinions*) below and do not extend, and should not be read as extending, by implication or otherwise, to any other matters.

2. **OPINIONS**

Subject to paragraph 1 (*Introduction*) and the other matters set out in this letter and its schedules, we are of the opinion that as at today's date:

- (a) the Company is a public limited company duly incorporated under English law, noting the Searches revealed no order or resolution for the winding-up of the Company and no notice of the appointment of a receiver or administrator in respect of it or any of its assets; and
- (b) the Shares, when issued and sold as contemplated in the Registration Statement, the Prospectus and any related Prospectus supplement(s) and in accordance with the Purchase Agreement, will be duly and validly authorised and issued, fully paid or credited as fully paid and will not be subject to any call for payment of further capital.

3. EXTENT OF OPINIONS

We express no opinion as to any agreement, instrument or other document other than as specified in this letter or as to any liability to tax or duty which may arise or be suffered as a result of or in connection with the transactions contemplated thereby.

This letter only applies to those facts and circumstances which exist as at today's date and we assume no obligation or responsibility to update or supplement this letter to reflect any facts or circumstances which may subsequently come to our attention, any changes in laws which may occur after today, or to inform the addressee of any change in circumstances happening after the date of this letter which would alter our opinion.

4. DISCLOSURE AND RELIANCE

This letter is addressed to you in connection with the Registration Statement. We consent to the filing of this letter as an exhibit to the Registration Statement. 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 Securities Act or the rules and regulations thereunder.

Other than for the purpose set out in the prior paragraph, this letter may not be relied upon, or assigned, for any purpose, without our prior written consent, which may be granted or withheld in our discretion.

Yours faithfully

/s/ Goodwin Procter (UK) LLP

Goodwin Procter (UK) LLP

SCHEDULE 1

ASSUMPTIONS

The opinions in this letter have been given on the basis of the following assumptions:

- (a) the genuineness of all signatures, stamps and seals on all documents, the authenticity and completeness of all documents submitted to us as originals, and the conformity to original documents of all documents submitted to us as copies;
- (b) that each of the individuals who signs as, or otherwise claims to be, an officer of the Company is the individual whom they claim to be and holds the office they claim to hold;
- (c) the accuracy as to factual matters of each document we have reviewed;
- (d) that, where a document has been examined by us in draft or specimen form, it will be or has been duly executed in the form of that draft or specimen, and that each of the signed documents examined by us has been duly executed and, where applicable, delivered on behalf of the Company;
- (e) that the Articles remain in full force and effect and no alteration has been made or will be made to such articles of association;
- (f) that all documents, forms and notices which should have been delivered to the Registrar of Companies in respect of the Company have been so delivered, that information revealed by the Searches was complete and accurate in all respects and has not, since the time of the Searches, been altered and that the results of the Searches will remain complete and accurate as at the date of the Registration Statement;
- (g) that the Registration Statement (including the Prospectus), as finally amended, has become effective under the Securities Act;
- (h) that the contents of the Certificate were true and not misleading when given and remain true and not misleading as at the date of this letter and there is no fact or matter not referred to in the Certificate which could make any of the information in the Certificate inaccurate or misleading;
- (i) that all documents, forms and notices which should have been delivered to the Registrar of Companies in respect of the Company have been so delivered, that information revealed by the Searches was complete and accurate in all respects and has not, since the time of the Searches, been altered and that the results of the Searches will remain complete and accurate as at the date of the Registration Statement;
- (j) an appropriate prospectus supplement with respect to the Shares has been prepared, delivered and filed in compliance with the Securities Act and the rules and regulations thereunder;

- (k) that the meeting of the Board was duly constituted and convened and all constitutional, statutory and other formalities were duly observed, the requisite majority of directors voted in favour of approving the resolutions and the resolutions passed thereby were duly adopted, have not been revoked or varied and remain in full force and effect;
- (l) that the meeting of the Pricing Committee was duly constituted and convened and all constitutional, statutory and other formalities were duly observed, the requisite majority of directors voted in favour of approving the resolutions and the resolutions passed thereby were duly adopted, have not been revoked or varied and remain in full force and effect;
- (m) that the resolutions of the shareholders of the Company provided to us in connection with the giving of this opinion and as referred to at paragraph 1.3(c)(ii) of this letter or otherwise contemplated in connection with the matters referred to herein were duly passed, all constitutional, statutory and other formalities were observed in relation to such resolutions and such resolutions have not been revoked or varied as at the date of this letter and remain in full force and effect;
- (n) that in relation to the allotment and issue of the Shares, the directors of the Company have acted and will act in the manner required by section 172 of the Companies Act (Duty to promote the success of the Company), and there has not been and will not be any bad faith, breach of trust, fraud, coercion, duress or undue influence on the part of any of the directors of the Company;
- (o) the Shares will be sold or issued in accordance with the Purchase Agreement, or similar agreement duly authorised, executed and delivered as may be required from time to time;
- (p) that the Shares when issued will be accurately and properly completed, duly authorised, executed and delivered on behalf of the Company and authenticated, issued and paid for and registered in the register of holders of Shares maintained for this purpose, in accordance with the then operative Articles and all applicable laws (for the avoidance of doubt, as in force at all relevant times);
- (q) the directors of the Company, including the Pricing Committee or other appropriate committee appointed thereby, and appropriate officers of the Company have taken all necessary corporate action to approve the allotment and issue of the Shares and related matters;
- (r) that the directors of the Company acted or will act in accordance with sections 171 to 174 of the UK Companies Act 2006 in approving the board resolutions and that all actions to be carried out by the Company are or will be in its commercial interests;
- (s) that there are no facts or circumstances (and no documents, agreements, instruments or correspondence) which are not apparent from the face of the documents listed in paragraph 1.3 or which have not been disclosed to us that may affect the validity or enforceability of the documents listed in paragraph 1.3 or any obligation therein or otherwise affect the opinions expressed in this letter;

- (t) that no Shares shall be allotted or issued, or are or shall be committed to be allotted or issued, at a discount to their nominal value (whether in dollars or equivalent in any other currency);
- (u) that no Shares or rights to subscribe for Shares have been or shall be offered to the public in the United Kingdom in breach of the Financial Services and Markets Act 2000 (“**FSMA**”) or of any other United Kingdom laws or regulations concerning offers of securities to the public, and no communication has been or shall be made in relation to the Shares in breach of section 21 of the FSMA or any other United Kingdom laws or regulations relating to offers or invitations to subscribe for, or to acquire rights to subscribe for or otherwise acquire, shares or other securities;
- (v) that the Company has not taken any corporate or other action nor have any steps been taken or legal proceedings been started against the Company for the liquidation, winding up, dissolution, reorganisation or bankruptcy of, or for the appointment of a liquidator, receiver, trustee, administrator, administrative receiver or similar officer of, the Company or all or any of its assets (or any analogous proceedings in any jurisdiction) and the Company is not unable to pay its debts as they fall due within the meaning of section 123 of the Insolvency Act 1986 and will not become unable to pay its debts within the meaning of that section as a result of any of the transactions contemplated herein, is not insolvent and has not been dissolved or declared bankrupt (although the Searches gave no indication that any winding-up, dissolution or administration order or appointment of a receiver, administrator, administrative receiver or similar officer has been made with respect to the Company); and
- (w) the Company is not, nor will be, engaging in criminal, misleading, deceptive or unconscionable conduct or seeking to conduct any relevant transaction or any associated activity in a manner or for a purpose which might render any transaction contemplated under any corporate approvals or any associated activity illegal, void or voidable.

SCHEDULE 2**RESERVATIONS**

The opinions in this letter are subject to the following reservations:

- (a) the Searches are not capable of revealing conclusively whether or not a winding-up or administration petition or order has been presented or made, a receiver appointed, a company voluntary arrangement proposed or approved or any other insolvency proceeding commenced, and the available records may not be complete or up-to-date. In particular, the Central Registry of Winding-Up Petitions in England may not contain details of administration applications filed, or appointments recorded in or orders made by, district registries and county courts outside London. Searches at Companies House and at the Central Registry of Winding Up Petitions in England are not capable of revealing whether or not a winding up petition or a petition for the making of an administration order has been presented and, further, notice of a winding up order or resolution, notice of an administration order and notice of the appointment of a receiver may not be filed at Companies House immediately and there may be a delay in the relevant notice appearing on the file of the company concerned. Further, not all security interests are registrable, such security interests have not in fact been registered or such security interests have been created by an individual or an entity which is not registered in England. We have not made enquiries of any District Registry or County Court in England;
- (b) the opinions set out in this letter are subject to: (i) any limitations arising from applicable laws relating to insolvency, bankruptcy, administration, reorganisation, liquidation, moratoria, schemes or analogous circumstances; and (ii) an English court exercising its discretion under section 426 of the Insolvency Act 1986 (*co-operation between courts exercising jurisdiction in relation to insolvency*) to assist the courts having the corresponding jurisdiction in any part of the United Kingdom or any relevant country or territory;
- (c) we express no opinion as to matters of fact;
- (d) save for the matters set out in the Certificate, we have made no enquiries of any individual connected with the Company and have relied entirely on the facts, statements and confirmations contained in the Certificate and we have not undertaken any independent investigation or verification of the matters referred to in the Certificate;
- (e) a certificate, documentation, notification, opinion or the like might be held by the English courts not to be conclusive if it can be shown to have an unreasonable or arbitrary basis or in the event of a manifest error; and
- (f) it should be understood that we have not been responsible for investigating or verifying (i) the accuracy of the facts, including statements of foreign law, or the reasonableness of any statements of opinion, contained in the Registration Statement; or (ii) that no material facts have been omitted from it.

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-3 of Orchard Therapeutics plc of our report dated March 2, 2021 relating to the financial statements, which appears in Orchard Therapeutics plc's Annual Report on Form 10-K for the year ended December 31, 2020. We also consent to the reference to us under the heading "Experts" in such Registration Statement.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
April 8, 2021