

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

SCHEDULE 13G  
Under the Securities Exchange Act of 1934

(Amendment No. 3)\*

**ORCHARD THERAPEUTICS PLC**

(Name of Issuer)

**Ordinary Shares, par value £0.10 (represented by American Depositary Shares)**

(Title of Class of Securities)

**68570P101**

(CUSIP Number)

**December 31, 2020**

(Date of Event Which Requires Filing of this Statement)

Check the appropriate box to designate the rule pursuant to which this Schedule is filed:

- Rule 13d-1(b)  
 Rule 13d-1(c)  
 Rule 13d-1(d)

\*The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter the disclosures provided in a prior cover page.

The information required in the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("**Act**") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

1. Names of Reporting Persons.  
I.R.S. Identification Nos. of above persons (entities only).

**RA Capital Management, L.P.**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)   
(b)

3. SEC Use Only

4. Citizenship or Place of Organization **Delaware**

Number of Shares Beneficially Owned by Each Reporting Person With	5. Sole Voting Power	<b>0 shares</b>
	6. Shared Voting Power	<b>12,315,213 shares</b>
	7. Sole Dispositive Power	<b>0 shares</b>
	8. Shared Dispositive Power	<b>12,315,213 shares</b>

9. Aggregate Amount Beneficially Owned by Each Reporting Person

**12,315,213 shares**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions)

11. Percent of Class Represented by Amount in Row (9)  
**12.6%<sup>1</sup>**

12. Type of Reporting Person (See Instructions)  
**IA, PN**

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<sup>1</sup> The reporting person is the beneficial owner of 12,315,213 of the Issuer's American Depositary Shares ("ADSs") representing 12,315,213 of the Issuer's ordinary shares, which constitute approximately 12.6% of the Issuer's outstanding ordinary shares. The percentage calculation assumes that there are currently 97,749,444 outstanding ordinary shares of the Issuer, based on the Issuer's Form 10-Q as filed with the Securities and Exchange Commission ("SEC") on November 3, 2020.

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1. Names of Reporting Persons.  
I.R.S. Identification Nos. of above persons (entities only).

**Peter Kolchinsky**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)   
(b)

3. SEC Use Only

4. Citizenship or Place of Organization **United States**

Number of Shares Beneficially Owned by Each Reporting Person With	5. Sole Voting Power	<b>0 shares</b>
	6. Shared Voting Power	<b>12,315,213 shares</b>
	7. Sole Dispositive Power	<b>0 shares</b>
	8. Shared Dispositive Power	<b>12,315,213 shares</b>

9. Aggregate Amount Beneficially Owned by Each Reporting Person

**12,315,213 shares**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions)

11. Percent of Class Represented by Amount in Row (9)

**12.6%<sup>1</sup>**

12. Type of Reporting Person (See Instructions)

**HC, IN**

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<sup>1</sup> The reporting person is the beneficial owner of 12,315,213 of the Issuer's American Depositary Shares ("ADSs") representing 12,315,213 of the Issuer's ordinary shares, which constitute approximately 12.6% of the Issuer's outstanding ordinary shares. The percentage calculation assumes that there are currently 97,749,444 outstanding ordinary shares of the Issuer, based on the Issuer's Form 10-Q as filed with the Securities and Exchange Commission ("SEC") on November 3, 2020.

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1. Names of Reporting Persons.  
I.R.S. Identification Nos. of above persons (entities only).

**Rajeev Shah**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)   
(b)

3. SEC Use Only

4. Citizenship or Place of Organization **United States**

Number of	5. Sole Voting Power	<b>0 shares</b>
Shares	6. Shared Voting Power	<b>12,315,213 shares</b>
Beneficially	7. Sole Dispositive Power	<b>0 shares</b>
Owned by	8. Shared Dispositive Power	<b>12,315,213 shares</b>
Each Reporting		
Person With		

9. Aggregate Amount Beneficially Owned by Each Reporting Person

**12,315,213 shares**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions)

11. Percent of Class Represented by Amount in Row (9)  
**12.6%<sup>1</sup>**

12. Type of Reporting Person (See Instructions)  
**HC, IN**

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<sup>1</sup> The reporting person is the beneficial owner of 12,315,213 of the Issuer's American Depositary Shares ("ADSs") representing 12,315,213 of the Issuer's ordinary shares, which constitute approximately 12.6% of the Issuer's outstanding ordinary shares. The percentage calculation assumes that there are currently 97,749,444 outstanding ordinary shares of the Issuer, based on the Issuer's Form 10-Q as filed with the Securities and Exchange Commission ("SEC") on November 3, 2020.

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1. Names of Reporting Persons.  
I.R.S. Identification Nos. of above persons (entities only).

**RA Capital Healthcare Fund, L.P.**

2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)   
(b)

3. SEC Use Only

4. Citizenship or Place of Organization **Delaware**

Number of	5. Sole Voting Power	<b>0 shares</b>
Shares	6. Shared Voting Power	<b>11,006,275 shares</b>
Beneficially	7. Sole Dispositive Power	<b>0 shares</b>
Owned by	8. Shared Dispositive Power	<b>11,006,275 shares</b>
Each Reporting		
Person With		

9. Aggregate Amount Beneficially Owned by Each Reporting Person

**11,006,275 shares**

10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares (See Instructions)

11. Percent of Class Represented by Amount in Row (9)  
**11.3%<sup>1</sup>**

12. Type of Reporting Person (See Instructions)  
**HC, IN**

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<sup>1</sup> The reporting person is the beneficial owner of 11,006,275 of the Issuer's American Depositary Shares ("ADSs") representing 11,006,275 of the Issuer's ordinary shares, which constitute approximately 11.3% of the Issuer's outstanding ordinary shares. The percentage calculation assumes that there are currently 97,749,444 outstanding ordinary shares of the Issuer, based on the Issuer's Form 10-Q as filed with the Securities and Exchange Commission ("SEC") on November 3, 2020.

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**Item 1.**

- (a) **Name of Issuer:** Orchard Therapeutics PLC (the “Issuer”).
- (b) **Address of the Issuer’s Principal Executive Offices:** 108 Cannon Street, London EC4N 6EU United Kingdom.

**Item 2.**

- (a) **Name of Person Filing:** This Amendment No. 3 to Schedule 13G amends and restates the Statement on Schedule 13G filed by RA Capital Management, L.P. (“RA Capital”), Peter Kolchinsky, and Rajeev Shah (collectively, the “Reporting Persons”) on February 14, 2019 and amended on February 14, 2020 and April 9, 2020.

The Common Stock reported herein includes 11,006,275 shares held by RA Capital Healthcare Fund, L.P. (the “Fund”) and 1,308,938 shares held in a separately managed account (the “Account”). RA Capital Healthcare Fund GP, LLC is the general partner of the Fund. The general partner of 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 the Account 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 and the Account. The Fund has delegated 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’s Common Stock 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 Schedule 13G 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.

- (b) **Address of Principal Business Office:** The principal business office of the Reporting Persons is c/o RA Capital Management, L.P., 200 Berkeley Street, 18<sup>th</sup> Floor, Boston, MA 02116.
- (c) **Citizenship:** RA Capital and the Fund are a Delaware limited partnerships. Dr. Kolchinsky and Mr. Shah are United States citizens.
- (d) **Title and Class of Securities:** American Depositary Shares (“ADSs”) of the Issuer.
- (e) **CUSIP Number:** 68570P101
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**Item 3. If this statement is filed pursuant to §§240.13d-1(b) or 240.13d-2(b) or (c), check whether the person filing is a:**

- (e) RA Capital Management, L.P. is a registered investment adviser and is filing this statement in accordance with §240.13d-1(b)(1)(ii)(E);
- (g) Peter Kolchinsky and Rajeev Shah are control persons and are filing this statement in accordance with §240.13d-1(b)(1)(ii)(G).

**Item 4. Ownership:**

Provide the following information regarding the aggregate number and percentage of the class of securities of the issuer identified in Item 1.

- (a) Amount Beneficially Owned:  
See the response(s) to Item 9 on the attached cover page(s).
- (b) Percent of Class:  
See the response(s) to Item 11 on the attached cover page(s).
- (c) Number of shares as to which such person has:
  - (i) sole power to vote or to direct the vote:  
See the response(s) to Item 5 on the attached cover page(s).
  - (ii) shared power to vote or to direct the vote  
See the response(s) to Item 6 on the attached cover page(s).
  - (iii) sole power to dispose or to direct the disposition of  
See the response(s) to Item 7 on the attached cover page(s).
  - (iv) shared power to dispose or to direct the disposition of  
See the response(s) to Item 8 on the attached cover page(s).

**Item 5. Ownership of Five Percent or Less of a Class:**

Not applicable.

**Item 6. Ownership of More than Five Percent on Behalf of Another Person:**

Not applicable.

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**Item 7. Identification and Classification of the Subsidiary Which Acquired the Security Being Reported on By the Parent Holding Company or Control Person:**

Not applicable.

**Item 8. Identification and Classification of Members of the Group:**

Not applicable.

**Item 9. Notice of Dissolution of Group:**

Not applicable.

**Item 10. Certification:**

By signing below I certify that, to the best of my knowledge and belief, the securities referred to above were acquired and are held in the ordinary course of business and were not acquired and are not held for the purpose of or with the effect of changing or influencing the control of the issuer of the securities and were not acquired and are not held in connection with or as a participant in any transaction having that purpose or effect, other than activities solely in connection with a nomination under § 240.14a-11.

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**SIGNATURE**

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

DATE: February 16, 2021

RA CAPITAL MANAGEMENT, L.P.

By: /s/ Peter Kolchinsky

Peter Kolchinsky

Authorized Signatory

PETER KOLCHINSKY

/s/ Peter Kolchinsky

RAJEEV SHAH

/s/ Rajeev Shah

RA CAPITAL HEALTHCARE FUND, L.P.

By: RA Capital Healthcare GP, LLC

By: /s/ Peter Kolchinsky

Peter Kolchinsky

Authorized Signatory

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## AGREEMENT

This Joint Filing Agreement, dated as of February 16, 2021, is by and among RA Capital Management, L.P., Peter Kolchinsky, Rajeev Shah, and RA Capital Healthcare Fund, L.P. (the foregoing are collectively referred to herein as the "Filers").

Each of the Filers may be required to file with the United States Securities and Exchange Commission a statement on Schedule 13G and/or 13D with respect to Ordinary Shares, par value £0.10 (represented by American Depositary Shares) of Orchard Therapeutics PLC beneficially owned by them from time to time.

Pursuant to and in accordance with Rule 13(d)(1)(k) promulgated under the Securities Exchange Act of 1934, as amended, the Filers hereby agree to file a single statement on Schedule 13G and/or 13D (and any amendments thereto) on behalf of each of such parties, and hereby further agree to file this Joint Filing Agreement as an exhibit to such statement, as required by such rule.

This Joint Filing Agreement may be terminated by any of the Filers upon one week's prior written notice or such lesser period of notice as the Filers may mutually agree.

Executed and delivered as of the date first above written.

RA CAPITAL MANAGEMENT, L.P.

By: /s/ Peter Kolchinsky

Name: Peter Kolchinsky  
Title: Authorized Signatory

PETER KOLCHINSKY

/s/ Peter Kolchinsky

RAJEEV SHAH

/s/ Rajeev Shah

RA CAPITAL HEALTHCARE FUND, L.P.

By: RA Capital Healthcare GP, LLC

By: /s/ Peter Kolchinsky

Name: Peter Kolchinsky  
Title: Manager

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